Circulation

AHA STATISTICAL UPDATE

# 2024 Heart Disease and Stroke Statistics: A Report of US and Global Data From the American Heart Association

Seth S. Martin, MD, MHS, FAHA, Chair; Aaron W. Aday, MD, MSc, FAHA; Zaid I. Almarzooq, MBBCh, MPH; Cheryl A.M. Anderson, PhD, MPH, FAHA; Pankaj Arora, MD, FAHA; Christy L. Avery, PhD, MPH, FAHA; Carissa M. Baker-Smith, MD, MPH, FAHA; Bethany Barone Gibbs, PhD, MSc, FAHA; Andrea Z. Beaton, MD, MS, FAHA; Amelia K. Boehme, PhD, MSPH; Yvonne Commodore-Mensah, PhD, MHS, RN, FAHA; Maria E. Currie, MD, PhD; Mitchell S.V. Elkind, MD, MS, FAHA; Kelly R. Evenson, PhD, MS, FAHA; Giuliano Generoso, MD, PhD; Debra G. Heard, PhD; Swapnil Hiremath, MD, MPH, FAHA; Michelle C. Johansen, MD, PhD; Rizwan Kalani, MD; Dhruv S. Kazi, MD, MSc, MS, FAHA; Darae Ko, MD, MSc; Junxiu Liu, PhD; Jared W. Magnani, MD, MS, FAHA; Erin D. Michos, MD, MHSc, FAHA; Michael E. Mussolino, PhD, FAHA; Sankar D. Navaneethan, MD, MS, MPH; Nisha I. Parikh, MD, MPH; Sarah M. Perman, MD, MSCE, MS, FAHA; Remy Poudel, MS, MPH, CPH; Mary Rezk-Hanna, PhD, FAHA; Gregory A. Roth, MD, MPH, FAHA; Nilay S. Shah, MD, MPH, FAHA; Marie-Pierre St-Onge, PhD, FAHA; Evan L. Thacker, PhD; Connie W. Tsao, MD, MPH, FAHA; Sarah M. Urbut, MD, PhD; Harriette G.C. Van Spall, MD, MPH; Jenifer H. Voeks, PhD, FAHA; Nae-Yuh Wang, PhD, MS, FAHA; Nathan D. Wong, PhD, MPH, FAHA; Sally S. Wong, PhD, RD, CDN, FAHA; Kristine Yaffe, MD; Latha P. Palaniappan, MD, MS, FAHA, Vice Chair; on behalf of the American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee

**BACKGROUND:** The American Heart Association (AHA), in conjunction with the National Institutes of Health, annually reports the most up-to-date statistics related to heart disease, stroke, and cardiovascular risk factors, including core health behaviors (smoking, physical activity, nutrition, sleep, and obesity) and health factors (cholesterol, blood pressure, glucose control, and metabolic syndrome) that contribute to cardiovascular health. The AHA Heart Disease and Stroke Statistical Update presents the latest data on a range of major clinical heart and circulatory disease conditions (including stroke, brain health, complications of pregnancy, kidney disease, congenital heart disease, rhythm disorders, sudden cardiac arrest, subclinical atherosclerosis, coronary heart disease, cardiomyopathy, heart failure, valvular disease, venous thromboembolism, and peripheral artery disease) and the associated outcomes (including quality of care, procedures, and economic costs).

**METHODS:** The AHA, through its Epidemiology and Prevention Statistics Committee, continuously monitors and evaluates sources of data on heart disease and stroke in the United States and globally to provide the most current information available in the annual Statistical Update with review of published literature through the year before writing. The 2024 AHA Statistical Update is the product of a full year's worth of effort in 2023 by dedicated volunteer clinicians and scientists, committed government professionals, and AHA staff members. The AHA strives to further understand and help heal health problems inflicted by structural racism, a public health crisis that can significantly damage physical and mental health and perpetuate disparities in access to health care, education, income, housing, and several other factors vital to healthy lives. This year's edition includes additional global data, as well as data on the monitoring and benefits of cardiovascular health in the population, with an enhanced focus on health equity across several key domains.



The 2024 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2024. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/CIR.0000000000001209

*Circulation* is available at www.ahajournals.org/journal/circ

**RESULTS:** Each of the chapters in the Statistical Update focuses on a different topic related to heart disease and stroke statistics.

**CONCLUSIONS:** The Statistical Update represents a critical resource for the lay public, policymakers, media professionals, clinicians, health care administrators, researchers, health advocates, and others seeking the best available data on these factors and conditions.

**Key Words:** AHA Scientific Statements ■ cardiovascular diseases ■ epidemiology ■ risk factors ■ statistics ■ stroke

## TABLE OF CONTENTS

*Each chapter listed here is a hyperlink. Click on the chapter name to be taken to that chapter.*



## FOREWORD

### A Century Later: Statistics Remain a Strong Foundation for Moving Forward in the Fight Against Heart Disease and Stroke

The American Heart Association (AHA) started reporting heart disease mortality statistics in May 1927, just 3 years after its founding, when Jessamine Sophia Whitney, an American statistician and public health professional, single-handedly examined statistics on heart disease dating back as early as 1915.[1] These early beginnings were especially significant in fueling awareness and education about heart disease, which, in the 1920s, was thought by many to be a death sentence.[2]

Nearly a century later, the AHA's annual Heart Disease and Stroke Statistical Update continues to provide the most up-to-date statistics on cardiovascular disease (CVD). As it has evolved over the years, the report has become a preeminent resource in identifying the overall impact of all types of CVDs, including who is most affected and where it is most prevalent. This type of information is of general interest to the lay public, policymakers, media professionals, clinicians, health care administrators, researchers, health advocates, and other stakeholders. Furthermore, it is crucial to the development of policy and the allocation of resources and provides a road map for cardiovascular research priorities.

Although some of the numbers show great improvements in our battle to conquer heart disease and stroke, other statistics point to gaps, increasing concern, and areas where we still need to make headway.

Overall, throughout the past century, people are living longer with less risk of having a heart attack or stroke or dying of coronary heart disease. Key numbers tell us the following:

- Heart disease has been the leading cause of death in the United States since 1921.[3]

- Since 1950, death rates from CVD have declined 60%[3]; the rates have fluctuated over the years and have recently trended upward.
- The age-adjusted death rate attributable to CVD decreased from 235.5 per 100 000 people in 2010 to 224.4 per 100 000 people in 2020, which amounts to a 4.7% decrease.[4]
- The number of people in the United States dying of a heart attack each year has dropped from 1 in 2 to now 1 in 8.[5]
- Stroke was first ranked as the third leading cause of death in 1938; however, stroke mortality has been on the decline since the early 20th century[6] and now ranks as the fifth leading cause of death in the United States.
- Cigarette smoking has fallen dramatically from >40% of US adults smoking in the mid-1960s[7] to ≈11% today.[8]

Still, there is much work to be done. After decades of decline in CVD rates, more recent trends are moving up, attributed in part to worsening risk factors such as diabetes, population aging, health inequities, and other factors. For example, according to the AHA Heart Disease and Stroke Statistical Update, from 2017 to March 2020[4]:

- Deaths attributable to diseases of the heart and CVD in the United States increased steadily during the 1900s to the 1980s and declined into the 2010s but increased again in the later 2010s to 2020.
- It is estimated that roughly 127.9 million Americans (48.6%) ≥20 years of age have CVD, including coronary heart disease, heart failure, stroke, or hypertension.
- Excluding hypertension, about 28.6 million American adults (9.9%) have some type of CVD.
- Overall, CVD prevalence remains highest among non-Hispanic Black females (59%) and non-Hispanic Black males (58.9%).
- More than half (50.4%) of US males and 43% of females ≥20 years of age have hypertension, again with prevalence highest among non-Hispanic Black males and females.
- More than 71% of US adults have overweight and obesity, identified as a body mass index ≥30.0 kg/m$^2$.
- Fewer than one-fourth (24.2%) of US adults meet national recommendations for physical activity.
- More people died of cardiovascular-related causes in 2020, the first year of the COVID-19 (coronavirus disease 2019) pandemic, than in any year since 2003. The largest increases in deaths were seen among Asian, Black, and Hispanic people.

The annual AHA Heart Disease and Stroke Statistical Update is an evolving publication, and the volunteer writing group continues to enhance the report to best serve its diverse readership:

- In 2020, social determinants of health were added in all chapters, and brain health was introduced in the Stroke (Cerebrovascular Disease) chapter.
- In 2021, the Adverse Pregnancy Outcomes chapter was added, and Global Burden of Disease data were expanded.
- In 2022, brain health was expanded into a dedicated chapter, and COVID-19 data were incorporated into the report.
- In 2023, there was an increased emphasis on health equity, as well as the addition of the Global Fact Sheets supplement and a toolkit that included fact sheets with key statistics by race, ethnicity, age, and sex translated into 7 languages to broaden the audience around the world.
- This year, we have expanded the focus on heart disease and stroke statistics throughout the world, as reflected in the report's new title, which includes the term "global." Additionally, we have enhanced visual tools for dissemination of the Statistical Update.

In a world full of misinformation, the AHA Heart Disease and Stroke Statistical Update is a credible source of information compiled by the AHA's largest scientific publishing writing group of professional members and staff with a diverse racial, ethnic, professional, and geographic background. The publication includes collaborative input from other organizations, including the American College of Cardiology, Cardiac Arrest Registry to Enhance Survival, Institute for Health Metrics and Evaluation, and National Institutes of Health–National Heart, Lung, and Blood Institute.

The AHA Heart Disease and Stroke Statistical Update continues to serve as one of our most powerful tools in building our road map for the next 100 years. Although the research and statistics included in each year's report illustrate the most recent data, the historical data pulled from the collective work over the years further define important trends that we must evaluate to continue to move forward in our mission to be a relentless force for a world of longer, healthier lives, furthering our vision of advancing health and hope for everyone everywhere.

As poet and activist Maya Angelou once said, "You can't really know where you are going until you know where you have been."[9] In 2024, the year the AHA celebrates its centennial, this sentiment rings even more true. We advance into our second century as a global force in fueling science and innovation, funding lifesaving research and boldly advocating for the rights of patients and caregivers. The AHA strives to empower healthier communities and to transcend the way we live, work, and play in the United States and globally. This relentless pursuit will continue until heart disease and stroke are the story of our past and not of our future.

*Seth S. Martin, MD, MHS*
*Sally S. Wong, PhD, RD, CDN*
*Debra G. Heard, PhD*
*Latha P. Palaniappan, MD, MS*

## SUMMARY

Each year, the American Heart Association (AHA), in conjunction with the National Institutes of Health and other government agencies, brings together in a single document the most up-to-date statistics related to heart disease (HD), stroke, and cardiovascular risk factors in the AHA's Life's Essential 8 (Figure),[10] which include core health behaviors (smoking, physical activity [PA], diet, and weight) and health factors (cholesterol, blood pressure [BP], and glucose control) that contribute to cardiovascular health (CVH). The AHA Heart Disease and Stroke Statistical Update represents a critical resource for the lay public, policymakers, media professionals, clinicians, health care administrators, researchers, health advocates, and others seeking the best available data on these factors and conditions. Cardiovascular disease (CVD) produces immense health and economic burdens in the United States and globally. The Statistical Update also presents the latest data on a range of major clinical heart and circulatory disease conditions (including stroke, congenital HD, rhythm disorders, subclinical atherosclerosis, coronary heart disease [CHD], heart failure [HF], valvular HD, venous disease, and peripheral artery disease) and the associated outcomes (including quality of care, procedures, and economic costs).

Each annual version of the Statistical Update undergoes revisions to include the newest nationally representative available data, add additional relevant published scientific findings, remove older information, add new sections or chapters, and increase the number of ways to access and use the assembled information. This year-long process, which begins as soon as the previous Statistical Update is published, is performed by the AHA Statistics Committee faculty volunteers and staff and government agency partners. Below are a few highlights from this year's Statistical Update. Please see each chapter for references for these highlights, CIs for statistics reported, and additional information.

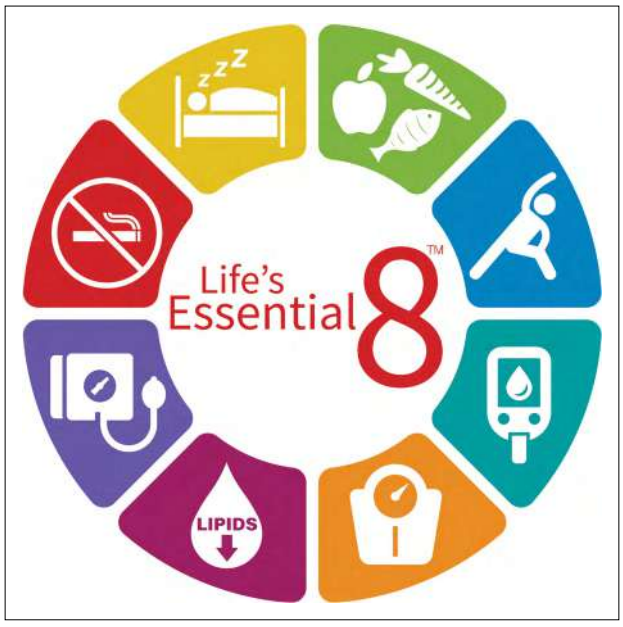



**Figure. AHA's My Life Check – Life's Essential 8.**
Source: Reprinted with permission from Lloyd-Jones et al.[10] Copyright © 2022, American Heart Association, Inc.

### Cardiovascular Health (Chapter 2)

- Over the past decade, mean CVH diet scores in the revised CVH metrics for US adults remained low and relatively unchanged, whereas mean PA, nicotine exposure, sleep health, and non–high-density lipoprotein blood lipids scores of the CVH metrics had encouraging trends of improvement. However, mean body mass index and blood glucose in the CVH metrics had sizable downward trends of decline over the same period in time. BP scores remained relatively unchanged.
- Applying the updated CVH metrics of Life's Essential 8 to the NHANES (National Health and Nutrition Examination Survey) data showed a 58% reduction (hazard ratio [HR], 0.42) in all-cause mortality rate and a 64% reduction (HR, 0.36) in CVD-specific mortality rate comparing the high CVH (overall score, 75–100) with the low CVH (overall score <50) group, whereas a 40% reduction (HR, 0.60) in all-cause mortality rate and a 38% reduction (HR, 0.62) in CVD-specific mortality rate were observed comparing the moderate CVH (score, 50–74) with the low CVH group. Life expectancy at 50 years of age, that is, the average number of years of life remaining after 50 years of age, for US adults was estimated to be 27.3 years in the low CVH group, defined as CVH overall score <50, 32.9 years in the moderate CVH group (CVH overall score between 50 and 79), and 36.2 years in the high CVH group, defined as overall CVH score of ≥80.
- Estimates of US life expectancy at birth decreased from 78.8 years in 2019 to 76.1 years in 2021 (−2.7 years) overall; corresponding life expectancy decreased from 76.3 to 73.2 years (−3.1 years) in males and from 81.4 to 79.1 years (−2.3 years) in females. Over the same 2-year period, life expectancy decreased from 74.7 to 70.8 years (−4.0 years) for non-Hispanic (NH) Black individuals, from 81.8 to 77.7 years (−4.2 years) for Hispanic individuals, and from 78.8 to 76.4 years (−2.4 years) for NH White individuals.

### Smoking/Tobacco Use (Chapter 3)

- The prevalence of cigarette use in the past 30 days among middle and high school students in the United States was 1.0% and 2.0%, respectively, in 2022.

- Although there has been a consistent decline in youth and adult cigarette use in the United States in the past 2 decades, significant disparities persist. In 2022, the prevalence of past 30-day cigarette use was comparable between NH White youth (1.8%) and Hispanic youth (1.8%) compared with NH multiracial youth (2.3%). In 2021, 11.7% of NH Black adults, 5.4% of NH Asian adults, 7.7% of Hispanic adults, and 11.7% of NH White adults reported cigarette use every day or some days.
- Electronic cigarettes were the most commonly used tobacco product among adolescents in 2022; the prevalence of use in the past 30 days among middle and high school students in the United States was 3.3% and 14.1%, respectively, with the majority (84.9%) of adolescent users using flavored electronic cigarettes.

## Physical Activity and Sedentary Behavior (Chapter 4)

- According to parental report in 2020 to 2021, the nationwide percentage of youth 6 to 17 years of age who were active ≥60 minutes every day of the week was 20.5%.
- According to self-report in 2020, the percentage of adults who reported meeting the aerobic PA guidelines for Americans (≥150 min/wk of moderate PA, ≥75 min/wk of vigorous PA, or an equivalent combination of the two) through leisure-time PA and participating in muscle strengthening ≥2 d/wk was 24.2%.
- Among 194 191 adults with a COVID-19 (coronavirus disease 2019)–positive test or diagnosis between January 1, 2020, and May 31, 2021, those who were always inactive, mostly inactive, or somewhat active at outpatient visits 2 years before the COVID-19 test or diagnosis had a higher odds of hospitalization and death compared with those in the always active category.

## Nutrition (Chapter 5)

- Most Americans do not consume a healthy dietary pattern. Using NHANES 2013 to 2018 applied to AHA's Life's Essential 8, we found that diet was among the 4 CVH metrics with the lowest scores. Scores on each metric range from 0 to 100. The range for diet across demographic groups was 23.8 to 47.7. Among children 2 to 5 years of age, a mean diet score of 61.1 was observed. The score for children 12 to 19 years of age was 28.5.
- Social and environmental factors observed to be associated with diet quality include education, income, race and ethnicity, neighborhood availability of supermarkets, and cost of food. The healthiest dietary patterns cost, on average, $1.50 more per day to consume. Increased consumption or purchases of fruits and vegetables have been documented with the use of pricing incentives.
- Globally, an estimated 7.9 million deaths (14% of all deaths) and 188 million disability-adjusted life-years (7% of all disability-adjusted life-years) were attributable to dietary risks in 2019. Diet-related death rates decreased between 1990 and 2019 from 154 to 101 per 100 000 population, although the proportion of deaths attributable to dietary risks was largely stable over this time period.

## Overweight and Obesity (Chapter 6)

- The age-adjusted prevalence of overweight or obesity among US adults ≥20 years of age was 71.2% (NHANES 2017–March 2020 data), with the prevalence of obesity at 41.9%.
- Among US children and adolescents 2 to 19 years of age, the prevalence of obesity was 19.7% (NHANES 2017–March 2020 data).
- The World Obesity Federation's 2023 Atlas has estimated that more than half of the world's population (51%), or more than 4 billion individuals, will be either overweight or obese by 2035, and among the total population, 1 in 4 persons, or nearly 2 billion individuals, will have obesity.

## High Blood Cholesterol and Other Lipids (Chapter 7)

- Mean age-adjusted total cholesterol levels decreased in the US population from 197 mg/dL in 2007 to 2008 to 189 mg/dL in 2017 to 2018. During this period, mean age-adjusted total cholesterol decreased in females from 199 to 192 mg/dL and in males from 195 to 185 mg/dL.
- In 2017 to 2018, cholesterol screening rates within the preceding 5 years were 65.8% for Hispanic adults, 75.0% for NH Asian adults, 70.7% for NH Black adults, and 74.1% for NH White adults.
- Recent randomized trial data among patients at elevated risk for atherosclerotic cardiovascular disease events showed no significant difference in incidence of major adverse cardiovascular events in participants receiving pemafibrate compared with placebo (HR, 1.03) and a significantly lower incidence of major adverse cardiovascular events in participants receiving bempedoic acid compared with placebo (HR, 0.87).

## High Blood Pressure (Chapter 8)

- The age-adjusted prevalence of hypertension among US adults ≥20 years of age was estimated

to be 46.7% in NHANES in 2017 to 2020 (50.4% for males and 43.0% for females), which equates to an estimated 122.4 million adults ≥20 years of age who have high BP.
- The prevalence of systolic and diastolic hypertension from awake ambulatory BP in children 11 to 19 years of age from the SHIP AHOY cohort study (Study of Hypertension in Pediatrics, Adult Hypertension Onset in Youth) was 17% and 11%, respectively, using the criteria of BP >95th percentile; the prevalence was 27% and 13%, respectively, using the 2017 American College of Cardiology/AHA adult thresholds of ≥130/80 mm Hg.
- In a prospective randomized controlled trial of 21 104 participants who were randomized to take all of their usual antihypertensive medications either in the morning (6–10 AM) or in the evening (8 PM–midnight), the incidence of the primary cardiovascular composite end point of vascular death, hospitalization for nonfatal myocardial infarction, or nonfatal stroke was not significantly higher in the evening group compared with the control group who took their medications in the morning (HR, 0.95), suggesting no benefit of taking BP-lowering medications at bedtime.

## Diabetes (Chapter 9)

- Age-adjusted prevalence of diagnosed diabetes in 2017 to 2020 varied greatly by sex and race and ethnicity, ranging from 7.7% in NH White females to 14.5% in Hispanic males.
- Fewer than 20% of US adults with diabetes are at target for 3 important measures: hemoglobin A1c, BP, and low-density lipoprotein cholesterol, which are closely related to CVD risk.
- Newer evidence-based therapies for diabetes proven to reduce CVD risk, including sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide 1 receptor agonists, remain highly underused.

## Metabolic Syndrome (Chapter 10)

- From 1999 to 2018, the prevalence of metabolic syndrome among US adults increased significantly from 36.2% to 47.3%.
- From 1999 to 2018, the prevalence of metabolic syndrome among US youth 12 to 19 years of age remained stable at 4.36%.
- Mexican American adults had the highest prevalence of metabolic syndrome in 2017 to 2018 (52.2%). Individuals with lower education and income levels exhibited higher prevalence of metabolic syndrome compared with their counterparts.

## Adverse Pregnancy Outcomes (Chapter 11)

- Mothers had higher mortality in 52 years after pregnancy if they had experienced preterm labor (HR, 1.07), premature rupture of membranes (HR, 1.23), hypertensive disorders of pregnancy (HR, 1.09), or gestational diabetes or impaired fasting glucose (HR, 1.14).
- Among women delivering in the hospital from 2017 to 2019, the prevalence of hypertensive disorders of pregnancy increased from 13.3% to 15.9%; Black women had the highest prevalence of hypertensive disorders of pregnancy (20.9%).
- Doing more intensive BP lowering (targeting <140/90 mm Hg compared with no treatment unless BP was severely elevated [≥160/105 mm Hg]) reduced rates of severe preeclampsia, preterm birth before 35 weeks, placental abruption, or fetal/neonatal death by 18%.

## Kidney Disease (Chapter 12)

- The overall prevalence of chronic kidney disease (estimated glomerular filtration rate <60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ or albumin-to-creatinine ratio ≥30 mg/g) in 2017 to 2020 was 14.0%.
- In 2020, the age-, race-, and sex-adjusted prevalence of end-stage renal disease in the United States was 363 per 1 million people, the lowest since 2000.
- In 2020, Medicare spent $85.4 billion caring for people with chronic kidney disease and $50.8 billion caring for people with end-stage renal disease.

## Sleep (Chapter 13)

- Short sleep duration is more prevalent on workdays (7.6 hours) than free days (8.2 hours), with adults sleeping ≈45 minutes less on workdays than free days.
- Trouble sleeping and maintaining sleep are more prevalent in females (odds ratio [OR], 2.26 and 2.05, respectively) than males.
- Meeting the ideal sleep health metric from Life's Essential 8 is associated with reduced all-cause mortality (HR, 0.97).

## Total Cardiovascular Diseases (Chapter 14)

According to 2017 to 2020 NHANES data:
- It is estimated that roughly 127 900 000 (48.6%) of Americans ≥20 years of age have CVD, including CHD, HF, stroke, or hypertension. Prevalences remain highest among NH Black females (59%) and NH Black males (58.9%). When hypertension is excluded, the prevalence of CVD remains highest among NH White males (11.3%) and NH Black males (11.3%).

- CVD, more than cancer, accounts for more deaths among individuals <85 years of age (596 786 versus 502 847 deaths).
- States with the highest age-adjusted CVD related death rates per 100 000 people between 2019 and 2021 were Alabama, Oklahoma, and Arkansas (308.6, 303.2, and 290.3 per 100 000 people, respectively).

## Stroke (Cerebrovascular Diseases) (Chapter 15)

- From 2011 to 2021, the age-adjusted stroke death rate in the United States increased 8.4% (from 37.9 per 100 000 to 41.1 per 100 000), whereas the actual number of stroke deaths increased 26.3% (from 128 932 to 162 890 deaths).
- A systematic review found among 50 studies in 20 countries that temporal trends in stroke incidence are diverging by age in high-income countries, with less favorable trends at younger compared with older ages (pooled relative temporal rate ratio, 1.57).
- In a meta-analysis of randomized trials comparing more and less intensive BP targets, which included 60 870 participants with an average 3.95 years of follow-up, more intensive BP control was associated with a lower risk of stroke (OR, 0.79). The trials differed in the specific BP targets, and the average achieved SBP reduction in the more intensive treatment was 7.69 mm Hg.

## Brain Health (Chapter 16)

- In a US cohort of >240 000 females diagnosed with breast cancer at ≥65 years of age with 26 years of follow-up, the incidence rate of Alzheimer disease compared with White females (18.74 cases per 1000 person-years) was higher in Black females (24.2 cases per 1000 person-years; adjusted HR versus White females, 1.21) and lower in Asian/Pacific Islander females (13.35 cases per 1000 person-years; adjusted HR versus White females, 0.77).
- Midlife overweight and obesity are associated with increased risk of cognitive impairment and dementia. In a meta-analysis of 11 longitudinal studies including >64 000 participants, midlife overweight compared with normal weight was associated with 1.14 times the risk of cognitive impairment and dementia, 1.64 times the risk of Alzheimer disease, and 1.49 times the risk of vascular dementia; midlife obesity compared with normal weight was associated with 1.31 times the risk of cognitive impairment and dementia, 2.23 times the risk of Alzheimer disease, and 3.18 times the risk of vascular dementia.
- The AHA's ideal CVH metrics are associated with reduced cognitive decline. In a meta-analysis of 14 studies including .300 000 participants, of whom 8006 experienced incident dementia, a 1-point increment in the AHA's My Life Check–Life's Simple 7 CVH score was associated with a 6% lower rate of dementia. The inverse relationship of higher CVH score with dementia risk was more pronounced for midlife CVH than for late-life CVH.

## Congenital Cardiovascular Defects and Kawasaki Disease (Chapter 17)

- Gestational age <37 weeks, birth weight <2.5 kg, a secondary cardiac lesion, extracardiac abnormalities, and genetic syndromes are associated with worse survival among those with CHD. Although the presence of a single high-risk diagnosis is not associated with decreased survival, an incremental increase in the number of high-risk diagnoses is associated with reduced survival to a first birthday (OR, 0.23). The presence of 3 to 5 high risk diagnoses is associated with an even greater odds of mortality (OR, 0.17).
- Institution of an interstage home monitoring program for infants with hypoplastic left-heart syndrome may be beneficial for reducing interstage mortality. Data from the National Pediatric Cardiology Quality Improvement Collaborative have reported a >40% reduction in interstage 1 mortality rate, reducing mortality rate to <2%, in the current era, after changes in practice such as institution of an interstage home monitoring program.
- Since May 2020, the Centers for Disease Control and Prevention has been tracking reports of multisystem inflammatory syndrome in children. As of March 17, 2023, 9370 cases and 76 attributable deaths (0.81%) have been reported.

## Disorders of Heart Rhythm (Chapter 18)

- The sex-specific, age-standardized mortality associated with atrial fibrillation (AF) increased in US states from 1990 to 2017. The greatest percentage increases were, for males, in Mississippi (26.4%), Oklahoma (24.9%), Idaho (24.8%), and New Hampshire (22.4%), and for females, Oregon (54.6%), Montana (46.7%), Utah (42.5%), and Nebraska (40.5%).
- The modifiable risk factors for AF of obesity, waist circumference, hypertension, and diabetes have different contributions to AF risk by age. In a large administrative analysis, diabetes was associated with an HR of 1.35 for incident AF in those 20 to 49 years of age compared with 1.10 and 0.93 in those 50 to 59 and 60 to 75 years of age, respectively.

- A large meta-analysis of 15 studies (N=1 821 422) identified an inverse, nonlinear relation between weekly PA and AF risk. The effect was most robust on those exercising up to 50 metabolic equivalents per week because data are limited for higher levels of PA.

## Sudden Cardiac Arrest, Ventricular Arrhythmias, and Inherited Channelopathies (Chapter 19)

- Survival to hospital discharge after emergency medical services–treated out-of-hospital cardiac arrest was 9.3% in the 2022 CARES registry (Cardiac Arrest Registry to Enhance Survival) with significant variation among states reporting data (range, 5.5%–15.4%).
- The median risk-adjusted in-hospital cardiac arrest incidence was 8.5 per 1000 admissions of Medicare beneficiaries. In-hospital cardiac arrest incidence varied across hospitals after adjustment for differences in case-mix index, from 2.4 per 1000 admissions to 25.5 per 1000 admissions.
- According to 2013 to 2019 CARES data, Black and Hispanic individuals with out-of-hospital cardiac arrest receive less bystander CPR at home (adjusted OR, 0.74) and in public (adjusted OR, 0.63).

## Subclinical Atherosclerosis (Chapter 20)

- In 3116 MESA (Multi-Ethnic Study of Atherosclerosis) participants (58±9 years of age; 63% females) who had no detectable coronary artery calcification at baseline and were followed up over 10 years, 53%, 36%, and 8% of individuals had coronary artery calcification >0, >10, and >100, respectively, at 10 years.
- Among 10528 females in Sweden with ≥1 deliveries in 1973 or later who later participated in an imaging study at a median of 57.3 years of age in 2013 to 2018, atherosclerosis was present by coronary computed tomography angiography in 32.1% of females with a history of any adverse pregnancy outcome. This prevalence was higher compared with females without any history of adverse pregnancy outcome (prevalence difference, 3.8%; prevalence ratio, 1.14).
- In the FAMILIA trial (Family-Based Approach in a Minority Community Integrating Systems–Biology for Promotion of Health) of 436 socioeconomically challenged young adults who underwent carotid and femoral vascular ultrasound, subclinical atherosclerosis was present in 12.6% of NH Black versus 6.6% of Hispanic individuals, with higher risk for prevalent disease (OR, 3.45) and multivascular disease (*P*=0.026) in analyses adjusted for CVD risk factors, as well as lifestyle and socioeconomic status factors.

## Coronary Heart Disease, Acute Coronary Syndrome, and Angina Pectoris (Chapter 21)

- Data from the BRFSS (Behavioral Risk Factor Surveillance System) 2021 survey indicate that 4.0% of respondents had been told that they had had a myocardial infarction. The highest age-adjusted prevalence was in West Virginia (5.6%); the lowest was in Colorado (2.4%).
- A systematic review of 181 studies conducted primarily in high-income countries found that lower socioeconomic position (education, income, insurance, occupation, or composite) was associated with higher incidence of acute coronary syndrome (incidence rate ratio, 1.1–4.7), prevalence of acute coronary syndrome (OR, 1.8–3.9), higher odds of receiving suboptimal medical care (OR, 1.1–10.0), and higher mortality after acute coronary syndrome (HR, 1.1–4.13).
- An analysis conducted in the CARDIA study (Coronary Artery Risk Development in Young Adults; N=5112) with a median follow-up of >33 years identified that premature CVD risk in Black participants was attenuated after adjustment for lifestyle, neighborhood, and socioeconomic factors. For example, the 2.4-fold increased CVD risk in Black females relative to White females was no longer significant after adjustment for clinical, lifestyle, socioeconomic, and neighborhood factors. The largest decreases in the race-specific estimate for CVD risk occurred with adjustment for clinical (87%), neighborhood (32%), and socioeconomic (23%) factors.

## Cardiomyopathy and Heart Failure (Chapter 22)

- In 2019, estimated 56.2 million people were living with HF across 204 countries globally, although the estimate likely underrepresents the true prevalence of HF because of data and diagnostic gaps in low-resource regions.
- CHD, hypertension, diabetes, obesity, and smoking account for 52% of incident HF with population attributable risks as follows: CHD, 20% (23% in males versus 16% in females); hypertension, 20% (28% in females versus 13% in males); cigarette smoking, 14%; obesity, 12%; and diabetes, 12%.
- Contemporary guideline-directed medical therapy for HF with reduced ejection fraction (quadruple therapy with angiotensin receptor/neprilysin inhibitors, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers; β-blockers; mineralocorticoid receptor antagonists; and sodium-glucose

cotransporter 2 inhibitors) may extend survival by an estimated 1.4 to 6.3 years according to modeling from clinical trials. Treatment efficacy with these classes is attenuated as left ventricular ejection fraction increases, particularly for the outcome of death, and there is no clear evidence to support β-blockers in HF with preserved ejection fraction.

## Valvular Diseases (Chapter 23)

- The global prevalence of nonrheumatic valvular HD is 32.6 million.
- Among the causes of HF between 1990 and 2019, calcific aortic valve disease increased by >90% in both males and females.
- The 276 316 patients treated with transcatheter aortic valve replacement who entered the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry between 2011 and 2019 demonstrated improved temporal trends, with 2018 or 2019 cohorts demonstrating lower event rates than more historic cohorts.

## Venous Thromboembolism (Deep Vein Thrombosis and Pulmonary Embolism), Chronic Venous Insufficiency, Pulmonary Hypertension (Chapter 24)

- In 2020, >1 million people were hospitalized in the United States due to venous thromboembolism, with ≈40% of them being pulmonary embolism cases.
- In the same year, after the onset of the COVID pandemic, mortality incidence associated with pulmonary embolism increased compared with preceding years.
- Mass vaccination against COVID-19 did not increase the risk of venous thromboembolism, regardless of the type of vaccine used.

## Peripheral Artery Disease and Aortic Diseases (Chapter 25)

- Among individuals with a normal baseline ankle-brachial index in the Veterans Affairs Birth Cohort, Black participants had an increased risk of incident peripheral artery disease compared with White participants (adjusted HR, 1.09), which was driven by a greater risk of amputation (adjusted HR, 1.20).
- In Medicare beneficiaries who underwent peripheral vascular interventions from 2016 to 2018, the age- and sex-adjusted incidence of death or major amputation was greater among Black compared with White individuals (25.03% versus 18.62%).
- Among Medicare beneficiaries hospitalized with acute type B aortic dissections from 2011 to 2018, initial thoracic endovascular aortic repair within 30 days was not associated with a decrease in mortality (HR, 0.95) or aorta-related hospitalizations (HR, 1.12) compared with initial medical therapy.

## Quality of Care (Chapter 26)

- In a nationwide analysis of BP control that evaluated 18 262 adults with hypertension, the age-adjusted estimated proportion with controlled BP, defined as BP <140/90 mm Hg, improved from 31.8% in 1999 to 2000 to 48.5% in 2007 to 2008, was similar in 2013 to 2014 (53.8%), and then worsened to 43.7% in 2017 to 2018.
- In 2023, a majority of Medicare beneficiaries were enrolled in Medicare Advantage plans rather than traditional fee-for-service Medicare. Thus, evaluations of quality of care among Medicare beneficiaries must include both fee-for-service and Medicare Advantage patients. A recent study showed that ≈1 in 4 "top-performing" hospitals (based on outcomes among fee-for-service patients) would be reclassified to a lower performance group when Medicare Advantage beneficiaries are included in the evaluation of hospital readmissions and mortality, and similar proportions of hospitals were reclassified from the bottom performance quintile to a higher one.
- The use of sodium-glucose cotransporter 2 inhibitors is of intermediate economic value (incremental cost-effectiveness ratio, $50 000 to <$150 000 per quality-adjusted life-year gained) in patients with HF with reduced ejection fraction, regardless of whether the patient has diabetes. However, their use in patients with HF with preserved ejection fraction is of low or low to intermediate value because of the absence of a mortality benefit and small benefit on quality of life.

## Medical Procedures (Chapter 27)

- According to the NCDR (National Cardiovascular Data Registry) Left Atrial Appendage Occlusion Registry, a US Food and Drug Administration–mandated postmarket registry, there were 38 158 left atrial appendage occlusion implantations from January 1, 2016, to December 31, 2018. Among the patients undergoing this procedure, 92.6% of the patients were White and 4.6% were Black.
- Percutaneous coronary intervention was the most common cardiovascular procedure in 2020 with 434 230 procedures.
- A total of 161 816 procedures involved isolated coronary artery bypass graft in 2019. Coronary artery bypass graft made up a little more than half of all adult cardiac surgical procedures performed (N=301 077) in 2019.

## Economic Cost of Cardiovascular Disease (Chapter 28)

- The average annual direct and indirect cost of CVD in the United States was an estimated $422.3 billion in 2019 to 2020.
- The estimated direct costs of CVD in the United States increased from $103.5 billion in 1996 to 1997 to $254.3 billion in 2019 to 2020.
- By event type, hospital inpatient stays for CVD (HD, stroke, hypertensive disease, and other circulatory conditions) accounted for $110.3 billion in direct costs in 2019 to 2020 in the United States.

## Conclusions

The AHA, through its Epidemiology and Prevention Statistics Committee, continuously monitors and evaluates sources of data on HD and stroke in the United States and globally to provide the most current information available in the Statistical Update. The 2024 Statistical Update is the product of a full year's worth of effort by dedicated volunteer clinicians and scientists, committed government professionals, and AHA staff members, without whom publication of this valuable resource would be impossible. Their contributions are gratefully acknowledged.

*Seth S. Martin, MD, MHS, FAHA, Chair*
*Latha P. Palaniappan, MD, MS, FAHA, Vice Chair*
*Sally S. Wong, PhD, RD, CDN, FAHA, National Senior Director, Science & Medicine*
*Debra G. Heard, PhD, AHA Consultant*
*On behalf of the American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee*

## ARTICLE INFORMATION



The American Heart Association requests that this document be cited as follows: Martin SS, Aday AW, Almarzooq ZI, Anderson CAM, Arora P, Avery CL, Baker-Smith CM, Barone Gibbs B, Beaton AZ, Boehme AK, Commodore-Mensah Y, Currie ME, Elkind MSV, Evenson KR, Generoso G, Heard DG, Hiremath S, Johansen MC, Kalani R, Kazi DS, Ko D, Liu J, Magnani JW, Michos ED, Mussolino ME, Navaneethan SD, Parikh NI, Perman SM, Poudel R, Rezk-Hanna M, Roth GA, Shah NS, St-Onge M-P, Thacker EL, Tsao CW, Urbut SM, Van Spall HGC, Voeks JH, Wang N-Y, Wong ND, Wong SS, Yaffe K, Palaniappan LP; on behalf of the American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. 2024 Heart disease and stroke statistics: a report of US and global data from the American Heart Association. *Circulation.* 2024;149:e347–e913. doi: 10.1161/CIR.0000000000001209



### Acknowledgments

The writing group thanks its colleagues Michael Wolz at the National Heart, Lung, and Blood Institute; the team at the Institute for Health Metrics and Evaluation at the University of Washington; Corinna Tanner and Troy Stoddard at Brigham Young University; Bryan McNally and Rabab Al-Araji at the CARES program; and Christina Koutras and Fran Thorpe at the American College of Cardiology for their valuable contributions and review.

### Disclosures

**Writing Group Disclosures**

| Writing group member | Employment | Research grant | Other research support | Speakers' bureau/ honoraria | Expert witness | Ownership interest | Consultant/ advisory board | Other |
|---|---|---|---|---|---|---|---|---|
| Seth S. Martin | Johns Hopkins University | American Heart Association†; NIH†; PCORI†; Merck†; Apple†; Google† | None | None | None | Corrie Health* | Sanofi*; BMS*; Merck*; AstraZeneca*; Premier Healthcare*; Novartis* | None |
| Latha P. Palaniappan | Stanford University | None | None | None | None | None | None | None |
| Aaron W. Aday | Vanderbilt University Medical Center | NIH†; Lipedema Foundation† | None | None | None | None | None | None |
| Zaid I. Almarzooq | Brigham and Women's Hospital | None | None | None | None | None | None | None |
| Cheryl A.M. Anderson | University of California at San Diego Family and Preventive Medicine | None | None | None | None | None | None | None |

(*Continued*)

**Writing Group Disclosures Continued**

| Writing group member | Employment | Research grant | Other research support | Speakers' bureau/ honoraria | Expert witness | Ownership interest | Consultant/ advisory board | Other |
|---|---|---|---|---|---|---|---|---|
| Pankaj Arora | University of Alabama at Birmingham | National Institutes of Health (principal investigator on 3 R01 and 1 K23 grants)† | None | None | None | None | Bristol Myers Squibb† | None |
| Christy L. Avery | University of North Carolina | None | None | None | None | None | None | None |
| Carissa M. Baker-Smith | Nemours' Children's Health | NIH (research project)†; DE INBRE (research project)†; Regeneron (clinical trial)† | None | National Continuing Medical Education* | None | None | Medscape*; PCORI (advisory board)* | Nemours (associate professor; director, Preventive Cardiology)† |
| Bethany Barone Gibbs | University of West Virginia Epidemiology and Biostatistics | NIH (PI, co-PI, co-I, and consultant)†; AHA (PI on 1 small project)* | None | None | None | None | None | None |
| Andrea Z. Beaton | The Heart Institute, Cincinnati Childrens Hospital Medical Center | None | None | None | None | None | None | None |
| Amelia K. Boehme | Columbia University | None | None | None | None | None | None | Aetion (director, Science)† |
| Yvonne Commodore-Mensah | Johns Hopkins University | None | None | None | None | None | None | None |
| Maria E. Currie | Stanford University School of Medicine | None | None | None | None | None | None | None |
| Mitchell S.V. Elkind | Columbia University | BMS-Pfizer Alliance for Eliquis (received study drug in kind for a federally funded clinical trial in stroke prevention)†; Roche Diagnostics (received ancillary funding for an NIH clinical trial in stroke prevention)† | None | None | None | None | None | None |
| Kelly R. Evenson | University of North Carolina | None | None | None | None | None | None | None |
| Giuliano Generoso | University Hospital, University of São Paulo Center for Clinical and Epidemiological Research (Brazil) | None | None | None | None | None | None | None |
| Debra G. Heard | American Heart Association | None | None | None | None | None | American Heart Association† | None |
| Swapnil Hiremath | University of Ottawa (Canada) | Hecht Foundation (research grant support [to institution, no personal payment])* | NephJC (NephJC is a nonprofit educational organization. I serve on the Board of Directors [volunteer position, no payments].)* | None | None | None | None | None |
| Michelle C. Johansen | Johns Hopkins University | NINDS (K23, R21)† | None | None | None | None | None | None |
| Rizwan Kalani | University of Washington | None | None | None | None | None | None | None |

(*Continued*)

**Writing Group Disclosures Continued**

| Writing group member | Employment | Research grant | Other research support | Speakers' bureau/ honoraria | Expert witness | Ownership interest | Consultant/ advisory board | Other |
|---|---|---|---|---|---|---|---|---|
| Dhruv S. Kazi | Beth Israel Deaconess Medical Center, Harvard Medical School | None | None | None | None | None | None | None |
| Darae Ko | Boston University | Boston Scientific Corp (investigator sponsored research grant to Boston Medical Center)† | None | None | None | None | None | None |
| Junxiu Liu | Icahn School of Medicine at Mount Sinai | None | None | None | None | None | None | None |
| Jared W. Magnani | University of Pittsburgh | None | None | None | None | None | None | None |
| Erin D. Michos | Johns Hopkins University | Merck (was a co-investigator on a 1-year grant that ended July 2023, paid to my institution)* | None | None | None | None | Amarin*; Amgen*; Esperion†; Edwards Lifescience*; Novartis*; Novo Nordisk†; Boehringer Ingelheim†; Medtronic*; Pfizer* | None |
| Michael E. Mussolino | NIH National Heart, Lung, and Blood Institute | None | None | None | None | None | None | None |
| Sankar D. Navaneethan | Baylor College of Medicine Jewish Institute for Research | None | None | None | None | None | ACI Clinical†; Bayer†; BI-Eli Lilly†; AstraZeneca*; Intercept Pharma†; GlaxoSmithKline†; Vertex* | None |
| Nisha I. Parikh | University of California, San Francisco | None | None | None | None | None | Mirvie* | None |
| Sarah M. Perman | University of Colorado | None | None | None | None | None | None | None |
| Remy Poudel | American Heart Association | None | None | None | None | None | None | None |
| Mary Rezk-Hanna | University of California, Los Angeles | National Heart, Lung, and Blood Institute (grant 1R01HL152435-01A1)† | None | None | None | None | None | None |
| Gregory A. Roth | University of Washington | Bill and Melinda Gates Foundation* | None | None | None | None | None | None |
| Nilay S. Shah | Northwestern University | National Heart, Lung, and Blood Institute (research grant [K23HL157766])† | None | None | None | None | None | None |
| Marie-Pierre St-Onge | Columbia University Irving Medical Center | None | None | None | None | None | None | None |
| Evan L. Thacker | Brigham Young University | NIA/NIH (multi-PI on funded grant that provides salary support)† | None | None | None | None | None | None |
| Connie W. Tsao | Beth Israel Deaconess Medical Center | NIH† | None | None | Smith Haughey Rice & Roegge† | None | None | None |

(*Continued*)

**Writing Group Disclosures Continued**

| Writing group member | Employment | Research grant | Other research support | Speakers' bureau/ honoraria | Expert witness | Ownership interest | Consultant/ advisory board | Other |
|---|---|---|---|---|---|---|---|---|
| Sarah M. Urbut | Massachusetts General Hospital | None | None | None | None | None | None | None |
| Harriette G.C. Van Spall | McMaster University | Canadian Institutes of Health Research†; Heart and Stroke† | None | None | None | None | None | None |
| Jenifer H. Voeks | Medical University of South Carolina | None | None | None | None | None | None | None |
| Nae-Yuh Wang | The Johns Hopkins Medical Institutions | NIH (multiple grants to my institution)†; NIH (multiple grants to immediate family member's institution)†; Maryland Department of Health (grants to my institution)†; Maryland Department of Health (grants to immediate family member's institution)† | None | None | None | None | None | None |
| Nathan D. Wong | Heart Disease Prevention Program; University of California, Irvine | Novartis (institution)†; Novo Nordisk (institution)†; Lilly (institution)†; Regeneron (institution)† | None | None | None | None | Novartis*; Ionis*; Kaneka* | None |
| Sally S. Wong | American Heart Association | None | None | None | None | None | None | None |
| Kristine Yaffe | University of California, San Francisco | None | None | None | None | None | Eli Lilly*; Alector† | None |

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $5000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $5000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

## REFERENCES


1. Olesen R. Heart disease: a brief review of the etiology and incidence, and possibilities of preventing the disease, especially the rheumatic type. *Public Health Rep (1896-1970)*. 1934;49:497–508.
2. American Heart Association. History of the American Heart Association. Accessed October 10, 2023. https://heart.org/-/media/Files/About-Us/History/History-of-the-American-Heart-Association.pdf
3. Centers for Disease Control and Prevention. Achievements in public health, 1900-1999: decline in deaths from heart disease and stroke–United States, 1900-1999. *MMWR*. 1999;48:649–656.
4. Martin SS, Aday AW, Almarzooq ZI, Anderson CAM, Arora P, Avery CL, Baker-Smith CM, Barone Gibbs B, Beaton AZ, Boehme AK, et al; on behalf of the American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. 2024 Heart disease and stroke statistics: a report of US and global data from the American Heart Association. *Circulation*. 2024;149:e347–e913. doi: 10.1161/CIR.0000000000001209
5. Laforgia PL, Auguadro C, Bronzato S, Durante A. The reduction of mortality in acute myocardial infarction: from bed rest to future directions. *Int J Prev Med*. 2022;13:56. doi: 10.4103/ijpvm.IJPVM_122_20
6. Lackland DT, Roccella EJ, Deutsch AF, Fornage M, George MG, Howard G, Kissela BM, Kittner SJ, Lichtman JH, Lisabeth LD, et al; on behalf of the American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Quality of Care and Outcomes Research; Council on Functional Genomics and Translational Biology. Factors influencing the decline in stroke mortality: a statement from the American Heart Association/American Stroke Association. *Stroke*. 2014;45:315–353. doi: 10.1161/01.str.0000437068.30550.cf
7. Cummings KM, Proctor RN. The changing public image of smoking in the United States: 1964-2014. *Cancer Epidemiol Biomarkers Prev*. 2014;23:32–36. doi: 10.1158/1055-9965.EPI-13-0798
8. Schiller JS, Norris T. Early release of selected estimates from the 2022 National Health Interview Survey. Division of Health Interview Statistics, National Center for Health Statistics, Centers for Disease Control and Prevention. Accessed October 10, 2023. https://cdc.gov/nchs/data/nhis/earlyrelease/earlyrelease202304.pdf
9. Academy of Achievement. America's Renaissance woman. January 22, 1997. Accessed October 10, 2023. https://achievement.org/achiever/maya-angelou/#interview
10. Lloyd-Jones DM, Allen NB, Anderson CAM, Black T, Brewer LC, Foraker RE, Grandner MA, Lavretsky H, Perak AM, Sharma G, et al; on behalf of the American Heart Association. Life's essential 8: updating and enhancing the American Heart Association's construct of cardiovascular health: a presidential advisory from the American Heart Association. *Circulation*. 2022;146:e18–e43. doi: 10.1161/CIR.0000000000001078

## ABBREVIATIONS TABLE

Click here to return to the Table of Contents

| | |
|---|---|
| 4D | Die Deutsche Diabetes Dialyze Studie |
| AAA | abdominal aortic aneurysm |
| AAMR | age-adjusted mortality rate |
| ABC-ACS | Age, Biomarkers, Clinical History, Acute Coronary Syndrome Score |
| ABI | ankle-brachial index |
| ACC | American College of Cardiology |
| ACCORD | Action to Control Cardiovascular Risk in Diabetes |
| ACE | angiotensin-converting enzyme |
| ACR | albumin-to-creatinine ratio |
| ACS | acute coronary syndrome |
| ACTION | Acute Coronary Treatment and Intervention Outcomes Network |
| AD | Alzheimer disease |
| ADAMS | Aging, Demographics, and Memory Study |
| ADRD | Alzheimer disease and related dementia |
| ADVANCE | Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation |
| AF | atrial fibrillation or atriofibrillation |
| AFFINITY | Assessment of Fluoxetine in Stroke Recovery |
| AGES | Age, Gene/Environment Susceptibility |
| AHA | American Heart Association |
| AHEI | Alternative Health Eating Index |
| AHI | apnea-hypopnea index |
| aHR | adjusted hazard ratio |
| AHS-2 | Adventist Health Study 2 |
| AIM-HIGH | Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes |
| aIRR | adjusted incidence rate ratio |
| AIS | acute ischemic stroke |
| ALLHAT | Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial |
| AMI | acute myocardial infarction |
| ANP | atrial natriuretic peptide |
| aOR | adjusted odds ratio |
| AP | angina pectoris |
| APACE | Advantageous Predictors of Acute Coronary Syndromes Evaluation |
| APO | adverse pregnancy outcome |
| app | application |
| ARB | angiotensin receptor blocker |
| ARGEN-IAM-ST | Pilot Study on ST Elevation Acute Myocardial Infarction |
| ARIC | Atherosclerosis Risk in Communities |
| ARIC-NCS | Atherosclerosis Risk in Communities–Neurocognitive Study |
| ARIC-PET | Atherosclerosis Risk in Communities–Positron Emission Tomography |
| aRR | adjusted relative risk |
| ARVC | arrhythmogenic right ventricular cardiomyopathy |
| ASB | artificially sweetened beverage |
| ASCOD | atherosclerosis, small vessel disease, cardiac pathology, other causes, dissection |
| ASCVD | atherosclerotic cardiovascular disease |
| ASCVD-PCE | Atherosclerotic Cardiovascular Disease Pooled Cohort Equation |
| ASD | atrial septal defect |
| ASPECTS | Alberta Stroke Program Early CT Score |
| ASPIRE | Assessing the Spectrum of Pulmonary Hypertension Identified at a Referral Centre Registry |
| ASPREE | Aspirin in Reducing Events in the Elderly |
| ATP III | Adult Treatment Panel III |
| AUC | area under the curve |
| AVAIL | Adherence Evaluation After Ischemic Stroke Longitudinal |
| AVATAR | Aortic Valve Replacement Versus Conservative Treatment in Asymptomatic Severe Aortic Stenosis |
| AWHS | Aragon Workers Health Study |
| BASIC | Brain Attack Surveillance in Corpus Christi |
| BEST | Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients With Multivessel Coronary Artery Disease |
| BEST-CLI | Best Surgical Therapy in Patients With Chronic Limb-Threatening Ischemia |
| BiomarCaRE | Biomarker for Cardiovascular Risk Assessment in Europe |
| BioSHaRe | Biobank Standardization and Harmonization for Research Excellence in the European Union |
| BMI | body mass index |
| BNP | B-type natriuretic peptide |
| BP | blood pressure |
| BRAVO | Building, Relating, Assessing, and Validating Outcomes |
| BRFSS | Behavioral Risk Factor Surveillance System |
| BWHS | Black Women's Health Study |
| CABANA | Catheter Ablation vs Antiarrhythmic Drug Therapy for Atrial Fibrillation |
| CABG | coronary artery bypass graft |
| CAC | coronary artery calcification |
| CAD | coronary artery disease |
| CAIDE | Cardiovascular Risk Factors, Aging and Dementia |
| CALIBER UK | Cardiovascular Research Using Linked Bespoke Studies and Electronic Health Records |
| CANHEART | Cardiovascular Health in Ambulatory Care Research Team |
| CARDIA | Coronary Artery Risk Development in Young Adults |
| CARDIo-GRAM | Coronary Artery Disease Genome-Wide Replication and Meta-Analysis |
| CARDIOo-GRAM-plusC4D | Coronary Artery Disease Genome-Wide Replication and Meta-Analysis Plus the Coronary Artery Disease (C4D) |
| CARES | Cardiac Arrest Registry to Enhance Survival |
| CAS | carotid artery stenting |
| CASCADE FH | Cascade Screening for Awareness and Detection of Familial Hypercholesterolemia |
| CASI | Cognitive Abilities Screening Instrument |
| CASQ2 | calsequestrin 2 |
| CAVIAAR | Conservation Aortique Valvulaire dans les Insuffisances Aortiques et les Anévrismes de la Racine aortique |
| CCD | congenital cardiovascular defect |
| CCTA | coronary computed tomography angiography |

| | |
|---|---|
| CDC | Centers for Disease Control and Prevention |
| CDC WONDER | Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research |
| CEA | carotid endarterectomy |
| CERAD-TS | Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Battery, Total Score |
| CGPS | Copenhagen General Population Study |
| $CHA_2DS_2$-VASc | clinical prediction rule for estimating the risk of stroke based on congestive heart failure, hypertension, diabetes, and sex (1 point each); age ≥75 years and stroke/transient ischemic attack/thromboembolism (2 points each); plus history of vascular disease, age 65 to 74 years, and (female) sex category |
| CHAMP-HF | Change the Management of Patients With Heart Failure |
| CHAP | Chicago Health and Aging Project |
| CHARGE-AF | Cohorts for Heart and Aging Research in Genomic Epidemiology–Atrial Fibrillation |
| CHARLS | China Health and Retirement Longitudinal Study |
| CHARM | Candesartan in Heart Failure–Assessment of Reduction in Mortality and Morbidity |
| CHD | coronary heart disease |
| CHS | Cardiovascular Health Study |
| CI | confidence interval |
| CICAT | Codi Ictus Catalunya Registry |
| CKD | chronic kidney disease |
| CKiD | Chronic Kidney Disease in Children |
| CLARIFY | Community Benefit of No-Charge Calcium Score Screening Program |
| CLEAR | Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen |
| CLTI | chronic limb-threatening ischemia |
| CNSR | China National Stroke Registries |
| COAPT | Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation |
| COAST | Comparative Outcomes Services Utilization Trends |
| COMPASS | Cardiovascular Outcomes for People Using Anticoagulation Strategies |
| CONFIRM | Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry |
| CORAL | Cardiovascular Outcomes in Renal Atherosclerotic Lesions |
| CORE-Thailand | Cohort of Patients With High Risk for Cardiovascular Events–Thailand |
| COSMIC | Cohort Studies of Memory in an International Consortium |
| COVID-19 | coronavirus disease 2019 |
| CPAP | continuous positive airway pressure |
| CPR | cardiopulmonary resuscitation |
| CPVT | catecholaminergic polymorphic ventricular tachycardia |
| CREOLE | Comparison of Three Combination Therapies in Lowering Blood Pressure in Black Africans |
| CRIC | Chronic Renal Insufficiency Cohort |
| CRP | C-reactive protein |
| CSA | community-supported agriculture |
| CSC | comprehensive stroke center |
| CT | computed tomography |
| CTEPH | chronic thromboembolic pulmonary hypertension |
| CVD | cardiovascular disease |
| CVD PREDICT | Cardiovascular Disease Policy Model for Risk, Events, Detection, Interventions, Costs, and Trends |
| CVH | cardiovascular health |
| CVI | chronic venous insufficiency |
| DALY | disability-adjusted life-year |
| DANISH | Danish Study to Assess the Efficacy of ICDs in Patients With Non-Ischaemic Systolic Heart Failure on Mortality |
| DASH | Dietary Approaches to Stop Hypertension |
| DBP | diastolic blood pressure |
| DCCT/EDIC | Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications |
| DCM | dilated cardiomyopathy |
| DEBATS | Discussion on the Health Effect of Aircraft Noise Study |
| DHA | docosahexaenoic acid |
| DIAMANTE | Diabetes Meta-Analysis of Trans-Ethnic Association Studies |
| DII | Dietary Inflammatory Index |
| DNA | deoxyribonucleic acid |
| DOAC | direct oral anticoagulant |
| DPP | Diabetes Prevention Program |
| DREAM-LDL | Diabetes (Fasting Blood Glucose Level), Rating (National Institutes of Health Stroke Scale), Level of Education, Age, Baseline Montreal Cognitive Assessment Scale Score, and LDL-C Level |
| DR's EXTRA | Dose Responses to Exercise Training |
| DVT | deep vein thrombosis |
| EAGLES | Study Evaluating the Safety and Efficacy of Varenicline and Bupropion for Smoking Cessation in Subjects With and Without a History of Psychiatric Disorders |
| e-cigarette | electronic cigarette |
| ECG | electrocardiogram |
| ED | emergency department |
| EDIC | Epidemiology of Diabetes Interventions and Complications |
| EF | ejection fraction |
| eGFR | estimated glomerular filtration rate |
| ELSA | English Longitudinal Study of Ageing |
| EMS | emergency medical services |
| EPA | eicosapentaenoic acid |
| EPIC | European Prospective Investigation Into Cancer and Nutrition |
| ERICA | Study of Cardiovascular Risks in Adolescents |
| ERP | early repolarization pattern |
| ESRD | end-stage renal disease |
| EUCLID | Examining Use of Ticagrelor in PAD |
| EVEREST | Endovascular Valve Edge-to-Edge Repair |
| EVEREST II HRS | Endovascular Valve Edge-to-Edge Repair High-Risk Study |
| EVITA | Effect of Vitamin D on Mortality in Heart Failure |
| EVITA | Evaluation of Varenicline in Smoking Cessation for Patients Post-Acute Coronary Syndrome |
| EXAMINE | Examination of Cardiovascular Outcomes With Alogliptin Versus Standard of Care |
| FAMILIA | Family-Based Approach in a Minority Community Integrating Systems–Biology for Promotion of Health |
| FDA | US Food and Drug Administration |
| FH | familial hypercholesterolemia |

| | |
|---|---|
| FHS | Framingham Heart Study |
| FIDELIO-DKD | Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease |
| FINGER | Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability |
| FinnDiane | Finnish Diabetic Nephropathy |
| FINRISK | Finnish Population Survey on Risk Factors for Chronic, Noncommunicable Diseases |
| FMD | flow-mediated dilation |
| FOURIER | Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk |
| FPG | fasting plasma glucose |
| FPL | federal poverty level |
| FRS | Framingham Risk Score |
| FVL | factor V Leiden |
| GARFIELD-VTE | Global Anticoagulant Registry in the Field–Venous Thromboembolism |
| GBD | Global Burden of Disease |
| GCNKSS | Greater Cincinnati/Northern Kentucky Stroke Study |
| GISSI-3 | Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico |
| GLORIA-AF | Global Registry on Long-Term Oral Antithrombotic Treatment in Patients With Atrial Fibrillation |
| GLP1-RA | glucagon-like peptide 1 receptor agonist |
| GRS | genetic risk score |
| GWAS | genome-wide association studies |
| GWTG | Get With The Guidelines |
| GWTG-AFIB | Get With The Guidelines–Atrial Fibrillation |
| HANDLS | Health Aging in Neighborhoods of Diversity Across the Life Span |
| HAPIEE | Health, Alcohol and Psychosocial Factors in Eastern Europe |
| HAPO | Hyperglycemia and Adverse Pregnancy Outcome |
| $HARMS_2$-AF | Hypertension, Age, Raised Body Mass Index, Male Sex, Sleep Apnea, Smoking, Alcohol |
| HbA1c | hemoglobin A1c (glycosylated total cholesterol) |
| HBP | high blood pressure |
| HCHS/SOL | Hispanic Community Health Study/Study of Latinos |
| HCM | hypertrophic cardiomyopathy |
| HCUP | Healthcare Cost and Utilization Project |
| HD | heart disease |
| HDL | high-density lipoprotein |
| HDL-C | high-density lipoprotein cholesterol |
| HDP | hypertensive disorders of pregnancy |
| HeartScore | Heart Strategies Concentrating on Risk Evaluation |
| HEI | Healthy Eating Index |
| HELENA | Healthy Lifestyle in Europe by Nutrition in Adolescence |
| HF | heart failure |
| HF-ACTION | Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training |
| HFpEF | heart failure with preserved ejection fraction |
| HFrEF | heart failure with reduced ejection fraction |
| High-STEACS | High-Sensitivity Troponin in the Evaluation of Patients With Suspected Acute Coronary Syndrome |
| HIV | human immunodeficiency virus |
| HLHS | hypoplastic left-heart syndrome |
| HPFS | Health Professionals Follow-Up Study |
| HPPCA | Health Promotion Program for Children and Adolescents |
| HPS | Heart Protection Study |
| HR | hazard ratio |
| HRRP | Hospital Readmissions Reduction Program |
| HRS | Health and Retirement Study |
| HYVET | Hypertension in the Very Elderly Trial |
| ICD | implantable cardioverter defibrillator |
| *ICD* | *International Classification of Diseases* |
| *ICD-9* | *International Classification of Diseases, 9th Revision* |
| *ICD-9-CM* | *International Classification of Diseases, 9th Revision, Clinical Modification* |
| *ICD-10* | *International Classification of Diseases, 10th Revision* |
| *ICD-10-CM* | *International Classification of Diseases, 10th Revision, Clinical Modification* |
| ICE-PLUS | International Collaboration on Endocarditis–PLUS |
| ICH | intracerebral hemorrhage |
| ICU | intensive care unit |
| IDF | International Diabetes Federation |
| IE | infective endocarditis |
| IE After TAVI | Infective Endocarditis After Transcatheter Aortic Valve Implantation |
| IHCA | in-hospital cardiac arrest |
| IHD | ischemic heart disease |
| IHM | interstage home monitoring program |
| ILCOR | International Liaison Committee on Resuscitation |
| IMPACT | International Model for Policy Analysis of Agricultural Commodities and Trade |
| IMPROVE | Carotid Intima–Media Thickness (IMT) and IMT Progression as Predictors of Vascular Events in a High-Risk European Population |
| IMPROVE-IT | Improved Reduction of Outcomes: Vytorin Efficacy International Trial |
| IMT | intima-media thickness |
| INTER-MACS | Interagency Registry for Mechanically Assisted Circulatory Support |
| IPSS | International Pediatric Stroke Study |
| IQR | interquartile range |
| IRAD | International Registry of Acute Aortic Dissection |
| IRR | incidence rate ratio |
| ISCHEMIA | International Study of Comparative Health Effectiveness With Medical and Invasive Approaches |
| IVIG | intravenous immunoglobulin |
| JHS | Jackson Heart Study |
| KD | Kawasaki disease |
| LASI | Longitudinal Aging Study in India |
| LBW | low birth weight |
| LDL | low-density lipoprotein |
| LDL-C | low-density lipoprotein cholesterol |
| LEAD | Louisiana Experiment Assessing Diabetes |
| LEADER | Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results |
| LIBRA | Lifestyle for Brain Health |
| LOAD | late-onset Alzheimer disease |
| Look AHEAD | Look: Action for Health in Diabetes |

| | |
|---|---|
| LOOP | Implantable Loop Recorder Detection of Atrial Fibrillation to Prevent Stroke |
| LQTS | long QT syndrome |
| LTPA | leisure-time physical activity |
| LV | left ventricular |
| LVAD | left ventricular assist device |
| LVEF | left ventricular ejection fraction |
| LVH | left ventricular hypertrophy |
| MACE | major adverse cardiovascular event |
| MAP | Memory and Aging Project |
| MAPT | Multidomain Alzheimer Preventive Trial |
| MARS | Minority Aging Research Study |
| MCI | mild cognitive impairment |
| MDCS | Malmö Diet and Cancer Study |
| MEPS | Medical Expenditure Panel Survey |
| MESA | Multi-Ethnic Study of Atherosclerosis |
| MET | metabolic equivalent |
| MetS | metabolic syndrome |
| MHAS | Mexican Health and Aging Study |
| MHO | metabolically healthy obesity |
| MI | myocardial infarction |
| MIDA | Mitral Regurgitation International Database |
| MIDUS | Midlife in the United States |
| MIMS | Monitor Independent Movement Summary |
| MIND-China | Multimodal Interventions to Delay Dementia and Disability in Rural China |
| MIS-C | multisystem inflammatory syndrome in children |
| MITRA-FR | Percutaneous Repair With the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation |
| MMSE | Mini-Mental State Examination |
| MONICA | Monitoring Trends and Determinants of Cardiovascular Disease |
| MR | mitral regurgitation |
| MRI | magnetic resonance imaging |
| MTF | Monitoring the Future |
| MUSIC | Muerte Súbita en Insuficiencia Cardiaca |
| MVP | Million Veterans Program |
| MVPA | moderate to vigorous physical activity |
| NACC | National Alzheimer's Dementia Coordinating Center |
| NAFLD | nonalcoholic fatty liver disease |
| NAMCS | National Ambulatory Medical Care Survey |
| NCDR | National Cardiovascular Data Registry |
| NCHS | National Center for Health Statistics |
| NH | non-Hispanic |
| NHAMCS | National Hospital Ambulatory Medical Care Survey |
| NHANES | National Health and Nutrition Examination Survey |
| NHATS | National Health and Aging Trends Study |
| NHDS | National Hospital Discharge Survey |
| NHIS | National Health Interview Survey |
| NHLBI | National Heart, Lung, and Blood Institute |
| NIH | National Institutes of Health |
| NIH-AARP | National Institutes of Health–American Association of Retired Persons |
| NIHSS | National Institutes of Health Stroke Scale |
| NINDS | National Institutes of Neurological Disorders and Stroke |
| NIPPON DATA | National Integrated Project for Prospective Observation of Noncommunicable Disease and Its Trends in Aged |
| NIS | National (Nationwide) Inpatient Sample |
| NNT5 | number needed to treat for 5 years |
| NOMAS | Northern Manhattan Study |
| NOTION | Nordic Aortic Valve Intervention |
| NSDUH | National Survey on Drug Use and Health |
| NSHDS | Northern Sweden Health and Disease Study |
| NSTEMI | non–ST-segment–elevation myocardial infarction |
| NT-proBNP | N-terminal pro-B-type natriuretic peptide |
| nuMoM2b | Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-be |
| NVSS | National Vital Statistics System |
| NYTS | National Youth Tobacco Survey |
| ODYSSEY Outcomes | Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab |
| OHCA | out-of-hospital cardiac arrest |
| ONTARGET | Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial and to Telmisartan Randomized Assessment |
| OR | odds ratio |
| ORBIT-AF | Outcomes Registry for Better Informed Treatment of Atrial Fibrillation |
| ORION-9 | Trial to Evaluate the Effect of Inclisiran Treatment on Low-Density Lipoprotein Cholesterol (LDL-C) in Subjects With Heterozygous Familial Hypercholesterolemia (HeFH) |
| ORION-10 | Inclisiran for Participants With Atherosclerotic Cardiovascular Disease and Elevated Low-Density Lipoprotein Cholesterol |
| ORION-11 | Inclisiran for Subjects With ASCVD or ASCVD-Risk Equivalents and Elevated Low-Density Lipoprotein Cholesterol |
| OSA | obstructive sleep apnea |
| OVER | Open Versus Endovascular Repair |
| PA | physical activity |
| PAD | peripheral artery disease |
| PAF | population attributable fraction |
| PAGE | Placental Abruption Genetic Epidemiology |
| PAH | pulmonary arterial hypertension |
| PAPE | Peruvian Abruptio Placentae Epidemiology |
| PAR | population attributable risk |
| PARADIGM | Progression of Atherosclerotic Plaque Determined by Computed Tomographic Angiography Imaging |
| PARTNER | Placement of Aortic Transcatheter Valve |
| PATH | Population Assessment of Tobacco and Health |
| PCAIS | posterior circulation arterial ischemic stroke |
| PCE | Pooled Cohort Equations |
| PCI | percutaneous coronary intervention |
| PCSK9 | proprotein convertase subtilisin/kexin type 9 |
| PD | Parkinson disease |
| PE | pulmonary embolism |
| PESA | Progression of Early Subclinical Atherosclerosis |
| PH | pulmonary hypertension |

| | |
|---|---|
| PHIRST | Pulmonary Arterial Hypertension and Response to Tadalafil Study |
| PINNACLE | Practice Innovation and Clinical Excellence |
| PLATO | A Comparison of Ticagrelor [AZD6140] and Clopidogrel in Patients With Acute Coronary Syndrome |
| PM2.5 | fine particulate matter <2.5-μm diameter |
| POINT | Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke |
| PORTRAIT | Patient-Centered Outcomes Related to Treatment Practices in Peripheral Arterial Disease: Investigating Trajectories |
| PPCM | peripartum cardiomyopathy |
| PPSW | Prospective Population Study of Women in Gothenburg |
| PR | prevalence ratio |
| PRECOM-BAT | Premier of Randomized Comparison of Bypass Surgery Versus Angioplasty Using Sirolimus Stents in Patients With Left Main Coronary Artery Disease |
| PREDIMED | Prevención con Dieta Mediterránea |
| PreDIVA | Prevention of Dementia by Intensive Vascular Care |
| PREMA | Prediction of Metabolic Syndrome in Adolescence |
| PREMIER | Lifestyle Interventions for Blood Pressure Control |
| PREVEND | Prevention of Renal and Vascular End-Stage Disease |
| ProDiGY | Progress in Diabetes Genetics in Youth |
| PROFESS | Prevention Regimen for Effectively Avoiding Second Stroke |
| PROG-RESS | Perindopril Protection Against Recurrent Stroke Study |
| PROMI-NENT | Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients With Diabetes |
| PROTECT-ED TAVR | Stroke Protection With Sentinel During Transcatheter Aortic Valve Replacement |
| PRS | polygenic risk score |
| PTB | preterm birth |
| $P_{trend}$ | *P* for trend |
| PTS | postthrombotic syndrome |
| PUFA | polyunsaturated fatty acid |
| PURE | Prospective Urban Rural Epidemiology |
| PWV | pulse-wave velocity |
| QALY | quality-adjusted life-year |
| QTc | corrected QT interval |
| RACECAT | Transfer to the Closest Local Stroke Center vs Direct Transfer to Endovascular Stroke Center of Acute Stroke Patients With Suspected Large Vessel Occlusion in the Catalan Territory |
| RCT | randomized controlled trial |
| REDINS-COR | Red Española de Insuficiencia Cardiaca |
| REGARDS | Reasons for Geographic and Racial Differences in Stroke |
| REMEDY | Global Rheumatic Heart Disease Registry |
| RENIS-T6 | Renal Iohexol Clearance Survey in Tromsø 6 |
| REPLACE | Riociguat Replacing PDE5i Therapy Evaluated Against Continued PDE5i Therapy |
| REVEAL | Registry to Evaluate Early and Long-Term PAH Disease Management |
| RE-SPECT ESUS | Randomized, Double-Blind, Evaluation in Secondary Stroke Prevention Comparing the Efficacy and Safety of the Oral Thrombin Inhibitor Dabigatran Etexilate Versus Acetylsalicylic Acid in Patients With Embolic Stroke of Undetermined Source |
| RR | relative risk |
| RV | right ventricular |
| RYR2 | ryanodine receptor 2 |
| S.AGES | Sujets AGÉS–Aged Subjects |
| SADHS | South African Demographic Health and Surveillance Study |
| SAFE-HEART | Spanish Familial Hypercholesterolemia Cohort Study |
| SAGE | Study on Global Ageing and Adult Health |
| SAH | subarachnoid hemorrhage |
| SARS-CoV-2 | severe acute respiratory syndrome coronavirus disease 2 |
| SAVE | Sleep Apnea Cardiovascular Endpoints |
| SAVR | surgical aortic valve replacement |
| SBP | systolic blood pressure |
| SC | subcutaneous |
| SCA | sudden cardiac arrest |
| SCD | sudden cardiac death |
| SCORE | Systematic Coronary Risk Evaluation |
| SD | standard deviation |
| SDB | sleep disordered breathing |
| SDI | sociodemographic index |
| SE | standard error |
| SEARCH | Search for Diabetes in Youth |
| SEMI-COVID-19 | Sociedad Española de Medicina Interna Coronavirus Disease 2019 |
| SES | socioeconomic status |
| SFA | saturated fatty acid |
| SGA | small for gestational age |
| SGLT-2 | sodium-glucose cotransporter 2 |
| SHEP | Systolic Hypertension in the Elderly Program |
| SHIP | Study of Health in Pomerania |
| SHIP AHOY | Study of Hypertension in Pediatrics, Adult Hypertension Onset in Youth |
| SHS | Strong Heart Study |
| SILVER-AMI | Comprehensive Evaluation of Risk Factors in Older Patients With Acute Myocardial Infarction |
| SMD | standard mean difference |
| SNAC-K | Swedish National Study on Aging and Care in Kungsholmen |
| SND | sinus node dysfunction |
| SNP | single-nucleotide polymorphism |
| SpecTRA | Spectrometry for Transient Ischemic Attack Rapid Assessment |
| SPRINT | Systolic Blood Pressure Intervention Trial |
| SSB | sugar-sweetened beverage |
| START | South Asian Birth Cohort |
| STEMI | ST-segment–elevation myocardial infarction |
| STEP 1 | Research Study Investigating How Well Semaglutide Works in People Suffering From Overweight or Obesity |
| STEP 3 | Research Study to Look at How Well Semaglutide Is at Lowering Weight When Taken Together With an Intensive Lifestyle Program |
| STOP-COVID | Study of the Treatment and Outcomes in Critically Ill Patients With COVID-19 |
| STROKE-AF | Rate of Atrial Fibrillation Through 12 Months in Patients With Recent Ischemic Stroke of Presumed Known Origin |

| | |
|---|---|
| STS | Society of Thoracic Surgeons |
| SUN | Seguimiento Universidad de Navarra |
| SURMOUNT-1 | Efficacy and Safety of Tirzepatide Once Weekly Versus Placebo in Participants Who Are Either Obese or Overweight With Weight-Related Comorbidities |
| SURTAVI | Surgical Replacement and Transcatheter Aortic Valve Implantation |
| SVT | supraventricular tachycardia |
| SWAN | Study of Women's Health Across the Nation |
| Swiss TAVI | Swiss Transcatheter Aortic Valve Implantation |
| SYNTAX | Synergy Between PCI With Taxus and Cardiac Surgery |
| SYST-EUR | Systolic Hypertension in Europe trial |
| TAA | thoracic aortic aneurysm |
| TAVI | transcatheter aortic valve implantation |
| TAVR | transcatheter aortic valve replacement |
| TC | total cholesterol |
| TdP | torsade de pointes |
| TECOS | Trial Evaluating Cardiovascular Outcomes With Sitagliptin |
| TEER | transcatheter-edge-to-edge repair |
| TGA | transposition of the great arteries |
| TGF | transforming growth factor |
| TIA | transient ischemic attack |
| TICS | Telephone Interview for Cognitive Status |
| TOAST | Trial of ORG 10172 in Acute Stroke Treatment |
| TODAY | Treatment Options for Type 2 Diabetes in Adolescents and Youth |
| TOF | tetralogy of Fallot |
| TOHP | Trials of Hypertension Prevention |
| T1D Exchange Clinic Registry | Type 1 Diabetes Exchange Clinic Registry |
| TOPCAT | Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist |
| TOPMed | Trans-Omics for Precision Medicine |
| tPA | tissue-type plasminogen activator |
| TRIUMPH | Treprostinil Sodium Inhalation Used in the Management of Pulmonary Arterial Hypertension |
| TVT | transcatheter valve therapy |
| UDS | Uniform Data Set |
| UI | uncertainty interval |
| UK | United Kingdom |
| UNICEF | United Nations Children's Fund |
| USRDS | US Renal Data System |
| VF | ventricular fibrillation |
| VITAL | Vitamin D and Omega-3 Trial |
| VITAL-HF | Vitamin D and Omega-3 Trial–Heart Failure |
| Vmax | aortic valve peak jet velocity |
| VOYAGER | Efficacy and Safety of Rivaroxaban in Reducing the Risk of Major Thrombotic Vascular Events in Subjects With Symptomatic Peripheral Artery Disease Undergoing Peripheral Revascularization Procedures of the Lower Extremities |
| VSD | ventricular septal defect |
| VT | ventricular tachycardia |
| VTE | venous thromboembolism |
| WC | waist circumference |
| WHI | Women's Health Initiative |
| WHICAP | Washington Heights-Hamilton Heights-Inwood Community Aging Project |
| WHO | World Health Organization |
| WHS | Women's Health Study |
| WIC | Special Supplemental Nutrition Program for Women, Infants, and Children |
| WMD | weighted mean difference |
| WMH | white matter hyperintensity |
| WPW | Wolff-Parkinson-White |
| YLD | years of life lived with disability or injury |
| YLL | years of life lost to premature mortality |
| Young ESUS | Young Embolic Stroke of Undetermined Source |
| YRBS | Youth Risk Behavior Survey |

# 1. ABOUT THESE STATISTICS

Click here to return to the Table of Contents

Click here to return to the Abbreviations

The AHA works with the NHLBI of the NIH to derive the annual statistics in the AHA Statistical Update. This chapter describes the most important sources and the types of data used from them. For more details, see Chapter 30 of this document, the Glossary.

The surveys and data sources used are the following:

- ACC NCDR's Chest Pain–MI Registry (formerly the ACTION Registry)—quality information for AMI
- ARIC—CHD and HF incidence rates
- BRFSS—ongoing telephone health survey system
- GBD—global disease prevalence, mortality, and healthy life expectancy
- GCNKSS—stroke incidence rates and outcomes within a biracial population
- GWTG—quality information for resuscitation, HF, and stroke
- HCUP—hospital inpatient discharges and procedures
- MEPS—data on specific health services that Americans use, how frequently they use them, the cost of these services, and how the costs are paid
- NAMCS—physician office visits
- NHAMCS—hospital outpatient and ED visits
- NHANES—disease and risk factor prevalence and nutrition statistics
- NHIS—disease and risk factor prevalence
- NVSS—mortality for the United States
- USRDS—kidney disease prevalence
- WHO—mortality rates by country
- YRBS—health-risk behaviors in youth and young adults

## Disease Prevalence

Prevalence is an estimate of how many people have a condition at a given point or period in time. The CDC/NCHS conducts health examination and health interview surveys that provide estimates of the prevalence of diseases and risk factors. In this Statistical Update, the health interview part of the NHANES is used for the prevalence of CVDs. NHANES is used more than the NHIS because in NHANES AP is based on the Rose Questionnaire; estimates are made regularly for HF; hypertension is based on BP measurements and interviews; and an estimate can be made for total CVD, including MI, AP, HF, stroke, and hypertension.

A major emphasis of the 2024 Statistical Update is to present the latest estimates of the number of people in the United States and globally who have specific conditions to provide a realistic estimate of burden. Most estimates based on NHANES prevalence rates are based on data collected from 2017 to 2020. These are applied to census population estimates for 2020. Differences in population estimates cannot be used to evaluate possible trends in prevalence because these estimates are based on extrapolations of rates beyond the data collection period by use of more recent census population estimates. Trends can be evaluated only by comparing prevalence rates estimated from surveys conducted in different years.

In the 2024 Statistical Update, there is an emphasis on health equity across the various chapters, and global estimates are provided when available.

## Risk Factor Prevalence

The NHANES 2017 to 2020 data are used in this Statistical Update to present estimates of the percentage of people with high LDL-C, high TC, elevated triglycerides, low HDL-C, hypertension, overweight, obesity, and diabetes. BRFSS 2020 and NHIS 2020 data are used for the prevalence of sleep issues. The NHIS 2021 data, BRFSS 2021, and NYTS 2022 are used for the prevalence of cigarette smoking. The prevalence of PA is obtained from YRBS 2021 and NHIS 2020.

## Incidence and Recurrent Attacks

An incidence rate refers to the number of new cases of a disease that develop in a population per unit of time. The unit of time for incidence is not necessarily 1 year, although incidence is often discussed in terms of 1 year. For some statistics, new and recurrent attacks or cases are combined. Our national incidence estimates for the various types of CVD are extrapolations to the US population from the FHS, the ARIC study, and the CHS, all conducted by the NHLBI, as well as the GCNKSS, which is funded by the NINDS. The rates change only when new data are available; they are not computed annually. Do not compare the incidence or the rates with those in past editions of the AHA Statistical Update (also known as the Heart and Stroke Statistical Update for editions before 2005). Doing so can lead to serious misinterpretation of time trends.

The 2024 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2024. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

## Mortality

Mortality data are generally presented according to the underlying cause of death. "Any-mention" mortality means that the condition was nominally selected as the underlying cause or was otherwise mentioned on the death certificate. For many deaths classified as attributable to CVD, selection of the single most likely underlying cause can be difficult when several major comorbidities are present, as is often the case in the elderly population. It is useful, therefore, to know the extent of mortality attributable to a given cause regardless of whether it is the underlying cause or a contributing cause (ie, the "any-mention" status). The number of deaths in 2021 with any mention of specific causes of death was tabulated by the NHLBI from the NCHS public-use electronic files on mortality.

The first set of statistics for each disease in the 2024 Statistical Update include the number of deaths for which the disease is the underlying cause. Two exceptions are Chapter 8 (High Blood Pressure) and Chapter 22 (Cardiomyopathy and Heart Failure). HBP, or hypertension, increases the mortality risks of CVD and other diseases, and HF should be selected as an underlying cause only when the true underlying cause is not known. In this Statistical Update, hypertension and HF death rates are presented in 2 ways: (1) as nominally classified as the underlying cause and (2) as any-mention mortality.

National and state mortality data presented according to the underlying cause of death were obtained from the CDC WONDER website or the CDC NVSS mortality file.[1] Any-mention numbers of deaths were tabulated from the CDC WONDER website or CDC NVSS mortality file.[1,2]

## Population Estimates

In this publication, we have used national population estimates from the US Census Bureau[3] for 2020 in the computation of morbidity data. CDC/NCHS population estimates for 2021 were used in the computation of death rate data. The Census Bureau website contains these data, as well as information on the file layout.

## Hospital Discharges and Ambulatory Care Visits

Estimates of the numbers of hospital discharges and numbers of procedures performed are for inpatients discharged from short-stay hospitals. Discharges include those discharged alive, dead, or with unknown status. Unless otherwise specified, discharges are listed according to the principal (first-listed) diagnosis, and procedures are listed according to all-listed procedures (principal and secondary). These estimates are from the HCUP 2020 NIS. Ambulatory care visit data include patient visits to primary health care professionals' offices and EDs. Ambulatory care visit data reflect the primary (first-listed) diagnosis. Primary health care professional office visit estimates are from the NAMCS 2019 of the CDC/NCHS. ED visit estimates are from the HCUP 2020 National Emergency Department Sample. Readers comparing data across years should note that beginning October 1, 2015, a transition was made from *ICD-9* to *ICD-10*. This should be kept in mind because coding changes could affect some statistics, especially when comparisons are made across these years.

## International Classification of Diseases

Morbidity (illness) and mortality (death) data in the United States have a standard classification system: the *ICD*. Approximately every 10 to 20 years, the *ICD* codes are revised to reflect changes over time in medical technology, diagnosis, or terminology. If necessary for comparability of mortality trends across *ICD-9* and *ICD-10*, comparability ratios computed by the CDC/NCHS are applied as noted.[4] Effective with mortality data for 1999, *ICD-10* is used.[5] Beginning in 2016, *ICD-10-CM* is used for hospital inpatient stays and ambulatory care visit data.

## Age Adjustment

Prevalence and mortality estimates for the United States or individual states comparing demographic groups or estimates over time are either age specific or age adjusted to the year 2000 standard population by the direct method.[6] International mortality data are age adjusted to the European standard population. Unless otherwise stated, all death rates in this publication are age adjusted, and are deaths per 100 000 population.

## Data Years for National Estimates

In the 2024 Statistical Update, we estimate the annual number of new (incidence) and recurrent cases of a disease in the United States by extrapolating to the US population in 2014 from rates reported in a community- or hospital-based study or multiple studies. Age-adjusted incidence rates by sex and race are also given in this report as observed in the study or studies. For US mortality, most numbers and rates are for 2021. For disease and risk factor prevalence, most rates in this report are calculated from NHANES 2017 to 2020. Because NHANES is conducted only in the noninstitutionalized population, we extrapolated the rates to the total US resident population on July 1, 2020, recognizing that this probably underestimates the total prevalence given the relatively high prevalence in the institutionalized population. The numbers of hospital inpatient discharges for the United States are for 2020. The numbers of visits to primary health care professionals' offices are for 2018. Except as noted, economic cost estimates are for 2019 to 2020.

## Cardiovascular Disease

For data on hospitalizations, primary health care professional office visits, and mortality, total CVD is defined according to *ICD* codes given in Chapter 14 (Total Cardiovascular Diseases) of the present document. This definition includes all diseases of the circulatory system. Unless otherwise specified, estimates for total CVD do not include congenital CVD. Prevalence of total CVD includes people with hypertension, CHD, stroke, and HF.

## Race and Ethnicity

Data published by governmental agencies for some racial and ethnic groups are considered unreliable because of the small sample size in the studies. Because we try to provide data for as many racial and ethnic groups as possible, we show these data for informational and comparative purposes.

## Global Burden of Disease

The AHA works with the Institute for Health Metrics and Evaluation to report statistics for the AHA Statistical Update from the Global Burden of Diseases, Injuries, and Risk Factors Study. This is an ongoing global effort to quantify health loss from hundreds of causes and risks from 1990 to the present for all countries. The study seeks to produce consistent and comparable estimates of population health over time and across locations, including summary metrics such as DALYs and healthy life expectancy. Results are made available to policymakers, researchers, governments, and the public with the overarching goals of improving population health and reducing health disparities.

The 2024 AHA Statistical Update uses GBD estimates that were produced for 1990 to 2021 for 204 countries and territories and stratified by age and sex. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in results across GBD cycles for both the most recent and earlier years.

For more information about the GBD and to access GBD resources, data visualizations, and most recent publications, please visit the study website.[7]

The Statistical Update Supplementary Material includes additional global and regional CVD statistics.

## Contacts

If you have questions about statistics or any points made in this Statistical Update, please contact the AHA National Center, Office of Science, Medicine and Health. Direct all media inquiries to News Media Relations at http://newsroom.heart.org/connect.

The AHA works diligently to ensure that the Statistical Update is error free. If we discover errors after publication, we will provide corrections at http://www.heart.org/statistics and in the journal *Circulation*.

## REFERENCES


1. Centers for Disease Control and Prevention and National Center for Health Statistics. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death micro-data files. Accessed April 8, 2023. https://cdc.gov/nchs/nvss/mortality_public_use_data.htm
2. Centers for Disease Control and Prevention and National Center for Health Statistics. Multiple cause of death, CDC WONDER online database. Accessed April 1, 2023. https://wonder.cdc.gov/mcd-icd10.html
3. US Census Bureau. US Census Bureau population estimates: historical data: 2000s. Accessed April 1, 2023. https://www.census.gov/programs-surveys/popest.html
4. Anderson RN, Minino AM, Hoyert DL, Rosenberg HM. Comparability of cause of death between ICD-9 and ICD-10: preliminary estimates. *Natl Vital Stat Rep*. 2001;49:1–32.
5. Centers for Disease Control and Prevention and National Center for Health Statistics. ICD-10-CM official guidelines for coding and reporting, FY 2019. Accessed May 1, 2023. https://cdc.gov/nchs/icd/data/10cmguidelines-FY2019-final.pdf
6. Anderson RN, Rosenberg HM. Age standardization of death rates: implementation of the year 2000 standard. *Natl Vital Stat Rep*. 1998;47:1–16, 20.
7. Global Burden of Disease Study and Institute for Health Metrics and Evaluation. University of Washington. Accessed August 1, 2023. http://ghdx.healthdata.org/

# 2. CARDIOVASCULAR HEALTH

*See Tables 2-1 through 2-10 and Charts 2-1 through 2-8*

Click here to return to the Table of Contents

Click here to return to the Abbreviations

In 2010, the AHA released an Impact Goal that included 2 objectives that would guide organizational priorities over the next decade: "by 2020, to improve the CVH of all Americans by 20%, while reducing deaths from CVDs and stroke by 20%."[1] The concept of CVH was introduced in this goal and characterized by 7 components (Life's Simple 7) that include health behaviors (diet quality, PA, smoking) and health factors (blood cholesterol, BMI, BP, blood glucose). For an individual to have ideal CVH overall, they must have an absence of clinically manifest CVD and the simultaneous presence of optimal levels of all 7 CVH components, including abstinence from smoking, a healthy diet pattern, sufficient PA, normal body weight, and normal levels of TC, BP, and FPG in the absence of medication treatment.

To update the construct of CVH metrics on the basis of extensive evidence and insights accumulated over the decade after introduction of Life's Simple 7, the AHA released a presidential advisory in 2022 to introduce an enhanced approach of accessing CVH: Life's Essential 8.[2] The components of Life's Essential 8 include updates for the original 7 CVH components to provide metrics that more broadly recognize the scope of current health behaviors and practices and in a more refined and continuous scale for better contrasting interindividual differences in CVH at a given point in time and improved tracking of intraindividual changes in CVH over time. Furthermore, sleep health was added into the CVH metrics to better reflect its important role in human biology and sustainment of life, as well as its impact on cardiometabolic health. Table 2-1 summarizes the definitions and scoring algorithms for each of the CVH components under this new approach in both adults and youth. It is important to note that the AHA presidential advisory recognized psychological health and well-being and social determinants of health not merely as individual CVH metrics equivalent to one of the Life's Essential 8 metrics but as 2 foundational factors underlying all 8 CVH components.

With this updated approach to assess CVH, this chapter now provides statistical updates focusing on the newer CVH metrics as the health research and clinical practice fields migrate toward the use of Life's Essential 8, with attention also given to the 2 foundational CVH factors. Changes in the leading causes and risk factors for YLDs and YLLs between 1990 and 2019, first added to the 2021 Statistical Update, highlight the influence of the components of CVH on premature death and disability in populations.

## Relevance of Ideal CVH

- Multiple independent investigations have confirmed the importance of having ideal levels of CVH components, along with the overall concept of CVH, based on the original Life's Simple 7 metrics. Findings include strong inverse, stepwise associations in the United States of the number of CVH components at ideal levels with all-cause mortality, CVD mortality, IHD mortality, CVD, and HF; with subclinical measures of atherosclerosis such as carotid IMT, arterial stiffness, and CAC prevalence and progression; with physical functional impairment and frailty; with cognitive decline and depression; and with longevity.[3–6] These associations were observed in all populations in the United States, including underrepresented racial and ethnic populations.[4,5] Similar relationships have also been seen in different patient populations internationally.[3,7–19]
- Results using NHANES III mortality data through 2011 estimated the PAFs of CVD mortality for components of CVH under revised definitions as follows[20]:
  - 47.5% (95% CI, 38.2%–57.3%) for HBP (using thresholds from the 2017 AHA/ACC guideline);
  - 10.7% (95% CI, 4.0%–17.0%) for smoking;
  - 10.1% (95% CI, 2.6%–18.6%) for TC;
  - 5.91% (95% CI, 0.03%–14.1%) for insufficient PA; and
  - 11.6% (95% CI, 6.1%–16.8%) for abnormal glucose levels.
  - A previous analysis using NHANES III mortality data through 2006 reported an estimated PAF of 13.2% (95% CI, 3.5%–29.2%) for poor diet.[21]
- Ideal health behaviors and ideal health factors are each independently associated with lower CVD risk in a stepwise fashion: Across any level of health behaviors, having a greater number of ideal health factors is associated with a graded decrease in risk of incident CVD, and conversely, across any level of health factors, having a greater number of ideal health behaviors is associated with a graded lowering of incident CVD risk.[22,23]

The 2024 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2024. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

- Many studies have been published in which investigators have assigned individuals a CVH score ranging from 0 to 14 on the basis of the sum of points assigned to each component of the original Life's Simple 7 CVH metrics (poor=0, intermediate=1, ideal=2 points). With this approach, data from the REGARDS cohort were used to demonstrate an inverse stepwise association between a higher CVH score component and a lower incidence of stroke. On the basis of this score, every unit increase in CVH was associated with an 8% lower risk of incident stroke (HR, 0.92 [95% CI, 0.88–0.95]), with a similar effect size for White (HR, 0.91 [95% CI, 0.86–0.96]) and Black (HR, 0.93 [95% CI, 0.87–0.98]) participants.[24] A similar association between CVH score and incidence of stroke was also observed in a large Chinese cohort.[25] CVH score and components were also shown to predict MACEs (first occurrence of MI, stroke, acute ischemic syndrome, coronary revascularization, or death) over a median follow-up of 12 years in a biracial community-based population.[26]
- By combining the 7 CVH component scores and categorizing the total score to define overall CVH (low, 0–8 points; moderate, 9–11 points; high, 12–14 points), a report pooled NHANES 2011 to 2016 data and individual-level data from 7 US community-based cohort studies to estimate the age-, sex-, and race and ethnicity–adjusted PAF of major CVD events (nonfatal MI, stroke, HF, or CVD death) associated with CVH and found that 70.0% (95% CI, 56.5%–79.9%) of major CVD events in the United States were attributable to low and moderate CVH.[27] According to the authors' estimates, 2.0 (95% CI, 1.6–2.3) million major CVD events could potentially be prevented each year if all US adults attain high CVH, and even a partial improvement in CVH scores to the moderate level among all US adults with low overall CVH could lead to a reduction of 1.2 (95% CI, 1.0–1.4) million major CVD events annually.
- A report from the CARDIA study observed a very low rate of CVD (aHR, 0.14 [95% CI, 0.09–0.22]) and CVD mortality (aHR, 0.17 [95% CI, 0.03–0.19]) over 32 years of follow-up being associated with a high (12–14 of 14 points) versus low (<8 points) level of CVH in late adolescence or early adulthood, as classified by Life's Simple 7.[28] A report from the Framingham Offspring Study showed increased risks of subsequent hypertension, diabetes, CKD, CVD, and mortality associated with having a shorter duration of ideal CVH in adulthood.[29] Another report from the ARIC study estimated CVD risk and all-cause mortality associated with patterns of overall CVH level (classified as poor, intermediate, and ideal to correspond to 0–2, 3–4, and 5–7 of the original CVH metrics at ideal levels) over time. The authors observed that participants attaining ideal CVH at the first follow-up visit had the lowest levels of CVD risks and mortality regardless of subsequent change in CVH level, and improvement from poor CVH over time was consistently associated with lower CVD risk (aHR, 0.67 [95% CI, 0.59–0.75]) and mortality (aHR, 0.80 [95% CI, 0.72–0.89]) subsequently compared with remaining in poor CVH over time.[30] Reduced CVD risk associated with improvement of CVH over time was also observed in the elderly and very elderly populations without CVD.[31]
- Ideal CVH in parents was associated with greater CVD-free survival in offspring, and maternal CVH (0–4 versus 10–14 CVH scores) was found to be a more robust predictor of an offspring's CVD-free survival (aHR, 2.09 [95% CI, 1.50–2.92]) than paternal CVH (aHR, 1.30 [95% CI, 0.87–1.93]).[32] Furthermore, better maternal CVH at 28 weeks' gestation during pregnancy was significantly associated with better offspring CVH in early adolescence: Having just 1 poor maternal CVH metric (versus all ideal) in pregnancy was associated with 33% lower chance of offspring attaining ideal CVH (aRR, 0.67 [95% CI, 0.58–0.77]) between 10 to 14 years of age.[33]
- The Cardiovascular Lifetime Risk Pooling Project showed that adults with all optimal risk factor levels (similar to having ideal CVH factor levels of cholesterol, blood sugar, and BP, as well as not smoking) have substantially longer overall and CVD-free survival than those who have poor levels of ≥1 of these CVH factors. For example, at an index of 45 years of age, males with optimal risk factor profiles lived on average 14 years longer free of all CVD events and 12 years longer overall than people with ≥2 risk factors.[34] A large community-based prospective study in China showed that greater CVH was associated with lower lifetime risk of CVD and that improvement in CVH could lower the lifetime risk of CVD and prolong the years of life free from CVD.[35] Another report based on a large data set from the UK Biobank found that having ideal CVH over poor CVH attenuated the all-cause and cardiometabolic disease–related mortality for males and females and was associated with life expectancy gains of 5.50 years (95% CI, 3.94–7.05) for males and 4.20 years (95% CI, 2.77–5.62) for females at an index of 45 years of age among participants with cardiometabolic diseases and correspondingly 4.55 years (95% CI, 3.62–5.48) in males and 4.89 years (95% CI, 3.99–5.79) in females for people without cardiometabolic diseases.[36]
- Better CVH as defined by the Life's Simple 7 is associated with less subclinical vascular disease,[6,12,13] better global cognitive performance and cognitive

function,[37] and lower hazard of subsequent dementia.[38–40] At 5 years of age, children with better CVH have greater neurodevelopment as measured by the intelligence quotient.[41] Better CVH is also associated with fewer depressive symptoms,[42–44] lower risks of proteinuria[45,46] and chronic obstructive pulmonary disease,[47] lower risk of AF,[48,49] and lower odds of having elevated resting heart rate.[50] Using the CVH scoring approach, the FHS demonstrated significantly lower odds of prevalent hepatic steatosis associated with more favorable CVH scores, and the decrease of liver fat associated with more favorable CVH scores was greater among people with a higher GRS for NAFLD.[51] In addition, a study based on NHANES data showed significantly decreased odds of ocular diseases (OR, 0.91 [95% CI, 0.87–0.95]), defined as age-related macular degeneration, any retinopathy, and cataract or glaucoma, and odds of diabetic retinopathy (OR, 0.71 [95% CI, 0.66–0.76]) associated with each unit increase in CVH among US adults.[52] Better CVH in midlife was associated with a lower prevalence of frailty in a large community-based cohort study.[53]

- According to NHANES 1999 to 2006 data, several social risk factors (low family income, low education level, underrepresented racial groups, and single-living status) were related to lower likelihood of attaining better CVH as measured by Life's Simple 7 scores.[54] A recent report from the ARIC study found that people of Black race (versus White race: OR, 0.68 [95% CI, 0.57–0.80]), with low income (OR, 0.71 [95% CI, 0.57–0.87]), or with low education (OR, 0.65 [95% CI, 0.53–0.79]) were at higher odds of having worsening CVH over time,[55] whereas analysis of NHANES data from 2013 to 2016 found that the association between educational attainment and likelihood of ideal CVH differed by race and ethnicity, underscoring the need for elucidating specific barriers preventing achievement of CVH across different racial and ethnic subgroups in the population.[56] A recent publication from the MESA study found that greater social disadvantage as measured by an aggregated score across 5 social determinants of health domains was associated with greater odds of unfavorable CVH risk factors, including hypertension, diabetes, smoking, and obesity, and higher risk of CVD, consistent with the notion of social determinants of health as a foundational factor for CVH.[57]
- Other recent reports on CVH disparity include a study focused on people with serious mental illness, which found that individuals of underrepresented races and ethnicities had significantly lower CVH scores based on 5 of the Life's Simple 7 components.[58] Data from BRFSS identifying racial and ethnic and geographic disparities in CVH among females of childbearing age in the United States showed that NH Black females were found to have lower adjusted odds (OR, 0.54 [95% CI, 0.46–0.63]) of attaining ideal CVH compared with NH White females, whereas 5 spatial clusters in the Southwest, South, Midwest, and Mid-Atlantic region were identified as having significantly lower prevalence of ideal CVH.[59] A systematic review and meta-analysis summarized the finding on demographic differences and socioeconomic disparities in ideal CVH in the literature through June 2020, with females having a significantly higher prevalence of ideal smoking (81% versus 60% in males), BP (41% versus 30% in males), and overall CVH (6% versus 3% in males) and people with higher education and individuals who were economically more affluent being more likely to have ideal CVH.[60]
- Neighborhood factors and contextual relationships have been linked to health disparities in CVH, but more research is needed to better understand these complex relationships.[61] Recent reports on the association between better neighborhood perceptions and higher CVH score in Black communities[62] and the relationship between greater perceived social status and higher CVH score in the Hispanic/Latino population in the United States[63] are some examples of effort toward identifying complex relationships between demographic and socioeconomic factors and attaining ideal CVH. A recently published narrative review[64] described knowledge gaps and outlined potential steps toward equity in CVH, which is the objective of the interim[65] and longer-term[66] Impact Goals set forth by the AHA.
- Having more ideal CVH components in middle age has been associated with lower non-CVD and CVD health care costs in later life.[67] An investigation of 4906 participants in the Cooper Center Longitudinal Study reported that participants with ≥5 ideal CVH components in the original metrics exhibited 24.9% (95% CI, 11.7%–36.0%) lower median annual non-CVD costs and 74.5% (95% CI, 57.5%–84.7%) lower median CVD costs than those with ≤2 ideal CVH components.[67] A report from a large, ethnically diverse insured population found that people with 6 or 7 and those with 3 to 5 of the CVH components in the ideal category had a $2021 and $940 lower annual mean health care expenditure, respectively, than those with 0 to 2 ideal health components.[68]
- The 2022 AHA presidential advisory on Life's Essential 8 also provided summaries of knowledge gained on CVH since 2010 and evidence supporting psychological health and well-being, as well as social determinants, as foundational factors for CVH.[2] Since the publication of the AHA presidential advisory on Life's Essential 8, Lloyd-Jones et al[69] reported CVH prevalence estimates in the United

States, analyzing NHANES data from 2013 to 2018 using the updated metrics. Independently, another report using 6 cycles of NHANES data from 2007 to 2018 focused on trajectories of overall and component CVH scores under the updated metrics for US adults between 18 and 44 years of age by sex and race and ethnicity subgroups, over 3 periods in time, each with 2 cycles, 4 years of NHANES data combined.[70] Similar statistics produced by the AHA using NHANES data are presented in the next section (Table 2-2 and Charts 2-1 through 2-8).

- Two additional reports used NHANES data from 2005 to 2018 to quantify CVH using Life's Essential 8 metrics and linked the NHANES participants to the National Death Index mortality file through 2019 to study the association between CVH and life expectancy, as well as all-cause and CVD-specific mortality. From 23 003 US adults 20 to 79 years of age, the life expectancy at 50 years of age, for example, the average number of years of life remaining after age 50, was estimated to be 27.3 years (95% CI, 26.1–28.4) in the low CVH group, defined as CVH overall score <50, 32.9 (95% CI, 32.3–33.4) in the moderate CVH group (CVH overall score between 50 and 79), and 36.2 (95% CI, 34.2–38.2) years in the high CVH group, defined as overall CVH score of ≥80.[71] With 19 951 US adults between 30 and 79 years of age over a median follow-up of 7.6 years, the second report found a 58% reduction (HR, 0.42 [95% CI, 0.32–0.56]) in all-cause mortality rate and a 64% reduction (HR, 0.36 [95% CI, 0.21–0.59]) in CVD-specific mortality rate when the high CVH (score, 75–100) was compared with the low CVH (score <50) group and a 40% reduction (HR, 0.60 [95% CI, 0.51–0.71]) in all-cause mortality rate and 38% reduction (HR, 0.62 [95% CI, 0.46–0.83]) in CVD-specific mortality rate when the moderate CVH group (score, 50–74) was compared with the low CVH group.[72] In a third report analyzing 23 110 US adults ≥20 years of age from NHANES between 2005 and 2014, also matching with the National Death Index data through 2019, the authors reported a 40% reduction (HR, 0.60 [95% CI, 0.48–0.75]) in all-cause mortality rate and a 54% reduction (HR, 0.46 [95% CI, 0.31–0.68]) in CVD-specific mortality rate over a median follow-up of 9.4 years when they compared the high CVH (defined as overall CVH score of 80–100) with the low CVH (score <50) group.[73]
- Several reports using UK Biobank data were also produced with the updated CVH metrics. With 250 825 participants observed over a median follow-up of 10.4 years, people in the lowest quartile of the overall CVH score had 2.1- (95% CI, 2.0–2.2) fold higher risk from MACEs (including IHD, MI, stroke, and HF) compared with participants in the highest quartile of CVH score. HF was the MACE component outcome that experienced the greatest elevated risk (HR, 2.7 [95% CI, 2.4–2.9]).[74] The mean difference in life expectancy at 45 years of age between these 2 groups of people was estimated as 7.2 years (95% CI, 5.5–8.9) in favor of people with ≥4 ideal components in the CVH metrics. According to data from 135 199 participants, the life expectancy free of 4 major chronic diseases, namely CVD, diabetes, cancer, and dementia, at 50 years of age was estimated to be 6.9 years (95% CI, 6.1–7.7) longer for males with high CVH level (overall score. 80–100) compared with males at the low CVH level (overall score <50) and 9.4 years (95% CI, 8.5–10.2) longer for females with high CVH level compared with females in the low CVH category. The corresponding estimates were 4.0 years (95% CI, 3.4–4.5) longer for males and 6.3 years (95% CI, 5.6–7.0) longer for females with moderate CVH level compared with their counterparts in the low CVH category.[75] In a study focusing on 33 236 participants with type 2 diabetes who were 40 to 72 years of age at baseline using the same database, people with ≥4 ideal components in the CVH metrics enjoyed a 65% reduction (HR, 0.35 [95% CI, 0.26–0.47]) in diabetes complications and a 47% reduction (HR, 0.53 [95% CI, 0.43–0.65]) in all-cause mortality rate compared with people with no more than 1 ideal CVH metric over a median of 11.7 years of follow-up.[76] Similar favorable risk reductions for risk of dying before 75 years of age were found for males and females with or without type 2 diabetes at the moderate to high CVH levels compared with low CVH among 309 789 adults from the same database.[77]
- Similar associations between greater CVH using the revised metrics and more favorable health or mortality outcomes were also reported by a Finnish[78] and 2 Chinese cohort[79,80] studies. The Healthy Start Study contrasted the original Life's Simple 7 and the revised Life's Essential 8 CVH metrics in 305 children between 4 and 7 years of age and observed modest concordance between these 2 CVH metrics. The authors noted the important role that sleep health played in classifying childhood CVH levels.[81] Additional information on the relevance of sleep to cardiometabolic health can be found in Chapter 13 (Sleep) of this Statistical Update.

## CVH in the United States: Mean CVH Scores (NHANES 2013–March 2020)

### (See Table 2-2)

- The national estimates of the 8 CVH components for children (2–19 years of age) and adults (≥20 years of age) are displayed in Table 2-2. Multiple

cycles of NHANES data were combined to provide more precise estimates on all CVH components. Dietary, PA, and BMI scores were calculated for all children who were 2 to 19 years of age; blood lipid and BP scores were calculated for children who were 6 to 19 and 8 to 19 years of age, respectively; and blood glucose and nicotine exposure scores were calculated for those who were 12 to 19 years of age in the sample. The sleep health score was available only for youth 16 to 19 years of age, so the mean score of this component and the overall CVH score were derived for this age range only. Dietary estimates were available only through data up to the 2017 to 2018 NHANES cycle at the time of this report.
  - For most components of CVH, mean scores were higher in US children (within corresponding age ranges of the components) than in US adults (≥20 years of age), except for the diet score and the sleep health score, for which mean scores in children were lower than in adults. Mean diet scores were the lowest among the 8 CVH components for both US children and adults.
  - Among US children, BP, blood glucose, and nicotine exposure were the CVH components scoring highest compared with the rest of the CVH components, with all mean scores in the 80s and the 90s (of 100 points as the ideal score) across race and ethnicity groups. In contrast, mean PA, lipids, and sleep health scores within the corresponding age ranges were all in the 70s across race and ethnicity categories.
  - Among US adults (Table 2-2), the lowest mean scores for CVH were observed in diet, PA, and BMI components, with mean scores ranging from the 30s to the 50s across all race and ethnicity categories. Sleep health scores were the highest among the CVH components in US adults, with mean scores in the 80s across all race and ethnicity groups except in the NH Black adult population, for whom the mean score was 75.6 (95% CI, 74.5–76.7). Mean scores for blood lipids, blood glucose, and BP among US adults were all in the 60s to the 70s range across race and ethnicity categories.
- From 2013 to March 2020, the overall CVH score combining health scores of all 8 components was, on average, 73.6 (95% CI, 72.4–74.7) for all US children between 16 and 19 years of age (Table 2-2). The corresponding mean overall CVH score was 78.4 (95% CI, 75.7–81.1) for NH Asian, 74.1 (95% CI, 72.0–76.2) for NH White, 72.7 (95% CI, 70.6–76.3) for Mexican American, and 71.3 (95% CI, 68.8–73.8) for NH Black children.
- During the same period, the mean overall CVH score was 65.2 (95% CI, 64.2–66.1) for all US adults, with mean score of 69.6 (95% CI, 68.1–71.1) for NH Asian, 66.0 (95% CI, 64.8–67.2) for NH White, 63.5 (95% CI, 62.2–64.8) for Mexican American, and 59.7 (95% CI, 58.4–60.9) for NH Black adults (Table 2-2).
- An article appeared online ahead of print on the same day as the presidential advisory on Life's Essential 8 providing CVH score estimates by additional sociodemographic categories under this new CVH metrics using NHANES data from 2013 to 2018.[69]

## CVH in the United States: Trend in Mean CVH Scores Over Time (NHANES 2007–March 2020) (See Charts 2-1 through 2-8)

- The overall trend for national estimates of the 8 CVH components for adults 20 to 79 years of age and trends by race and ethnicity subgroups are displayed in Charts 2-1 through 2-8 (unpublished AHA tabulation using NHANES[82]). Adults who self-reported a history of CHD, MI, angina, or stroke; were pregnant; or were breastfeeding at time of examination were not included in these analyses. Dietary estimates were available only through the 2017 to 2018 NHANES data cycle at the time of this report because of the availability of the Food Patterns Equivalents Database from the US Department of Agriculture, whereas mean scores for the rest of the CVH metrics were derived through the 2017 to March 2020 combined NHANES cycle. As a result, the trends over time for the overall CVH score are not presented here. Furthermore, data for the NH Asian population are available only for CVH evaluation starting from the 2011 to 2012 NHANES data cycle.
  - During this time period, CVH diet scores for US adults remained low and relatively unchanged (Chart 2-1). Adult NH Asian individuals observed slightly higher average diet scores since 2011 to 2012 compared with other race and ethnicity subgroups. The age-adjusted mean score for NH Asian adults in 2017 to 2018 was 47.8 (95% CI, 44.3–55.3). NH Black individuals had the lowest diet score on average during the past decade. In 2017 to 2018, the adjusted mean score for NH Black adults was 22.4 (95% CI, 19.1–27.7).
  - Although still low overall, a gradual upward trend in mean CVH PA scores was observed for adults in every race and ethnicity subgroup presented, except for NH Asian adults, for whom the trend is less obvious (Chart 2-2). In the period of 2017 to March 2020, the age-adjusted mean PA scores ranged from 47.9 (95% CI, 45.6–50.3) for Hispanic adults to 57.7 (95% CI, 54.0–61.4) for NH White adults.

- Upward trends in mean nicotine exposure CVH scores were observed for adults in all race and ethnicity subgroups presented (Chart 2-3). The mean scores for the updated nicotine exposure CVH score, which now takes into account secondhand smoking exposure as well, were significantly higher in NH Asian and Hispanic individuals compared with NH White and NH Black individuals. The age-adjusted mean scores ranged between 66.8 (95% CI, 62.7–70.8) for NH Black adults and 87.0 (95% CI, 84.4–89.5) among NH Asian adults during 2017 to March 2020.
- Upward trends were also observed across all race and ethnicity subgroups for the newest addition to the updated CVH metrics, the sleep health score, although the age-adjusted mean scores were significantly lower for NH Black individuals, ranging from 71.5 (95% CI, 69.3–73.6) in 2007 to 2008, to 78.5 (95% CI, 76.4–80.6) in 2015 to 2016, and then to 76.6 (95% CI, 74.9–78.3) in 2017 to March 2020 compared with other race and ethnicity subgroups (Chart 2-4).
- Although mean CVH BMI scores were higher in NH White and NH Asian individuals compared with NH Black and the Hispanic individuals, all race and ethnicity subgroups presented here observed a steep downward trend in this CVH metric over the past decade. (Chart 2-5). In the period of 2017 to March 2020, the age-adjusted mean BMI scores ranged between 57.5 (95% CI, 54.8–60.2) for NH White adults and 50.3 (95% CI, 48.5–52.2) for NH Black adults.
- Trends in age-adjusted mean scores of the non-HDL lipids metric over the past decade improved for all race and ethnicity subgroups, except for the NH Asian population, for which the mean scores were relatively unchanged (Chart 2-6). NH Black individuals had significantly higher mean scores in this metric, ranging from 69.0 (95% CI, 67.0–71.1) in 2007 to 2008 to 74.9 (95% CI, 72.8–77.0) in 2017 to March 2020, compared with the other race and ethnicity subgroups.
- Although they remained relatively stable through 2014, the mean CVH blood glucose scores had a steady worsening for all race and ethnicity subgroups over the past 6 years (Chart 2-7). The mean scores for all US individuals were 79.4 (95% CI, 78.2–80.6) in 2007 to 2008 and 80.5 (95% CI, 79.4–81.5) in 2013 to 2014 but declined to 76.0 (95% CI, 75.2–76.9) in 2017 to March 2020.
- During this time period, age-adjusted mean BP scores for US adults remained relatively unchanged (Chart 2-8). NH Black individuals had the lowest mean BP score and had a seemingly more pronounced downward trend over time in this CVH metric, from 65.8 (95% CI, 62.2–69.3) in 2007 to 2008 to 57.9 (95% CI, 55.8–59.9) in 2017 to March 2020, compared with the rest of US adult populations.

## Trends in Risk Factors and Causes for YLL and YLD in the United States: 1990 to 2019

## (See Tables 2-3 through 2-6)

- The leading risk factors for YLLs from 1990 to 2019 in the United States and the corresponding percent change in age-standardized YLL rates attributable to these risk factors are presented in Table 2-3.
  - Smoking and high SBP remained the first and second leading YLL risk factors in both 1990 and 2019. Age-standardized rates of YLL attributable to smoking declined by 46.4%, whereas age-standardized rates attributable to high SBP declined 45.8%.
  - From 1990 to 2019, YLLs caused by drug use rose from the 18th to 5th leading YLL risk factor with a 242.3% increase in the age-standardized YLL rate.
  - In 2019, CVH components accounted for 13 (among which 7 were related to poor diet) of the 20 leading YLL risk factors, with 6 of the 7 diet-related risk factors rising in the risk factor rankings since 1990.
- The leading causes of YLLs from 1990 to 2019 in the United States and the corresponding percent change in age-standardized YLL rates attributable to these risk factors are presented in Table 2-4.
  - IHD and tracheal, bronchus, and lung cancer were the first and second leading YLL causes in both 1990 and 2019. Age-standardized YLL rates attributable to IHD declined 50.9%, whereas age-standardized YLL rates resulting from tracheal, bronchus, and lung cancer declined 36.1%.
  - From 1990 to 2019, opioid use disorders rose from the 46th to 4th leading YLL cause with a 799.2% increase in the age-standardized YLL rate. Type 2 diabetes also rose from the 12th to 6th leading YLL cause, whereas AD and other dementias also rose from the 15th to 7th leading YLL cause.
- The leading risk factors for YLDs from 1990 to 2019 in the United States and the corresponding percent change in age-standardized YLD rates attributable to these risk factors are presented in Table 2-5.
  - High BMI, high FPG, and smoking are among the first, second, and third leading YLD risk factors

in both 1990 and 2019, with high BMI and high FPG rising in ranking and smoking dropping from the first to third leading YLD risk factor during this time period. Age-standardized YLD rates attributable to smoking declined by 25.8%, and age-standardized rates attributable to high BMI and high FPG increased by 44.4% and 47.4%, respectively, between 1990 and 2019.

- The leading causes of YLDs from 1990 to 2019 in the United States and the corresponding percent change in age-standardized YLD rates attributable to these risk factors are presented in Table 2-6.
  - Low back pain and other musculoskeletal disorders were the first and second leading causes of YLDs in both 1990 and 2019. The age-standardized rates of YLD attributable to low back pain decreased 12.5%, whereas age-standardized YLD rates for other musculoskeletal disorders increased 44.2%.
  - From 1990 to 2019, type 2 diabetes rose from the ninth to third leading YLD cause with a 55.8% increase in the age-standardized YLD rates.
  - Opioid use disorders rose from the 16th to 4th leading YLD cause between 1990 and 2019 with a 288.7% increase in age-standardized rates of YLD.

## Trends in Global Risk Factors and Causes for YLL and YLD: 1990 to 2019

## (See Tables 2-7 through 2-10)

- The leading global YLL risk factors from 1990 to 2019 and the corresponding percent change in age-standardized YLL rates attributable to these risk factors are presented in Table 2-7.
  - High SBP and smoking were the first and second leading YLL risk factors globally in 2019. Age-standardized YLL rates attributable to HBP and smoking declined 29.0% and 41.3%, respectively, between 1990 and 2019.
  - From 1990 to 2019, high FPG rose from the 14th to 5th leading risk factor of global YLLs with a 1.5% decrease in the age-standardized YLL rates over this period.
- The leading global YLL causes from 1990 to 2019 and the corresponding percent change in age-standardized YLL rates attributable to these risk factors are presented in Table 2-8.
  - IHD rose from the third to first leading global YLL cause between 1990 and 2019, whereas age-standardized YLL rates declined by 29.1% during this period. This shift resulted in lower respiratory infections moving from the first to second leading cause, and age-standardized YLL rates declined 62.7%.
  - ICH and ischemic stroke rose from the ninth to fourth and from the 13th to 8th leading cause of global YLL, respectively, between 1990 and 2019.
  - Type 2 diabetes also rose from the 28th to 14th leading global YLL cause, showing a 9.1% increase in age-standardized YLL rate.
- The leading global risk factors for YLDs from 1990 to 2019 and the corresponding percent change in age-standardized YLD rates attributable to these risk factors are presented in Table 2-9.
  - High FPG and high BMI were the first and second leading YLD risk factors globally in 2019, replacing iron deficiency and smoking, which ranked fourth and third, respectively, in 2019. Age-standardized YLD rates attributable to high FPG and high BMI increased 44.1% and 60.2%, respectively, whereas age-standardized global YLD rates attributable to smoking and iron deficiency decreased 22.9% and 16.7%, respectively.
  - Ambient particulate matter pollution rose from the 17th to 8th leading global risk factor for YLD, resulting in a 64.9% increase in the age-standardized global YLD rates.
- The leading global causes of YLDs from 1990 to 2019 and the corresponding percent change in age-standardized YLD rates attributable to these risk factors are presented in Table 2-10.
  - Low back pain and migraine were the first and second leading global causes of YLDs in both 1990 and 2019. The age-standardized rates of YLD attributable to low back pain decreased 16.3%, whereas rates for migraine increased 1.5% across the same time period.
  - From 1990 to 2019, type 2 diabetes rose from the 10th to 6th leading global cause of YLD during this time period, with a 50.2% increase in the age-standardized global YLD rate.

## COVID-19 Mortality in the United States

- The large number of individuals in the United States who contracted severe illness attributable to COVID-19 resulted in a huge mortality toll, with disproportionate rates of deaths occurring among US counties with metropolitan areas and with higher proportions of the population who are NH Black and Hispanic people and in poverty.
  - As of March 15, 2023, the cumulative number of COVID-19 deaths in the United States was 1 123 538, which equates to ≈338 deaths per 100 000 people. In metropolitan areas in the United States, the cumulative COVID-19 death rate was ≈322 deaths per 100 000 compared with ≈433 deaths per 100 000 in nonmetropolitan areas.

- In US counties with a high percentage (>37%) of the population that is NH Black individuals, the COVID-19 death rate was ≈387 deaths per 100 000 compared with ≈329 deaths per 100 000 in counties with a low percentage (<2.5%) of the population that is NH Black individuals.[83]
- In US counties with a high percentage (>45.5%) of the population that is Hispanic individuals, the cumulative COVID-19 death rate was ≈376 deaths per 100 000 compared with ≈342 deaths per 100 000 in counties with a low percentage (≤18.3%) of the population that is Hispanic individuals.[83]
- In US counties with a high percentage (>17.3%) of the population in poverty, the cumulative COVID-19 death rate was ≈430 deaths per 100 000 compared with ≈277 deaths per 100 000 in counties with a low percentage (≤12.3%) of the population that is living in poverty.[83]

## Impact of COVID-19 on Life Expectancy in the United States

- As a result of the high COVID-19 mortality rates, life expectancy in the United States for 2020 has been estimated to decline with disproportionate impacts on populations with high COVID-19 mortality rates.
- US life expectancy estimates released in August 2022[84] indicate that life expectancy (at birth) decreased from 78.8 years in 2019 to 76.1 years in 2021 (—2.7 years) overall; corresponding life expectancy decreased from 76.3 to 73.2 years (—3.1 years) in males and from 81.4 to 79.1 years (—2.3 years) in females. Provisional estimates released in August 2022 indicated that life expectancy decreased from 74.7 to 70.8 years (—4.0 years) for NH Black individuals, from 81.8 to 77.7 years (—4.2 years) for Hispanic individuals, and from 78.8 to 76.4 years (—2.4 years) for NH White individuals.

## Furthering the AHA's Impact Through Continued Efforts to Improve CVH (See Tables 2-3 through 2-6)

- Renewed efforts to maintain and improve CVH will be foundational to successful reductions in mortality and disability in the United States and globally. Individuals with more favorable levels of CVH have significantly lower risk for several of the leading causes of death and YLD, including IHD,[22] AD,[85] stroke,[86,87] CKD,[88] diabetes,[89,90] and breast cancer[91,92] (Tables 2-4 and 2-6). In addition, 6 of the 10 leading US risk factors for YLL and 4 of the 10 leading risk factors for YLD in 2019 were components of CVH (Tables 2-3 and 2-5). Taken together, these data demonstrate the tremendous importance of continued efforts to improve CVH.
- The expanding efforts of the AHA and American Stroke Association in areas of brain health are also well poised to drive toward improvement in several leading causes of death and disability that influence YLLs and YLDs, including stroke, AD, depression and anxiety disorders, and alcohol and substance use disorders.
- Despite improvements observed in CVH and brain health over the past decade, further progress is needed to more fully realize these benefits. Details are described in the AHA presidential advisory on brain health.[93]

## Global Efforts to Improve CVH (See Tables 2-7 through 2-10)

- Renewal of efforts to improve CVH is a continuing challenge that requires collaboration throughout the global community in ways that aim targeted skills and resources at improving the top causes and risk factors for death and disability in countries. Such efforts are required in countries at all income levels with an emphasis on efforts to halt the continued worsening of the components of CVH (Tables 2-7 through 2-10).
- Many challenges exist related to implementation of prevention and treatment programs in international settings; some challenges are unique to individual countries/cultures, whereas others are universal. Partnerships and collaborations with local, national, regional, and global partners are foundational to effectively addressing relevant national health priorities in ways that facilitate contextualization within individual countries and cultures.

**Table 2-1. Life's Essential 8: New and Updated Metrics for Measurement and Quantitative Assessment of Cardiovascular Health**

| Domain | CVH metric | Method of measurement | Quantification of CVH metric: adults (≥20 y of age) | Quantification of CVH metric: children (up to 19 y of age) |
|---|---|---|---|---|
| Health behaviors | Diet | Measurement: Self-reported daily intake of a DASH-style eating pattern<br>Example tools for measurement: DASH diet score[94,95] (populations); MEPA[96] (individuals) | Quantiles of DASH-style diet adherence or HEI-2015 (population)<br>Scoring (population):<br>Points — Quantile<br>100 — ≥95th percentile (top/ideal diet)<br>80 — 75th–94th percentile<br>50 — 50th–74th percentile<br>25 — 25th–49th percentile<br>0 — 1st–24th percentile (bottom/least ideal quartile)<br>Scoring (individual):<br>Points — MEPA score (points)<br>100 — 15–16<br>80 — 12–14<br>50 — 8–11<br>25 — 4–7<br>0 — 0–3 | Quantiles of DASH-style diet adherence or HEI-2015 (population) or MEPA (individuals)*; 2–19 y of age (see Supplemental Material for younger ages)<br>Scoring (population):<br>Points — Quantile<br>100 — ≥95th percentile (top/ideal diet)<br>80 — 75th–94th percentile<br>50 — 50th–74th percentile<br>25 — 25th–49th percentile<br>0 — 1st–24th percentile (bottom/least ideal quartile)<br>Scoring (individual):<br>Points — MEPA score (points)<br>100 — 9–10<br>80 — 7–8<br>50 — 5–6<br>25 — 3–4<br>0 — 0–2 |
| | PA | Measurement: Self-reported minutes of moderate or vigorous PA per week<br>Example tools for measurement: NHANES PAQ-K questionnaire[97] | Metric: Minutes of moderate- (or greater) intensity activity per week<br>Scoring:<br>Points — Minutes<br>100 — ≥150<br>90 — 120–149<br>80 — 90–119<br>60 — 60–89<br>40 — 30–59<br>20 — 1–29<br>0 — 0 | Metric: Minutes of moderate- (or greater) intensity activity per week; 6–19 y of age (see notes and Supplemental Material for younger ages)<br>Scoring:<br>Points — Minutes<br>100 — ≥420<br>90 — 360–419<br>80 — 300–359<br>60 — 240–299<br>40 — 120–239<br>20 — 1–119<br>0 — 0 |
| | Nicotine exposure | Measurement: Self-reported use of cigarettes or inhaled NDS<br>Example tools for measurement: NHANES SMQ[98] | Metric: Combustible tobacco use or inhaled NDS use or secondhand smoke exposure<br>Scoring:<br>Points — Status<br>100 — Never-smoker<br>75 — Former smoker, quit ≥5 y<br>50 — Former smoker, quit 1–<5 y<br>25 — Former smoker, quit <1 y, or currently using inhaled NDS<br>0 — Current smoker<br>Subtract 20 points (unless score is 0) for living with active indoor smoker in home | Metric: Combustible tobacco use or inhaled NDS use at any age (per clinician discretion) or secondhand smoke exposure<br>Scoring:<br>Points — Status<br>100 — Never tried<br>50 — Tried any nicotine product but >30 d ago<br>25 — Currently using inhaled NDS<br>0 — Current combustible use (any within 30 d)<br>Subtract 20 points (unless score is 0) for living with active indoor smoker in home |

(*Continued*)

**Table 2-1. Continued**

| Domain | CVH metric | Method of measurement | Quantification of CVH metric: adults (≥20 y of age) | Quantification of CVH metric: children (up to 19 y of age) |
|---|---|---|---|---|
| | Sleep health | Measurement: Self-reported average hours of sleep per night<br>Example tools for measurement: "On average, how many hours of sleep do you get per night?"<br>Consider objective sleep/actigraphy data from wearable technology if available | Metric: Average hours of sleep per night<br>Scoring:<br>Points / Level<br>100 / 7–<9<br>90 / 9–<10<br>70 / 6–<7<br>40 / 5–<6 or ≥10<br>20 / 4–<5<br>0 / <4 | Metric: Average hours of sleep per night (or per 24 h for ≤5 y of age; see notes for age-appropriate ranges)<br>Scoring:<br>Points / Level<br>100 / Age-appropriate optimal range<br>90 / <1 h above optimal range<br>70 / <1 h below optimal range<br>40 / 1–<2 h below or ≥1 h above optimal<br>20 / 2–<3 h below optimal range<br>0 / ≥3 h below optimal range |
| Health factors | BMI | Measurement: Body weight (kilograms) divided by height squared (meters squared)<br>Example tools for measurement: Objective measurement of height and weight | Metric: BMI (kg/m$^2$)<br>Scoring:<br>Points / Level<br>100 / <25<br>70 / 25.0–29.9<br>30 / 30.0–34.9<br>15 / 35.0–39.9<br>0 / ≥40.0 | Metric: BMI percentiles for age and sex, starting in infancy; see Supplemental Material for suggestions for <2 y of age<br>Scoring:<br>Points / Level<br>100 / 5th–<85th percentile<br>70 / 85th–<95th percentile<br>30 / 95th percentile–<120% of the 95th percentile<br>15 / 120% of the 95th percentile–<140% of the 95th percentile<br>0 / ≥140% of the 95th percentile |
| | Blood lipids | Measurement: Plasma TC and HDL-C with calculation of non–HDL-C<br>Example tools for measurement: Fasting or nonfasting blood sample | Metric: Non–HDL-C (mg/dL)<br>Scoring:<br>Points / Level<br>100 / <130<br>60 / 130–159<br>40 / 160–189<br>20 / 190–219<br>0 / ≥220<br>If drug-treated level, subtract 20 points | Metric: Non–HDL-C (mg/dL), starting no later than 9–11 y of age and earlier per clinician discretion<br>Scoring:<br>Points / Level<br>100 / <100<br>60 / 100–119<br>40 / 120–144<br>20 / 145–189<br>0 / ≥190<br>If drug-treated level, subtract 20 points |
| | Blood glucose | Measurement: FBG or casual HbA1c<br>Example tools for measurement: Fasting (FBG, HbA1c) or nonfasting (HbA1c) blood sample | Metric: FBG (mg/dL) or HbA1c (%)<br>Scoring:<br>Points / Level<br>100 / No history of diabetes and FBG <100 (or HbA1c <5.7)<br>60 / No diabetes and FBG 100–125 (or HbA1c 5.7–6.4; prediabetes)<br>40 / Diabetes with HbA1c <7.0<br>30 / Diabetes with HbA1c 7.0–7.9<br>20 / Diabetes with HbA1c 8.0–8.9<br>10 / Diabetes with HbA1c 9.0–9.9<br>0 / Diabetes with HbA1c ≥10.0 | Metric: FBG (mg/dL) or HbA1c (%), symptom-based screening at any age or risk-based screening starting at ≥10 y of age or onset of puberty per clinician discretion<br>Scoring:<br>Points / Level<br>100 / No history of diabetes and FBG <100 (or HbA1c <5.7)<br>60 / No diabetes and FBG 100–125 (or HbA1c 5.7–6.4; prediabetes)<br>40 / Diabetes with HbA1c <7.0<br>30 / Diabetes with HbA1c 7.0–7.9<br>20 / Diabetes with HbA1c 8.0–8.9<br>10 / Diabetes with HbA1c 9.0–9.9<br>0 / Diabetes with HbA1c ≥10.0 |

(*Continued*)

**Table 2-1. Continued**

| Domain | CVH metric | Method of measurement | Quantification of CVH metric: adults (≥20 y of age) | Quantification of CVH metric: children (up to 19 y of age) |
|---|---|---|---|---|
| | BP | Measurement: Appropriately measured SBP and DBP<br>Example tools for measurement: Appropriately sized BP cuff | Metric: SBP and DBP (mm Hg)<br>Scoring:<br>Points / Level<br>100 / <120/<80 (optimal)<br>75 / 120–129/<80 (elevated)<br>50 / 130–139 or 80–89 (stage 1 hypertension)<br>25 / 140–159 or 90–99<br>0 / ≥160 or ≥100<br>Subtract 20 points if treated level | Metric: SBP and DBP (mm Hg) percentiles for ≤12 y of age. For ≥13 y of age, use adult scoring. Screening should start no later than 3 y of age and earlier per clinician discretion<br>Scoring:<br>Points / Level<br>100 / Optimal (<90th percentile)<br>75 / Elevated (≥90th–<95th percentile or ≥120/80 mm Hg to <95th percentile, whichever is lower)<br>50 / Stage 1 hypertension (≥95th–<95th percentile+12 mm Hg or 130/80 to 139/89 mm Hg, whichever is lower)<br>25 / Stage 2 hypertension (≥95th percentile+12 mm Hg or ≥140/90 mm Hg, whichever is lower)<br>0 / SBP ≥160 or ≥95th percentile+30 mm Hg SBP, whichever is lower, and/or DBP ≥100 or ≥95th percentile+20 mm Hg DBP<br>Subtract 20 points if treated level |

BMI indicates body mass index; BP, blood pressure; CVH, cardiovascular health; DASH, Dietary Approaches to Stop Hypertension; DBP, diastolic blood pressure; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HEI, Healthy Eating Index; MEPA, Mediterranean Eating Pattern for Americans; NDS, nicotine-delivery system; NHANES, National Health and Nutrition Examination Surveys; PA, physical activity; PAQ-K, Physical Activity Questionnaire K; SBP, systolic blood pressure; SMQ, smoking assessment; and TC, total cholesterol.

*Cannot meet these metrics until solid foods are being consumed.

Notes on implementation:

Diet: See Supplemental Material Appendix 1. For adults and children, a score of 100 points for the CVH diet metric should be assigned for the top (95th percentile) or a score of 15 to 16 on the MEPA (for individuals) or for those in the ≥95th percentile on the DASH score or HEI-2015 (for populations). The 75th to 94th percentile should be assigned 80 points, given that improvement likely can be made even among those in this top quartile. For individuals, the MEPA points are stratified for the 100-point scoring system approximately by quantiles. In children, a modified MEPA is suggested that is based on age-appropriate foods. The writing group recognizes that the quantiles may need to be adjusted or recalibrated at intervals with population shifts in eating patterns. In children, the scoring applies only once solid foods are being consumed. For now, the reference population for quantiles of HEI or DASH score should be the NHANES sample from 2015 to 2018. The writing group acknowledges that this may need to change or be updated over time. Clinicians should use judgment in assigning points for culturally contextual healthy diets. For additional notes on scoring in children, see Supplemental Material Appendix 2.

PA: Thresholds are based in part on US Physical Activity Guidelines. For adults, each minute of moderate activity should count as 1 minute and each minute of vigorous activity should count as 2 minutes toward the total for the week. For children, each minute of moderate or vigorous activity should count as 1 minute. The score for PA is not linear, given that there is a greater increase in health benefit for each minute of marginal exercise at the lower end of the range and the association tends to approach an asymptote at the higher end of the range.

If scoring is desired for children ≤5 years of age, see Supplemental Material. For additional notes on scoring in children, see Supplemental Material Appendix 2.

Nicotine exposure: The writing group recommends subtracting 20 points for children and adults exposed to indoor secondhand smoke at home, given its potential for long-term effects on cardiopulmonary health.[99] For additional notes on scoring in children, see Supplemental Material Appendix 2.

Sleep health: Thresholds are based in part on sleep guidelines. Clinicians may consider subtracting 20 points from the sleep score for adults or children with untreated or undertreated sleep apnea if information is available. Note that overall scoring reflects the inverse-U–shaped association of sleep duration with health outcomes such that excessive sleep duration is also considered to be suboptimal for CVH.

For children, age-appropriate optimal sleep durations are as follows[100]:

4 to 12 months of age, 12 to 16 hours per 24 hours (includes naps);
1 to 2 years of age, 11 to 14 hours per 24 hours;
3 to 5 years of age, 10 to 13 hours per 24 hours;
6 to 12 years of age, 9 to 12 hours; and
13 to 18 years of age, 8 to 10 hours.

For additional notes on scoring in children, see Supplemental Material Appendix 2.

BMI: Thresholds are based in part on National Heart, Lung, and Blood Institute (NHLBI) guidelines. The writing group acknowledges that BMI is an imperfect metric for determining healthy body weight and body composition. Nonetheless, it is widely available and routinely calculated in clinical and research settings. BMI ranges may differ for individuals from diverse ancestries. For example, the World Health Organization has recommended different BMI ranges for individuals of Asian or Pacific ancestry. For individuals in these groups, point scores should be aligned as appropriate:

| Points | Level, kg/m$^2$ |
|---|---|
| 100 | 18.5–22.9 |
| 75 | 23.0–24.9 |
| 50 | 25.0–29.9 |
| 25 | 30.0–34.9 |
| 0 | ≥35.0 |

Clinicians may want to assign 100 points for overweight individuals (BMI, 25.0–29.9 kg/m$^2$) who are lean with higher muscle mass. For underweight individuals (<18.5 kg/m$^2$ in adults or below the fifth percentile in children), the writing group defers to clinician judgment in assigning points on the basis of individual assessment

(*Continued*)

**Table 2-1. Continued**

as to whether the underweight BMI is healthy or unhealthy. Conditions that should be considered unhealthy include chronic catabolic illnesses (eg, cancer), eating disorders, and growth failure (for children). For additional notes on scoring in children, see Supplemental Material Appendix 2.

Blood lipids: Thresholds are based in part on 2018 Cholesterol Clinical Practice Guideline.[101] The levels of non–HDL-C for adults were selected on the basis of current guideline recommendations and in concert with the observation that non–HDL-C levels are generally ≈30 mg/dL higher than low-density lipoprotein cholesterol levels in normative ranges in the population. For children, thresholds for non–HDL-C were chosen on the basis of NHLBI pediatric guidelines, pediatric low-density lipoprotein cholesterol thresholds for diagnosis of familial hypercholesterolemia phenotypes (+30 mg/dL), and current distributions of non–HDL-C to smooth transitions to adult point scales. The writing group recommends subtracting 20 points from the blood lipid score if the level of non–HDL-C represents a treated value, given the residual risk present in those who require treatment. There may be a modest shift in point scores for this metric as individuals age from pediatric to adult metrics. For additional notes on scoring in children, see Supplemental Material Appendix 2.

Blood glucose: Thresholds are based in part on American Diabetes Association guidelines.[102] If an individual patient with prediabetes (ie, not yet diagnosed formally with diabetes) is being treated with metformin to prevent the onset of diabetes and has normoglycemic levels, the writing group recommends clinician judgment for assigning point values (ie, consider subtracting 20 points). The maximal point value for patients with well-controlled diabetes was set at 40, given the residual risk present in those with diabetes. For additional notes on scoring in children, see Supplemental Material Appendix 2.

BP: Thresholds are based in part on the 2017 Hypertension Clinical Practice Guidelines and the guidelines for children.[103] The writing group recommends subtracting 20 points from the BP score if the level of BP represents a treated value, given the residual risk present in those who require treatment. For additional notes on scoring in children, see Supplemental Material Appendix 2.

Source: Reprinted with permission from Lloyd-Jones et al.[2] Copyright © 2022, American Heart Association, Inc.

**Table 2-2. Mean (95% CI) Score for Each Component of CVH Metrics by Race and Ethnicity Strata Among US Children 2 to 19 Years of Age and US Adults ≥20 Years of Age: NHANES 2013 to March 2020**

| Individual component of CVH metrics | NHANES years | Overall | NH Black | NH White | NH Asian | MA |
|---|---|---|---|---|---|---|
| Health behaviors | | 2–19 y of age | | | | |
| Diet* score (2–19 y) | 2013–2018 | 41.2 (39.0–43.5) | 31.7 (28.8–34.6) | 41.1 (37.6–44.5) | 49.8 (43.0–56.5) | 44.3 (40.8–47.8) |
| PA score (2–19 y) | 2013–March 2020 | 75.2 (74.2–76.3) | 74.7 (73.0–76.3) | 77.5 (76.0–78.9) | 72.5 (69.9–74.9) | 71.0 (68.4–73.7) |
| Nicotine exposure score (12–19 y) | 2013–March 2020 | 85.4 (84.1–86.7) | 86.8 (84.6–88.9) | 83.3 (81.0–85.5) | 92.8 (90.5–95.1) | 88.0 (85.7–90.3) |
| Sleep health score (16–19 y) | 2013–March 2020 | 77.8 (76.0–79.6) | 72.5 (70.0–75.0) | 79.8 (77.1–82.5) | 77.9 (74.7–81.2) | 77.7 (75.1–80.4) |
| Health factors | | | | | | |
| BMI score (2–19 y) | 2013–March 2020 | 81.4 (80.0–82.8) | 78.9 (75.7–82.0) | 84.3 (82.5–86.0) | 89.3 (87.0–91.7) | 74.9 (72.6–77.2) |
| Blood lipids score (6–19 y) | 2013–March 2020 | 73.7 (72.6–74.8) | 77.3 (75.3–79.2) | 73.6 (71.8–75.4) | 69.9 (66.9–73.0) | 73.5 (71.6–75.4) |
| Blood glucose score (12–19 y) | 2013–March 2020 | 92.5 (91.7–93.2) | 89.3 (88.0–90.7) | 93.3 (92.0–94.5) | 93.0 (90.8–95.2) | 91.7 (90.2–93.2) |
| BP score (8–19 y) | 2013–March 2020 | 95.5 (95.0–96.0) | 94.2 (93.3–95.0) | 95.8 (95.1–96.3) | 96.1 (95.1–97.0) | 95.5 (94.6–96.3) |
| Overall score (16–19 y) | 2013–March 2020 | 73.6 (72.4–74.7) | 71.3 (68.8–73.8) | 74.1 (72.0–76.2) | 78.4 (75.7–81.1) | 72.7 (70.6–76.3) |
| Health behaviors | | ≥20 y of age† | | | | |
| Diet* score | 2013–2018 | 44.38 (42.6–46.1) | 31.4 (28.5–34.3) | 46.6 (44.4–48.8) | 53.1 (49.7–56.5) | 42.9 (40.9–44.9) |
| PA score | 2013–March 2020 | 49.23 (47.4–51.0) | 45.1 (42.7–47.6) | 51.0 (48.9–53.1) | 51.8 (48.3–55.3) | 42.4 (39.9–44.9) |
| Nicotine exposure score | 2013–March 2020 | 69.3 (68.0–70.5) | 64.0 (62.1–65.9) | 68.1 (66.3–69.9) | 85.4 (83.5–82.3) | 75.7 (73.8–77.6) |
| Sleep health score | 2013–March 2020 | 84.2 (83.6–84.8) | 75.6 (74.5–76.7) | 86.1 (85.4–86.9) | 86.3 (84.9–87.7) | 83.1 (81.9–84.3) |
| Health factors | | | | | | |
| BMI score | 2013–March 2020 | 57.2 (56.2–58.2) | 52.0 (50.5–53.5) | 58.9 (57.6–60.2) | 58.5 (57.0–60.1) | 50.9 (49.2–52.5) |
| Blood lipids score | 2013–March 2020 | 67.7 (66.8–68.6) | 73.7 (72.4–74.9) | 67.0 (65.9–68.1) | 66.9 (65.4–68.5) | 66.2 (64.4–68.0) |
| Blood glucose score | 2013–March 2020 | 76.4 (75.7–77.2) | 72.2 (71.3–73.2) | 77.8 (76.9–78.6) | 74.7 (72.9–76.5) | 73.2 (71.2–75.2) |
| BP score | 2013–March 2020 | 68.2 (67.3–69.0) | 60.6 (59.2–62.0) | 68.2 (67.1–69.4) | 70.7 (68.9–72.5) | 73.4 (71.8–75.0) |
| Overall score | 2013–March 2020 | 65.2 (64.2–66.1) | 59.7 (58.4–60.9) | 66.0 (64.8–67.2) | 69.6 (68.1–71.1) | 63.5 (62.2–64.8) |

Values are mean (95% CI). In March 2020, the COVID-19 (coronavirus disease 2019) pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.[104]

BMI indicates body mass index; BP, blood pressure; CVH, cardiovascular health; MA, Mexican American; NH, non-Hispanic; NHANES, National Health and Nutrition Examination Survey; and PA, physical activity.

*Scaled to 2000 kcal/d and in the context of appropriate energy balance and a Dietary Approaches to Stop Hypertension–type eating pattern. Dietary estimates were available only through data up to the 2017 to 2018 NHANES cycle at the time of this report.

†Standardized to the age distribution of the 2000 US standard population.

Dietary estimates were available only through data up to the 2017 to 2018 NHANES cycle at the time of this report.

Source: Unpublished American Heart Association tabulation using NHANES.[82]

**Table 2-3. Leading 20 Risk Factors of YLL and Death in the United States: Rank, Number, and Percentage Change, 1990 and 2019**

| Risk factors for disability | YLL rank (for total number) | | Total No. of YLLs, in thousands (95% UI) | | Percent change, 1990–2019 (95% UI) | | Corresponding total No. of deaths, in thousands (95% UI) | | Corresponding percent change, 1990–2019 (95% UI) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1990 | 2019 | 1990 | 2019 | Total No. of YLLs | Age-standardized YLL rate | 1990 | 2019 | Total No. of deaths | Age-standardized death rate |
| Smoking | 1 | 1 | 11 005.06 (10 692.42 to 11 351.22) | 10 371.03 (10 017.19 to 10 728.28) | −5.76% (−8.46% to −2.93%) | −46.43% (−47.91% to −44.85%) | 515.41 (496.77 to 537.03) | 527.74 (505.55 to 550.83) | 2.39% (−1.3% to 6.28%) | −42.21% (−44.18% to −40.15%) |
| High SBP | 2 | 2 | 8466.11 (7465.95 to 9424.27) | 7815.63 (6814.38 to 8821.87) | −7.68% (−13.09% to −2.58%) | −45.76% (−48.82% to −42.81%) | 503.63 (425.60 to 573.56) | 495.20 (407.47 to 574.65) | −1.67% (−9.73% to 6.05%) | −45.94% (−49.57% to −42.07%) |
| High BMI | 4 | 3 | 4994.23 (3131.76 to 6877.86) | 7778.57 (5416.09 to 9912.24) | 55.75% (41.31% to 80.47%) | −9.18% (−17.75% to 5.86%) | 232.16 (138.00 to 334.08) | 393.86 (257.61 to 528.44) | 69.65% (52.54% to 98.96%) | −5.82% (−15.3% to 10%) |
| High FPG | 5 | 4 | 4664.81 (3563.73 to 6006.04) | 7121.62 (5548.50 to 9006.14) | 52.67% (37.87% to 68%) | −12.25% (−20.59% to −3.79%) | 263.41 (193.27 to 355.67) | 439.38 (320.11 to 582.66) | 66.81% (48.24% to 85.48%) | −8.01% (−17.9% to 2.09%) |
| Drug use | 18 | 5 | 999.47 (899.54 to 1135.28) | 4265.41 (4080.78 to 4494.41) | 326.77% (277.64% to 372.57%) | 242.34% (202.34% to 280.43%) | 24.76 (22.26 to 27.73) | 104.74 (100.39 to 109.98) | 323.09% (280.5% to 364.71%) | 214.02% (181.7% to 245.57%) |
| Alcohol use | 6 | 6 | 2708.90 (2327.61 to 3129.89) | 3936.71 (3457.94 to 4524.58) | 45.33% (30.7% to 60.18%) | −5.97% (−14.74% to 2.75%) | 76.48 (61.08 to 93.37) | 136.66 (115.68 to 162.66) | 78.69% (54.74% to 108.25%) | 6.66% (−6.18% to 22.33%) |
| High LDL-C | 3 | 7 | 6291.91 (5210.65 to 7354.85) | 3863.72 (3077.21 to 4730.88) | −38.59% (−43.38% to −34.18%) | −63.6% (−66.17% to −61.13%) | 353.09 (267.44 to 443.65) | 226.34 (158.85 to 304.37) | −35.9% (−43.1% to −29.38%) | −64.86% (−68.02% to −61.77%) |
| Kidney dysfunction | 7 | 8 | 2138.32 (1781.84 to 2527.38) | 3159.52 (2795.42 to 3536.01) | 47.76% (37.73% to 60.92%) | −13.36% (−19.3% to −5.75%) | 138.81 (111.85 to 167.70) | 214.74 (182.32 to 248.84) | 54.71% (43.24% to 69.01%) | −15% (−20.89% to −6.95%) |
| Diet low in whole grains | 9 | 9 | 1897.21 (868.61 to 2445.35) | 1778.79 (855.23 to 2258.78) | −6.24% (−10% to 0.74%) | −44.83% (−47.05% to −40.69%) | 103.24 (46.57 to 133.79) | 102.25 (48.18 to 131.55) | −0.96% (−5.31% to 6.17%) | −45.32% (−47.42% to −41.37%) |
| Low temperature | 13 | 10 | 1320.06 (1079.50 to 1579.76) | 1734.12 (1488.09 to 1989.52) | 31.37% (21.84% to 42.8%) | −28.03% (−33.6% to −21.47%) | 92.53 (76.50 to 108.86) | 123.09 (104.13 to 141.28) | 33.02% (24.01% to 42.4%) | −28.1% (33.15% to 22.91%) |
| Diet low in legumes | 12 | 11 | 1471.67 (348.59 to 2464.41) | 1299.03 (337.88 to 2145.69) | −11.73% (−15.97% to 2.02%) | −48.26% (−50.62% to −39.91%) | 80.91 (20.30 to 134.49) | 76.84 (19.83 to 126.33) | −5.03% (−10.1% to 8.8%) | −48.05% (−50.45% to −41.09%) |
| Diet high in red meat | 16 | 12 | 1258.35 (677.77 to 1830.45) | 1268.70 (754.94 to 1787.30) | 0.82% (−7.68% to 16.14%) | −40.06% (−45.03% to −30.7%) | 59.84 (31.13 to 88.85) | 65.65 (37.01 to 94.39) | 9.71% (−0.52% to 29.65%) | −38.55% (−44.31% to −27.11%) |
| Diet high in *trans* fatty acids | 14 | 13 | 1311.91 (77.03 to 1776.96) | 1097.24 (55.44 to 1490.02) | −16.36% (−24.34% to −12.35%) | −50.97% (−55.84% to −48.6%) | 71.37 (4.33 to 97.34) | 64.39 (3.44 to 88.07) | −9.78% (−18.55% to −4.86%) | −50.56% (−55.32% to −48.06%) |
| Diet high in processed meat | 19 | 14 | 850.40 (283.64 to 1366.73) | 969.35 (405.97 to 1459.61) | 13.99% (−0.22% to 53.8%) | −32.69% (−41.36% to −9.36%) | 42.16 (13.90 to 69.60) | 50.90 (20.97 to 78.62) | 20.71% (5.93% to 59.18%) | −32.15% (−40.76% to −9.05%) |
| Ambient particulate matter pollution | 8 | 15 | 2001.60 (842.72 to 3490.50) | 931.95 (526.95 to 1361.42) | −53.44% (−76.57% to 3.52%) | −71.21% (−84.9% to −39.42%) | 95.26 (37.62 to 171.26) | 47.79 (26.06 to 71.53) | −49.84% (−75.93% to 18.1%) | −71.29% (−85.9% to −33.4%) |
| Diet high in sodium | 24 | 16 | 574.46 (36.43 to 1999.45) | 914.24 (61.08 to 2622.57) | 59.15% (25.57% to 270.02%) | −4.75% (−25.72% to 132.21%) | 31.62 (2.16 to 113.50) | 48.50 (3.26 to 151.35) | 53.38% (23.18% to 208.55%) | −13.04% (−30.53% to 82.94%) |
| LBW | 10 | 17 | 1512.98 (1436.65 to 1601.27) | 853.24 (778.57 to 935.91) | −43.61% (−49.31% to −37.44%) | −38.47% (−44.69% to −31.75%) | 17.04 (16.18 to 18.03) | 9.61 (8.77 to 10.54) | −43.62% (−49.32% to −37.46%) | −38.49% (−44.71% to −31.77%) |
| Short gestation | 11 | 18 | 1492.43 (1415.76 to 1577.76) | 830.26 (756.11 to 909.70) | −44.37% (−49.91% to −38.33%) | −39.3% (−45.36% to −32.72%) | 16.81 (15.94 to 17.77) | 9.35 (8.51 to 10.24) | −44.38% (−49.92% to −38.35%) | −39.32% (−45.37% to −32.74%) |

(*Continued*)

**Table 2-3. Continued**

| Risk factors for disability | YLL rank (for total number) | | Total No. of YLLs, in thousands (95% UI) | | Percent change, 1990–2019 (95% UI) | | Corresponding total No. of deaths, in thousands (95% UI) | | Corresponding percent change, 1990–2019 (95% UI) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1990 | 2019 | 1990 | 2019 | Total No. of YLLs | Age-standardized YLL rate | 1990 | 2019 | Total No. of deaths | Age-standardized death rate |
| Secondhand smoke | 17 | 19 | 1072.52 (858.49 to 1288.00) | 765.32 (597.81 to 943.60) | −28.64% (−35.48% to −21.24%) | −58.57% (−62.38% to −54.53%) | 44.43 (35.48 to 53.61) | 35.58 (27.27 to 44.12) | −19.92% (−28.44% to −10.64%) | −55.34% (−59.81% to −50.32%) |
| Diet low in fruits | 21 | 20 | 845.55 (505.63 to 1141.76) | 745.10 (463.85 to 1006.64) | −11.88% (−21.92% to 0.05%) | −47.98% (−53.6% to −41.37%) | 42.79 (25.00 to 57.89) | 40.17 (24.61 to 54.38) | 6.13% (−18.07% to 9.22%) | −47.6% (−53.99% to −39.31%) |

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

BMI indicates body mass index; FPG, fasting plasma glucose; GBD, Global Burden of Disease; LBW, low birth weight; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; UI, uncertainty interval; and YLL, year of life lost to premature mortality.

Source: Data derived from GBD Study 2019. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[105]

**Table 2-4. Leading 20 Causes of YLL and Death in the United States: Rank, Number, and Percent Change, 1990 and 2019**

| Diseases and injuries | YLL rank (for total number) | | Total No. of YLLs, in thousands (95% UI) | | Percent change, 1990–2019 (95% UI) | | Corresponding total No. of deaths, in thousands (95% UI) | | Corresponding percent change, 1990–2019 (95% UI) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1990 | 2019 | 1990 | 2019 | Total No. of YLLs | Age-standardized YLL rate | 1990 | 2019 | Total No. of deaths | Age-standardized death rate |
| IHD | 1 | 1 | 10 181.09 (9690.92 to 10 439.15) | 8651.61 (8081.02 to 9124.13) | −15.02% (−17.54% to −11.72%) | −50.89% (−52.28% to −48.96%) | 604.09 (558.11 to 627.32) | 557.65 (496.86 to 594.41) | −7.69% (−11.14% to −3.43%) | −49.86% (−51.39% to −47.6%) |
| Tracheal, bronchus, and lung cancer | 2 | 2 | 3559.62 (3479.49 to 3617.41) | 4124.65 (3950.45 to 4261.93) | 15.87% (11.75% to 19.93%) | −36.1% (−38.35% to −33.86%) | 156.26 (151.01 to 159.34) | 206.20 (193.72 to 214.28) | 31.96% (26.46% to 37.09%) | −26.83% (−29.74% to −24.01%) |
| Chronic obstructive pulmonary disease | 4 | 3 | 1592.74 (1505.38 to 1778.28) | 3100.42 (2620.31 to 3305.63) | 94.66% (63.07% to 109.95%) | 11.21% (−6.25% to 19.76%) | 90.48 (83.71 to 103.20) | 195.83 (161.22 to 212.29) | 116.42% (72.76% to 137.51%) | 21.67% (−2.03% to 33%) |
| Opioid use disorders | 46 | 4 | 219.00 (209.51 to 229.51) | 286.80 (2182.91 to 2418.61) | 944.2% (875.88% to 1027.46%) | 799.2% (738.44% to 878.48%) | 4.35 (4.18 to 4.55) | 47.34 (45.39 to 49.24) | 987.66% (922.91% to 1054.34%) | 795.34% (741.01% to 859.05%) |
| Colon and rectum cancer | 7 | 5 | 1291.48 (1249.20 to 1320.46) | 1640.65 (1574.85 to 1689.21) | 27.04% (23.7% to 30.48%) | −24.11% (−26.08% to −21.94%) | 65.58 (61.89 to 67.69) | 84.03 (77.99 to 87.52) | 28.12% (24.34% to 31.56%) | −26.31% (−28.25% to −24.39%) |
| Type 2 diabetes | 12 | 6 | 856.92 (809.02 to 882.74) | 1365.65 (1299.49 to 1422.98) | 59.37% (54.2% to 65.34%) | −7.31% (−10.46% to −3.84%) | 43.92 (40.93 to 45.55) | 73.41 (67.73 to 76.76) | 67.15% (61.31% to 72.93%) | −5.46% (−8.66% to 2.26%) |
| AD and other dementias | 15 | 7 | 743.80 (180.25 to 2011.60) | 139.08 (333.70 to 3431.38) | 80.03% (65.82% to 99.45%) | −3.65% (−10.86% to 5.5%) | 73.08 (18.40 to 194.71) | 143.92 (37.07 to 354.96) | 96.94% (80.52% to 119.01%) | −1.92% (−9.65% to 7.87%) |
| Motor vehicle road injuries | 3 | 8 | 1836.51 (1812.57 to 1864.76) | 1231.24 (1152.15 to 1272.09) | −32.96% (−37.75% to −30.48%) | −46.42% (−50.42% to −44.35%) | 35.67 (35.13 to 36.27) | 28.25 (26.71 to 29.14) | −20.82% (−25.88% to −18.17%) | −42.5% (−46.41% to −40.47%) |
| Breast cancer | 9 | 9 | 1199.58 (1165.78 to 1222.05) | 1212.43 (1157.03 to 1261.82) | 1.07% (−3% to 4.94%) | −40.05% (−42.49% to −37.71%) | 48.21 (45.76 to 49.51) | 55.02 (51.01 to 57.90) | 14.12% (9.23% to 18.83%) | −35.5% (−38.05% to −33.07%) |
| Lower respiratory infections | 8 | 10 | 1223.88 (1159.84 to 1261.53) | 1210.65 (1124.89 to 1262.59) | −1.08% (−4.06% to 1.99%) | −40.39% (−42.03% to −38.65%) | 72.72 (66.22 to 76.44) | 81.92 (72.24 to 87.40) | 12.66% (8.1% to 16.85%) | −38.93% (−40.75% to −36.94%) |
| Ischemic stroke | 6 | 11 | 1324.40 (1218.20 to 1381.45) | 1185.52 (1045.83 to 1295.90) | −10.49% (−15.56% to −3.94%) | −50.06% (−52.58% to −46.54%) | 103.35 (92.02 to 109.29) | 108.95 (92.44 to 120.30) | 5.42% (−1.45% to 14.3%) | −44.68% (−47.72% to −40.18%) |

(*Continued*)

**Table 2-4. Continued**

| Diseases and injuries | YLL rank (for total number) | | Total No. of YLLs, in thousands (95% UI) | | Percent change, 1990–2019 (95% UI) | | Corresponding total No. of deaths, in thousands (95% UI) | | Corresponding percent change, 1990–2019 (95% UI) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1990 | 2019 | 1990 | 2019 | Total No. of YLLs | Age-standardized YLL rate | 1990 | 2019 | Total No. of deaths | Age-standardized death rate |
| Pancreatic cancer | 17 | 12 | 587.36 (568.59 to 599.72) | 1134.93 (1078.47 to 1178.70) | 93.23% (85.27% to 100.27%) | 10.36% (5.85% to 14.28%) | 28.60 (27.10 to 29.43) | 57.49 (53.67 to 60.25) | 101.03% (92.1% to 109.18%) | 14.29% (9.49% to 18.74%) |
| ICH | 14 | 13 | 772.31 (741.63 to 799.80) | 1099.70 (1033.09 to 1188.13) | 42.39% (35.89% to 50.11%) | −16.7% (−20.47% to −12.21%) | 38.33 (35.84 to 39.86) | 59.73 (54.34 to 64.89) | 55.82% (47.69% to 66.31%) | −12.28% (−16.49% to −6.65%) |
| Self-harm by other specified means | 16 | 14 | 686.74 (629.95 to 767.19) | 961.37 (835.09 to 1004.91) | 39.99% (28.48% to 45.86%) | 12.77% (3.34% to 17.66%) | 14.65 (13.31 to 16.22) | 21.98 (19.00 to 23.04) | 50.1% (40.1% to 55.9%) | 12.88% (4.55% to 17.5%) |
| Hypertensive HD | 23 | 15 | 447.65 (373.87 to 469.58) | 957.73 (599.24 to 1027.23) | 113.95% (43.15% to 126.64%) | 29.98% (−15.61% to 38.05%) | 23.73 (20.11 to 25.47) | 52.96 (35.45 to 57.78) | 123.18% (58.64% to 136.08%) | 23.67% (−13.76% to 30.56%) |
| Self-harm by firearm | 13 | 16 | 853.20 (767.29 to 906.88) | 895.00 (844.35 to 1014.78) | 4.9% (1.11% to 13.45%) | −20.52% (−23.51% to −13.82%) | 19.32 (17.67 to 20.57) | 23.36 (22.13 to 26.18) | 20.95% (17.12% to 28.48%) | −16.01% (−18.8% to −10.1%) |
| Cirrhosis and other chronic liver diseases caused by hepatitis C | 24 | 17 | 434.18 (390.04 to 483.14) | 839.29 (746.47 to 938.91) | 93.3% (82.11% to 103.87%) | 19.63% (14.07% to 25.01%) | 14.46 (12.96 to 16.10) | 29.91 (26.55 to 33.43) | 106.84% (97.17% to 116.53%) | 23.07% (18.06% to 28.21%) |
| Endocrine, metabolic, blood, and immune disorders | 35 | 18 | 272.90 (226.89 to 362.60) | 772.39 (598.36 to 893.98) | 183.04% (139% to 197.28%) | 77.55% (62.97% to 84.21%) | 8.68 (7.45 to 12.18) | 34.54 (24.72 to 37.44) | 297.78% (180.95% to 332.08%) | 123.05% (67.99% to 138.77%) |
| Physical violence by firearm | 11 | 19 | 980.04 (963.97 to 993.74) | 735.86 (682.89 to 761.54) | −24.92% (−29.57% to −22.24%) | −34.98% (−39.02% to −32.65%) | 16.74 (16.47 to 16.96) | 13.00 (12.12 to 13.43) | −22.33% (−26.91% to −19.9%) | −35.1% (−39.01% to −32.96%) |
| Prostate cancer | 18 | 20 | 581.18 (403.13 to 650.19) | 712.79 (628.11 to 1037.53) | 22.65% (9.65% to 66.94%) | −29.34% (−36.77% to −4.07%) | 36.24 (25.66 to 40.65) | 48.32 (41.35 to 70.59) | 33.36% (19.07% to 78.37%) | −24.46% (−32.33% to 1.1%) |

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

AD indicates Alzheimer disease; GBD, Global Burden of Disease; HD, heart disease; ICH, intracerebral hemorrhage; IHD, ischemic heart disease; UI, uncertainty interval; and YLL, year of life lost to premature mortality.

Source: Data derived from GBD Study 2019. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[106]

**Table 2-5. Leading 20 Risk Factors for YLDs in the United States: Rank, Number, and Percentage Change, 1990 and 2019**

| Risk factors for disability | YLD rank (for total number) | | Total No. of YLDs, in thousands (95% UI) | | Percent change, 1990–2019 (95% UI) | |
|---|---|---|---|---|---|---|
| | 1990 | 2019 | 1990 | 2019 | Total No. of YLDs | Age-standardized YLD rate |
| High BMI | 2 | 1 | 2014.44 (1191.63 to 3041.53) | 4757.53 (3035.97 to 6728.53) | 136.17% (116.67% to 171.6%) | 44.45% (32.86% to 65.18%) |
| High FPG | 3 | 2 | 1473.97 (1043.23 to 1958.70) | 3705.54 (2636.55 to 4926.74) | 151.4% (140.32% to 165.13%) | 47.37% (40.86% to 54.89%) |
| Smoking | 1 | 3 | 2927.37 (2152.15 to 3726.22) | 3580.31 (2711.48 to 4421.59) | 22.3% (15.58% to 30.13%) | −25.75% (−29.66% to −21.37%) |
| Drug use | 5 | 4 | 1031.70 (712.04 to 1385.17) | 3009.85 (2080.84 to 4025.99) | 191.74% (158.71% to 224.78%) | 148.76% (118.72% to 178.48%) |
| High SBP | 6 | 5 | 884.49 (639.70 to 1142.32) | 1287.04 (929.96 to 1667.98) | 45.51% (35.52% to 55.15%) | −13.11% (−18.82% to −7.75%) |
| Alcohol use | 4 | 6 | 1102.64 (760.00 to 1520.68) | 1259.73 (879.63 to 1722.34) | 14.25% (4.96% to 25.06%) | −16.46% (−21.27% to −11.03%) |

(*Continued*)

**Table 2-5. Continued**

| Risk factors for disability | YLD rank (for total number) | | Total No. of YLDs, in thousands (95% UI) | | Percent change, 1990–2019 (95% UI) | |
|---|---|---|---|---|---|---|
| | 1990 | 2019 | 1990 | 2019 | Total No. of YLDs | Age-standardized YLD rate |
| Occupational ergonomic factors | 7 | 7 | 769.12 (531.07 to 1052.57) | 909.32 (640.04 to 1206.98) | 18.23% (8.01% to 30.5%) | −14.3% (−21.29% to −6.44%) |
| Low bone mineral density | 8 | 8 | 411.39 (289.23 to 569.28) | 782.17 (549.97 to 1077.01) | 90.13% (85.32% to 95.57%) | 6.66% (4.03% to 9.54%) |
| Kidney dysfunction | 9 | 9 | 399.32 (297.80 to 524.36) | 775.02 (582.79 to 1002.90) | 94.08% (83.38% to 105.14%) | 19.75% (14.04% to 25.57%) |
| Diet high in red meat | 14 | 10 | 230.60 (158.70 to 317.03) | 485.27 (322.95 to 687.22) | 110.44% (91.62% to 126.96%) | 25.76% (15.64% to 34.5%) |
| Diet high in processed meat | 17 | 11 | 172.86 (104.84 to 255.78) | 471.02 (287.52 to 692.65) | 172.5% (148.34% to 205.98%) | 58.21% (44.23% to 76.99%) |
| Short gestation | 10 | 12 | 371.84 (284.50 to 469.16) | 468.88 (365.55 to 581.92) | 26.1% (16.16% to 36.48%) | 4.21% (−3.87% to 12.88%) |
| LBW | 11 | 13 | 371.84 (284.50 to 469.16) | 468.88 (365.55 to 581.92) | 26.1% (16.16% to 36.48%) | 4.21% (−3.87% to 12.88%) |
| High LDL-C | 13 | 14 | 297.03 (185.95 to 446.89) | 303.55 (190.21 to 472.68) | 2.19% (−8.4% to 12.75%) | −37.09% (−43.62% to −30.57%) |
| Ambient particulate matter pollution | 12 | 15 | 308.85 (111.01 to 556.89) | 291.90 (139.49 to 500.08) | −5.49% (−55.19% to 120.72%) | −44.15% (−73.38% to 30.06%) |
| Bullying victimization | 22 | 16 | 132.13 (29.00 to 322.15) | 268.38 (58.82 to 613.61) | 103.12% (81.47% to 133.27%) | 81.82% (61.43% to 105.89%) |
| Occupational injuries | 15 | 17 | 196.96 (134.56 to 279.88) | 265.30 (176.61 to 390.65) | 34.7% (5.8% to 73.94%) | 0.01% (−21.72% to 29.35%) |
| Childhood sexual abuse | 19 | 18 | 164.32 (72.88 to 313.28) | 251.15 (121.67 to 443.14) | 52.84% (27.67% to 94.68%) | 22.66% (3.32% to 54.56%) |
| Intimate partner violence | 20 | 19 | 161.94 (26.50 to 326.56) | 250.12 (31.52 to 514.75) | 54.45% (27.68% to 63.76%) | 23.3% (−4.55% to 30.31%) |
| Secondhand smoke | 16 | 20 | 173.12 (106.23 to 245.30) | 246.72 (146.07 to 362.41) | 42.51% (23% to 59.97%) | −16.37% (−27.46% to −6.05%) |

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

BMI indicates body mass index; FPG, fasting plasma glucose; GBD, Global Burden of Disease; LDL-C, low-density lipoprotein cholesterol; LBW, low birth weight; SBP, systolic blood pressure; UI, uncertainty interval; and YLD, year of life lived with disability or injury.

Source: Data derived from GBD Study 2019. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[105]

**Table 2-6. Leading 20 Causes for YLDs in the United States: Rank, Number, and Percent Change, 1990 and 2019**

| Diseases and injuries | YLD rank (for total number) | | Total No. of YLDs, in thousands (95% UI) | | Percent change, 1990–2019 (95% UI) | |
|---|---|---|---|---|---|---|
| | 1990 | 2019 | 1990 | 2019 | Total No. of YLDs | Age-standardized YLD rate |
| Low back pain | 1 | 1 | 4504.86 (3168.68 to 6039.64) | 5697.15 (4114.14 to 7474.69) | 26.47% (18.72% to 34.96%) | −12.46% (−17.42% to −7.02%) |
| Other musculoskeletal disorders | 2 | 2 | 1731.90 (1200.59 to 2420.19) | 3530.50 (2522.22 to 4747.29) | 103.85% (83.83% to 126.23%) | 44.17% (30.42% to 59.6%) |
| Type 2 diabetes | 9 | 3 | 1030.39 (715.25 to 1387.82) | 2761.76 (1939.08 to 3738.03) | 168.03% (153.55% to 185.2%) | 55.84% (47.58% to 65.14%) |
| Opioid use disorders | 16 | 4 | 554.70 (366.80 to 787.88) | 2489.58 (1684.54 to 3394.11) | 348.82% (308.52% to 396.89%) | 288.67% (253.85% to 332.48%) |
| Major depressive disorder | 4 | 5 | 1341.83 (930.71 to 1837.66) | 2242.30 (1552.73 to 3056.52) | 67.11% (62.83% to 72.26%) | 33.07% (29.58% to 36.62%) |
| Age-related and other hearing loss | 5 | 6 | 1340.58 (932.94 to 1865.97) | 2187.37 (1524.78 to 3048.08) | 63.17% (58.93% to 67.46%) | −1.4% (−3.46% to 0.7%) |
| Migraine | 3 | 7 | 1671.80 (241.76 to 3778.40) | 2078.81 (333.85 to 4660.27) | 24.35% (18.96% to 37.7%) | −2.61% (−5.89% to 1.17%) |

(*Continued*)

**Table 2-6. Continued**

| Diseases and injuries | YLD rank (for total number) | | Total No. of YLDs, in thousands (95% UI) | | Percent change, 1990–2019 (95% UI) | |
|---|---|---|---|---|---|---|
| | 1990 | 2019 | 1990 | 2019 | Total No. of YLDs | Age-standardized YLD rate |
| Neck pain | 7 | 8 | 1201.62 (792.53 to 1709.09) | 2043.52 (1392.66 to 2886.40) | 70.06% (55.99% to 82.82%) | 18.41% (9.89% to 27.58%) |
| Chronic obstructive pulmonary disease | 8 | 9 | 1111.88 (924.35 to 1262.67) | 1921.11 (1606.46 to 2147.99) | 72.78% (66.73% to 79.98%) | −0.62% (−3.94% to 3.51%) |
| Anxiety disorders | 6 | 10 | 1331.27 (932.18 to 1816.40) | 1872.34 (1314.62 to 2530.62) | 40.64% (37% to 44.94%) | 8.41% (6.85% to 10.06%) |
| Falls | 10 | 11 | 971.06 (690.51 to 1336.57) | 1594.64 (1136.33 to 2190.22) | 64.22% (57.72% to 71.62%) | 0.07% (−2.87% to 3.35%) |
| Asthma | 11 | 12 | 904.55 (587.17 to 1330.72) | 1296.66 (857.41 to 1849.88) | 43.35% (31.26% to 56.15%) | 11.01% (1.8% to 21.71%) |
| Schizophrenia | 13 | 13 | 767.43 (562.88 to 970.69) | 993.34 (732.79 to 1243.07) | 29.44% (25.28% to 34.45%) | −1.22% (−3.13% to 0.79%) |
| Osteoarthritis in the hand | 18 | 14 | 486.85 (249.46 to 1017.65) | 930.08 (466.70 to 1964.92) | 91.04% (74.27% to 108.64%) | 7.82% (−0.72% to 17.23%) |
| Ischemic stroke | 15 | 15 | 559.93 (399.70 to 724.14) | 870.59 (628.48 to 1114.77) | 55.48% (47.94% to 63.39%) | −5.16% (−9.35% to −0.14%) |
| Alcohol use disorders | 12 | 16 | 785.98 (523.84 to 1106.57) | 784.98 (538.64 to 1092.19) | −0.13% (−5.58% to 5.53%) | −21.58% (−24.39% to −18.84%) |
| Osteoarthritis in the knee | 19 | 17 | 450.96 (227.51 to 906.41) | 759.11 (380.59 to 1527.66) | 68.33% (62.62% to 75.07%) | −2.68% (−6.62% to 1.66%) |
| Endocrine, metabolic, blood, and immune disorders | 14 | 18 | 629.50 (428.40 to 868.36) | 726.71 (500.66 to 990.69) | 15.44% (6.81% to 23.95%) | −23.84% (−29.21% to −18.2%) |
| AD and other dementias | 22 | 19 | 391.77 (276.91 to 523.54) | 687.80 (497.57 to 889.29) | 75.56% (59.97% to 94.86%) | −3.82% (−12.02% to 6.33%) |
| Edentulism | 17 | 20 | 491.91 (304.02 to 742.02) | 668.95 (424.02 to 985.05) | 35.99% (29.73% to 43.73%) | −17.13% (−22.52% to −10.71%) |

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

AD indicates Alzheimer disease; GBD, Global Burden of Disease; UI, uncertainty interval; and YLD, year of life lived with disability or injury.

Source: Data derived from GBD Study 2019. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[106]

**Table 2-7. Leading 20 Global Risk Factors of YLL and Death: Rank, Number, and Percentage Change, 1990 and 2019**

| Risk factors for disability | YLL rank (for total number) | | Total No. of YLLs, in thousands (95% UI) | | Percent change, 1990–2019 (95% UI) | | Corresponding total No. of deaths, in thousands (95% UI) | | Corresponding percent change, 1990–2019 (95% UI) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1990 | 2019 | 1990 | 2019 | Total No. of YLLs | Age-standardized YLL rate | 1990 | 2019 | Total No. of deaths | Age-standardized death rate |
| High SBP | 6 | 1 | 143 603.62 (129 333.91 to 157 734.25) | 214 260.28 (191 165.39 to 236 748.61) | 49.2% (38.51% to 59.21%) | −28.96% (−33.93% to −24.37%) | 6787.71 (6072.71 to 7495.92) | 10 845.60 (9514.14 to 12 130.85) | 59.78% 49.19% to 69.4%) | −29.81% (−34.25% to −25.76%) |
| Smoking | 7 | 2 | 140 203.56 (132 792.85 to 147 036.56) | 168 238.03 (155 801.16 to 180 393.21) | 20% (10.41% to 30.71%) | −41.31% (−45.98% to −36.16%) | 5868.49 (5578.08 to 6152.89) | 7693.37 (7158.45 to 8200.59) | 31.1% (21.21% to 42.07%) | −38.67% (−43.11% to −33.68%) |
| LBW | 2 | 3 | 269 478.56 (250 822.80 to 288 996.54) | 151 317.48 (128 528.30 to 179 613.60) | −43.85% (−52.35% to −33.52%) | −43.1% (−51.71% to −32.64%) | 3033.43 (2823.41 to 3253.23) | 1703.12 (1446.63 to 2021.58) | −43.85% (−52.35% to −33.53%) | −43.11% (−51.72% to −32.65%) |
| Short gestation | 3 | 4 | 221 314.76 (206 273.76 to 238 540.80) | 128 741.23 (109 481.34 to 153 683.78) | −41.83% (−50.32% to −30.76%) | −41.05% (−49.66% to −29.84%) | 2491.34 (2321.98 to 2685.26) | 1449.04 (1232.27 to 1729.80) | −41.84% (−50.33% to −30.77%) | −41.06% (−49.67% to −29.85%) |

(*Continued*)

**Table 2-7. Continued**

| Risk factors for disability | YLL rank (for total number) | | Total No. of YLLs, in thousands (95% UI) | | Percent change, 1990–2019 (95% UI) | | Corresponding total No. of deaths, in thousands (95% UI) | | Corresponding percent change, 1990–2019 (95% UI) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1990 | 2019 | 1990 | 2019 | Total No. of YLLs | Age-standardized YLL rate | 1990 | 2019 | Total No. of deaths | Age-standardized death rate |
| High FPG | 14 | 5 | 61 627.96 (51 459.07 to 74 728.01) | 126 654.90 (104 234.74 to 153 148.03) | 105.52% (91.63% to 119.7%) | −1.5% (−7.92% to 5.66%) | 2910.09 (2340.62 to 3753.67) | 6501.40 (5110.28 to 8363.05) | 123.41% (108.53% to 138.04%) | −1.46% (−7.48% to 5.12%) |
| High BMI | 16 | 6 | 54 375.58 (30 163.43 to 84 361.01) | 119 383.76 (79 596.11 to 163 875.52) | 119.55% (88.91% to 166.91%) | 8.27% (−6.61% to 31.18%) | 2198.13 (1205.50 to 3432.16) | 5019.36 (3223.36 to 7110.74) | 128.35% (101.34% to 170.06%) | 4.93% (−7.26% to 24.58%) |
| Ambient particulate matter pollution | 13 | 7 | 66 492.55 (44 569.97 to 94 108.79) | 104 895.28 (84 911.25 to 123 445.01) | 57.75% (20.29% to 113.82%) | −4.23% (−24.76% to 26.13%) | 2047.17 (1454.74 to 2739.85) | 4140.97 (3454.41 to 4800.29) | 102.28% (60.27% to 160.61%) | −0.92% (−19.85% to 26.25%) |
| High LDL-C | 12 | 8 | 66 683.88 (56 074.15 to 79 392.34) | 92 904.81 (75 590.22 to 111 436.78) | 39.32% (28.6% to 48.91%) | −33.26% (−37.98% to −28.66%) | 3002.61 (2350.83 to 3761.88) | 4396.98 (3301.26 to 5651.79) | 46.44% (35.21% to 55.63%) | −36.74% (−40.61% to −33.09%) |
| Household air pollution from solid fuels | 4 | 9 | 200 169.50 (154 731.29 to 248 560.54) | 83 565.87 (60 754.11 to 108 481.62) | −58.25% (−66.65% to −48.52%) | −69.1% (−74.78% to −62.42%) | 4358.21 (3331.29 to 5398.69) | 2313.99 (1631.34 to 3118.14) | −46.91% (−58.07% to −34.49%) | −69.88% (−75.85% to −63.27%) |
| Child wasting | 1 | 10 | 292 012.74 (241 855.36 to 351 715.87) | 79 187.22 (61 262.34 to 100 812.43) | −72.88% (−78.47% to −66.32%) | −73.89% (−79.28% to −67.54%) | 3430.42 (2851.24 to 4125.93) | 993.05 (786.46 to 1245.24) | −71.05% (−76.85% to −64.32%) | −73.05% (−78.35% to −66.7%) |
| Alcohol use | 15 | 11 | 55 971.37 (49 934.31 to 62 781.18) | 75 813.95 (66 966.44 to 85 498.40) | 35.45% (23.85% to 47.91%) | −25.69% (−32.08% to −18.91%) | 1639.87 (1442.38 to 1845.20) | 2441.97 (2136.99 to 2784.90) | 48.91% (35.99% to 63.1%) | −23.77% (−30.55% to −16.4%) |
| Kidney dysfunction | 19 | 12 | 37 087.06 (32 724.00 to 41 606.93) | 65 204.46 (57 219.63 to 73 512.12) | 75.81% (64.57% to 87.42%) | −11.26% (−17.07% to −5.57%) | 1571.72 (1344.42 to 1805.60) | 3161.55 (2723.36 to 3623.81) | 101.15% (88.45% to 112.88%) | −10.02% (−15.49% to −4.64%) |
| Unsafe water source | 5 | 13 | 153 905.20 (115 315.56 to 190 197.92) | 57 641.09 (41 786.87 to 75 887.40) | −62.55% (−71.19% to −49.83%) | −68.27% (−75.24% to −57.55%) | 2442.07 (1764.95 to 3147.03) | 1230.15 (817.82 to 1788.90) | −49.63% (−61.95% to −29.85%) | −65.76% (−73.6% to −53.37%) |
| Unsafe sex | 25 | 14 | 18 492.16 (14 813.00 to 23 832.65) | 41 999.23 (37 398.24 to 49 078.72) | 127.12% (100.78% to 162.48%) | 35.87% (21.91% to 54.45%) | 429.99 (356.20 to 533.21) | 984.37 (904.99 to 1106.17) | 128.93% (102.2% to 164.15%) | 27.64% (13.89% to 44.6%) |
| Diet high in sodium | 20 | 15 | 31 285.63 (10 435.19 to 63 583.27) | 40 722.69 (11 550.13 to 86 326.74) | 30.16% (−3.03% to 47.85%) | −36.45% (−52.02% to −28.15%) | 1320.34 (412.33 to 2796.87) | 885.36 (476.84 to 4194.71) | 42.79% (4.76% to 61.05%) | −34.18% (−50.81% to −26.58%) |
| Diet low in whole grains | 22 | 16 | 26 467.42 (12 815.63 to 33 041.82) | 38 954.84 (19 130.31 to 49 094.51) | 47.18% (37.22% to 57.73%) | −28.99% (−33.76% to −24.05%) | 1178.22 (579.63 to 1474.66) | 1844.84 (921.29 to 2338.61) | 56.58% (47.07% to 65.85%) | −31.16% (−35.14% to −27.26%) |
| Unsafe sanitation | 9 | 17 | 115 547.43 (92 118.35 to 138 980.27) | 37 183.90 (29 008.07 to 48 393.08) | −67.82% (−75.33% to −56.89%) | −72.65% (−78.73% to −63.04%) | 1836.46 (1390.57 to 2325.10) | 756.58 (542.45 to 1095.44) | −58.8% (−68.54% to −43.12%) | −71.89% (−78.23% to −62.13%) |
| No access to handwashing facility | 10 | 18 | 80 929.22 (58 183.31 to 102 881.65) | 32 224.40 (22 228.24 to 42 981.39) | −60.18% (−67.34% to −51.09%) | −65.26% (−71.61% to −57.2%) | 1200.09 (854.11 to 1553.29) | 627.92 (427.17 to 846.29) | −47.68% (−56.38% to −36.7%) | −62.55% (−68.93% to −54.77%) |
| Secondhand smoke | 18 | 19 | 44 029.71 (31 252.42 to 57 353.06) | 31 489.25 (24 218.79 to 38 792.35) | −28.48% (−39.18% to −15.29%) | −54.89% (−60.57% to −48.97%) | 1161.96 (878.27 to 1431.85) | 1304.32 (1006.96 to 1605.39) | 12.25% (1.01% to 25.04%) | −42.45% (−47.47% to −36.76%) |
| Low temperature | 21 | 20 | 26 827.37 (20 973.96 to 33 .52) | 25 954.68 (21 667.68 to 30 902.49) | −3.25% (−18.13% to 13.86%) | −51.56% (−57.31% to −45.99%) | 1276.64 (1092.81 to 1461.24) | 1652.98 (1413.03 to 1913.43) | 29.48% (18.11% to 41.67%) | −43.63% (−47.8% to −38.92%) |

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

BMI indicates body mass index; FPG, fasting plasma glucose; GBD, Global Burden of Disease; LBW, low birth weight; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; UI, uncertainty interval; and YLL, year of life lost because of premature mortality.

Source: Data derived from GBD Study 2019. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[105]

**Table 2-8. Leading 20 Global Causes of YLL and Death: Rank, Number, and Percentage Change, 1990 and 2019**

| Diseases and injuries | YLL rank (for total number) | | Total No. of YLLs, in thousands (95% UI) | | Percent change, 1990–2019 (95% UI) | | Corresponding total No. of deaths, in thousands (95% UI) | | Corresponding percent change, 1990–2019 (95% UI) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1990 | 2019 | 1990 | 2019 | Total No. of YLLs | Age-standardized YLL rate | 1990 | 2019 | Total No. of deaths | Age-standardized death rate |
| IHD | 3 | 1 | 118 399.43 (113 795.23 to 122 787.19) | 176 634.92 (165 028.83 to 188 453.38) | 49.19% (38.17% to 59.29%) | −29.14% (−34.13% to −24.56%) | 5695.89 (5405.19 to 5895.40) | 9137.79 (8395.68 to 9743.55) | 60.43% (50.23% to 69.14%) | −30.8% (−34.83% to −27.17%) |
| Lower respiratory infections | 1 | 2 | 223 807.88 (198 291.93 to 258 361.55) | 96 536.65 (84 197.05 to 112 404.97) | −56.87% (−64.43% to −47.7%) | −62.66% (−69.13% to −55.03%) | 3320.01 (3018.49 to 3715.06) | 2493.20 (2268.18 to 2736.18) | −24.9% (−34.42% to −15.39%) | −48.54% (−53.95% to −42.93%) |
| Diarrheal diseases | 2 | 3 | 182 456.67 (146 519.78 to 217 965.17) | 69 887.49 (54 617.33 to 92 161.23) | −61.7% (−70.34% to −49.12%) | −67.6% (−74.63% to −56.89%) | 2896.27 (2222.66 to 3644.59) | 1534.44 (1088.68 to 2219.10) | −47.02% (−59.64% to −27.06%) | −64.05% (−72.05% to −51.35%) |
| ICH | 9 | 4 | 52 648.78 (48 739.14 to 57 507.05) | 65 306.22 (60 073.84 to 70 392.27) | 24.04% (10.38% to 35.4%) | −37.37% (−44.17% to −31.5%) | 2099.76 (1932.53 to 2328.41) | 2886.20 (2644.48 to 3099.35) | 37.45% (21.73% to 50.92%) | −35.61% (−42.76% to −29.23%) |
| Neonatal PTB | 4 | 5 | 112 709.17 (103 574.46 to 122 915.10) | 58 942.91 (49 829.35 to 70 084.83) | −47.7% (−56.13% to −37.42%) | −47.02% (−55.56% to −36.61%) | 1269.04 (1166.14 to 1383.98) | 663.52 (560.96 to 788.95) | −47.71% (−56.14% to −37.44%) | −47.04% (−55.57% to −36.63%) |
| Chronic obstructive pulmonary disease | 11 | 6 | 48 769.20 (40 770.89 to 52 860.94) | 54 594.90 (48 711.47 to 59 513.37) | 11.95% (−0.47% to 35.12%) | −46.81% (−52.61% to −36.11%) | 2520.22 (2118.06 to 2719.39) | 3280.64 (2902.85 to 3572.37) | 30.17% (15.74% to 55.05%) | −41.74% (−48.03% to −31.07%) |
| Neonatal encephalopathy caused by birth asphyxia and trauma | 6 | 7 | 71 832.72 (64 553.03 to 80 228.20) | 50 368.25 (42 242.80 to 59 745.92) | −29.88% (−41.7% to −15.68%) | −28.91% (−40.9% to −14.52%) | 808.68 (726.80 to 903.20) | 566.98 (475.54 to 672.55) | −29.89% (−41.71% to −15.69%) | −28.92% (−40.91% to −14.54%) |
| Ischemic stroke | 13 | 8 | 34 004.54 (31 954.95 to 37 258.43) | 50 349.74 (46 232.45 to 54 066.67) | 48.07% (32.31% to 61.3%) | −33.35% (−40% to −27.56%) | 2049.67 (1900.02 to 2234.21) | 3293.40 (2973.54 to 3536.08) | 60.68% (45.83% to 74.65%) | −33.64% (−39.16% to −28.15%) |
| Tracheal, bronchus, and lung cancer | 19 | 9 | 26 859.81 (25 598.42 to 28 199.92) | 45 313.75 (41 866.20 to 48 831.01) | 68.7% (52.68% to 85.03%) | −16.34% (−24.19% to −8.38%) | 1065.14 (1019.22 to 1117.18) | 2042.64 (1879.24 to 2193.27) | 91.77% (74.52% to 108.97%) | −7.77% (−15.93% to 0.23%) |
| Malaria | 8 | 10 | 63 480.60 (34 802.94 to 103 091.05) | 43 824.70 (21 055.36 to 77 962.79) | −30.96% (−58.84% to 6.4%) | −39.03% (−63.65% to −6.42%) | 840.55 (463.32 to 1356.07) | 643.38 (301.60 to 1153.66) | −23.46% (−54.89% to 18.46%) | −37.93% (−63.46% to −4.52%) |
| Drug-susceptible tuberculosis | 5 | 11 | 74 658.58 (68 441.13 to 81 346.25) | 38 431.33 (33 206.79 to 43 219.46) | −48.52% (−55.92% to −40.77%) | −67.54% (−72.12% to −62.69%) | 1760.71 (610.86 to 1908.32) | 1061.29 (924.21 to 1186.12) | −39.72% (−48.03% to −30.36%) | −66.82% (−71.34% to −61.52%) |
| Other neonatal disorders | 12 | 12 | 47 950.24 (40 831.64 to 57 251.83) | 33 099.91 (27 646.20 to 40 129.55) | −30.97% (−48% to −11.34%) | −30.12% (−47.35% to −10.26%) | 539.95 (459.81 to 644.56) | 372.68 (311.26 to 451.84) | −30.98% (−48% to −11.37%) | −30.13% (−47.36% to −10.29%) |
| HIV/AIDS resulting in other diseases | 32 | 13 | 12 728.09 (9716.63 to 17 727.71) | 32 470.01 (26 796.66 to 40 802.58) | 155.11% (119.22% to 204.68%) | 77.01% (51.97% to 111.74%) | 216.91 (162.89 to 308.68) | 646.76 (551.85 to 780.47) | 198.17% (147.74% to 269.45%) | 94.13% (61.07% to 141.2%) |
| Type 2 diabetes | 28 | 14 | 13 851.47 (13 104.90 to 14 647.61) | 31 149.12 (29 302.02 to 33 148.25) | 124.88% (110.14% to 141.3%) | 9.11% (2.06% to 16.65%) | 606.41 (573.07 to 637.51) | 1472.93 (1371.94 to 1565.86) | 142.9% (128.32% to 158.37%) | 10.77% (4.42% to 17.44%) |
| Self-harm by other specified means | 15 | 15 | 32 879.52 (29 065.89 to 35 287.35) | 30 986.82 (27 870.17 to 34 246.63) | −5.76% (−14.84% to 4.31%) | −38.8% (−44.56% to −32.43%) | 687.85 (607.61 to 736.36) | 706.33 (633.90 to 777.33) | 2.69% (−6.38% to 13.66%) | −38.83% (−43.96% to −32.27%) |
| Colon and rectum cancer | 34 | 16 | 12 013.14 (11 481.93 to 12 503.78) | 23 218.75 (21 662.64 to 24 591.16) | 93.28% (79.51% to 106.26%) | −5.29% (−11.8% to 0.81%) | 518.13 (493.68 to 537.88) | 1085.80 (1002.80 to 1149.68) | 109.56% (96.2% to 121.74%) | −4.37% (−10.03% to 0.93%) |

(*Continued*)

**Table 2-8. Continued**

| Diseases and injuries | YLL rank (for total number) | | Total No. of YLLs, in thousands (95% UI) | | Percent change, 1990–2019 (95% UI) | | Corresponding total No. of deaths, in thousands (95% UI) | | Corresponding percent change, 1990–2019 (95% UI) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1990 | 2019 | 1990 | 2019 | Total No. of YLLs | Age-standardized YLL rate | 1990 | 2019 | Total No. of deaths | Age-standardized death rate |
| Motor vehicle road injuries | 21 | 17 | 22 260.33 (19 219.44 to 25 401.32) | 21 982.25 (19 334.80 to 24 633.49) | −1.25% (−14.6% to 15.23%) | −30.61% (−39.82% to −19.51%) | 399.99 (349.88 to 452.26) | 448.73 (396.67 to 500.41) | 12.19% (−2.49% to 28.58%) | −27.7% (−37.11% to −17.51%) |
| Stomach cancer | 24 | 18 | 20 241.69 (19 030.22 to 21 513.16) | 21 872.43 (19 972.71 to 23 712.52) | 8.06% (−2.52% to 19.94%) | −45.85% (−51.1% to −39.99%) | 788.32 (742.79 to 834.00) | 957.19 (870.95 to 1034.65) | 21.42% (10.17% to 33.59%) | −41.98% (−47.18% to −36.33%) |
| Neonatal sepsis and other neonatal infections | 20 | 19 | 23 105.79 (18 521.37 to 26 599.32) | 20 118.04 (16 896.71 to 24 474.48) | −12.93% (−29.92% to 11.86%) | −11.91% (−29.12% to 13.14%) | 260.15 (208.54 to 299.46) | 226.52 (190.25 to 275.55) | −12.93% (−29.93% to 11.86%) | −11.91% (−29.12% to 13.15%) |
| Hypertensive HD | 31 | 20 | 13 303.40 (10 669.61 to 14 984.15) | 19 991.58 (14 951.10 to 22 179.67) | 50.27% (31.09% to 74.64%) | −28.13% (−38.1% to −17.04%) | 654.91 (530.57 to 732.73) | 1156.73 (859.83 to 1278.56) | 76.63% (49.7% to 103.4%) | −21.49% (−35.18% to −10.13%) |

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Disease; HD, heart disease; ICH, intracerebral hemorrhage; IHD, ischemic heart disease; PTB, preterm birth; UI, uncertainty interval; and YLL, year of life lost to premature mortality.

Source: Data derived from GBD Study 2019. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[106]

**Table 2-9. Leading 20 Global Risk Factors for YLDs: Rank, Number, and Percentage Change, 1990 and 2019**

| Risk factors for disability | YLD rank (for total number) | | Total No. of YLDs, in thousands (95% UI) | | Percent change, 1990–2019 (95% UI) | |
|---|---|---|---|---|---|---|
| | 1990 | 2019 | 1990 | 2019 | Total No. of YLDs | Age-standardized YLD rate |
| High FPG | 3 | 1 | 15 581.99 (11 024.37 to 20 775.85) | 45 413.83 (31 849.57 to 60 894.87) | 191.45% (186.87% to 196.13%) | 44.07% (41.68% to 46.29%) |
| High BMI | 4 | 2 | 12 907.42 (6901.43 to 20 969.73) | 40 881.60 (24 508.83 to 60 876.50) | 216.73% (178.46% to 276.78%) | 60.16% (41.28% to 90.24%) |
| Smoking | 2 | 3 | 20 484.09 (15 154.19 to 26 177.63) | 31 556.71 (23 686.35 to 40 009.32) | 54.05% (49.57% to 59.1%) | −22.88% (−24.83% to −20.74%) |
| Iron deficiency | 1 | 4 | 25 379.25 (16 986.41 to 36 524.20) | 28 798.47 (19 425.22 to 41 491.77) | 13.47% (10.15% to 16.89%) | −16.67% (−19.02% to −14.23%) |
| High SBP | 7 | 5 | 10 128.23 (7295.78 to 13 093.83) | 21 164.35 (15 195.78 to 27 235.49) | 108.96% (102.17% to 116.39%) | 0.98% (−2.31% to 4.4%) |
| Alcohol use | 5 | 6 | 11 836.52 (8147.05 to 16 305.10) | 17 182.28 (12 000.25 to 23 497.81) | 45.16% (39.58% to 51.25%) | −13.47% (−15.96% to −10.79%) |
| Occupational ergonomic factors | 6 | 7 | 11 784.36 (8098.99 to 15 893.42) | 15 310.68 (10 544.90 to 20 762.41) | 29.92% (24.65% to 34.57%) | −24.61% (−26.93% to −22.45%) |
| Ambient particulate matter pollution | 17 | 8 | 3985.80 (2637.74 to 5634.02) | 13 320.10 (9643.12 to 17 166.65) | 234.19% (172.63% to 322.4%) | 64.91% (34.85% to 107.76%) |
| Drug use | 9 | 9 | 7479.41 (5163.69 to 10 042.08) | 12 664.94 (8804.75 to 16 725.98) | 69.33% (60.93% to 78.15%) | 14.49% (9.59% to 19.37%) |
| Kidney dysfunction | 14 | 10 | 5003.27 (3651.06 to 6508.03) | 11 282.48 (8232.55 to 14 676.40) | 125.5% (118.26% to 132.74%) | 20.24% (16.89% to 23.23%) |
| Short gestation | 12 | 11 | 5054.73 (3854.95 to 6433.30) | 9673.88 (7598.43 to 12 021.19) | 91.38% (75.26% to 106.94%) | 43.44% (31.94% to 54.79%) |
| LBW | 13 | 12 | 5054.73 (3854.95 to 6433.30) | 9673.88 (7598.43 to 12 021.19) | 91.38% (75.26% to 106.94%) | 43.44% (31.94% to 54.79%) |
| Low bone mineral density | 16 | 13 | 4082.06 (2923.34 to 5511.96) | 8620.52 (6115.78 to 11 640.10) | 111.18% (108.01% to 114.56%) | −1.7% (−2.77% to −0.66%) |
| Household air pollution from solid fuels | 8 | 14 | 8277.99 (5837.95 to 11 127.29) | 7908.60 (5254.80 to 11 299.35) | −4.46% (−20.63% to 15.04%) | −52.14% (−60.18% to −42.55%) |

(*Continued*)

**Table 2-9. Continued**

| Risk factors for disability | YLD rank (for total number) | | Total No. of YLDs, in thousands (95% UI) | | Percent change, 1990–2019 (95% UI) | |
|---|---|---|---|---|---|---|
| | 1990 | 2019 | 1990 | 2019 | Total No. of YLDs | Age-standardized YLD rate |
| Unsafe water source | 11 | 15 | 6054.63 (3781.50 to 8815.37) | 7455.38 (4530.39 to 10 914.15) | 23.14% (16.02% to 29.05%) | −11.82% (−16.58% to −8.1%) |
| Occupational noise | 18 | 16 | 3933.44 (2688.10 to 5599.97) | 7001.45 (4760.56 to 10 059.34) | 78% (71.39% to 83.61%) | −1.71% (−4.07% to 0.35%) |
| Occupational injuries | 10 | 17 | 6779.60 (4833.81 to 9123.27) | 6842.83 (4831.64 to 9300.85) | 0.93% (−10.59% to 13.14%) | −39.26% (−46.08% to −31.85%) |
| High LDL-C | 22 | 18 | 3035.02 (1990.11 to 4342.73) | 5713.21 (3677.82 to 8268.24) | 88.24% (82.75% to 94.36%) | −7.77% (−9.68% to −6.05%) |
| Secondhand smoke | 24 | 19 | 2652.31 (1685.26 to 3741.03) | 5512.81 (3246.56 to 8105.45) | 107.85% (84.4% to 123.61%) | 6.66% (−4.51% to 14.89%) |
| Unsafe sex | 32 | 20 | 1609.09 (1135.71 to 2172.24) | 4646.23 (3296.41 to 6215.68) | 188.75% (161.84% to 225.83%) | 80.75% (63.79% to 103.78%) |

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

BMI indicates body mass index; FPG, fasting plasma glucose; GBD, Global Burden of Disease; LBW, low birth weight; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; UI, uncertainty interval; and YLD, year of life lived with disability or injury.

Source: Data derived from GBD Study 2019. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[105]

**Table 2-10. Leading 20 Global Causes for YLDs: Rank, Number, and Percentage Change, 1990 and 2019**

| Diseases and injuries | YLD rank (for total number) | | Total No. of YLD, in thousands (95% UI) | | Percent change, 1990–2019 (95% UI) | |
|---|---|---|---|---|---|---|
| | 1990 | 2019 | 1990 | 2019 | Total No. of YLDs | Age-standardized YLD rate |
| Low back pain | 1 | 1 | 43 361.65 (30 529.53 to 57 934.97) | 63 685.12 (44 999.20 to 85 192.92) | 46.87% (43.31% to 50.52%) | −16.34% (−17.12% to −15.55%) |
| Migraine | 2 | 2 | 26 863.35 (3969.24 to 61 445.23) | 42 077.67 (6418.38 to 95 645.21) | 56.64% (52.61% to 62.08%) | 1.54% (−4.43% to 3.27%) |
| Age-related and other hearing loss | 5 | 3 | 22 008.10 (14 914.22 to 31 340.37) | 40 235.30 (27 393.19 to 57 131.94) | 82.82% (75.22% to 88.94%) | −1.82% (−3.65% to −0.14%) |
| Other musculoskeletal disorders | 7 | 4 | 16 608.89 (11 264.34 to 23 176.10) | 38 459.70 (26 253.49 to 53 553.79) | 131.56% (124.6% to 139.54%) | 32.24% (28.82% to 36.45%) |
| Major depressive disorder | 4 | 5 | 23 461.28 (16 026.05 to 32 502.66) | 37 202.74 (25 650.21 to 51 217.04) | 58.57% (53.61% to 62.96%) | −2.83% (−4.06% to −1.63%) |
| Type 2 diabetes | 10 | 6 | 11 626.63 (7964.90 to 15 799.45) | 35 150.63 (23 966.55 to 47 810.13) | 202.33% (197.13% to 207.63%) | 50.23% (48.08% to 52.22%) |
| Anxiety disorders | 6 | 7 | 18 661.02 (12 901.15 to 25 547.29) | 28 676.05 (19 858.08 to 39 315.12) | 53.67% (48.76% to 59.06%) | −0.12% (−0.95% to 0.74%) |
| Dietary iron deficiency | 3 | 8 | 25 069.79 (16 835.78 to 36 058.21) | 28 534.68 (19 127.59 to 41 139.28) | 13.82% (10.49% to 17.17%) | −16.39% (−18.72% to −14%) |
| Neck pain | 9 | 9 | 12 393.48 (8128.87 to 17 740.32) | 22 081.32 (14 508.24 to 31 726.93) | 78.17% (69.45% to 87.06%) | −0.34% (−2.47% to 1.85%) |
| Falls | 8 | 10 | 12 639.31 (8965.44 to 17 334.90) | 21 383.29 (15 161.79 to 29 501.22) | 69.18% (65.42% to 73.71%) | −7% (−8.56% to −5.35%) |
| Chronic obstructive pulmonary disease | 13 | 11 | 10 472.74 (8682.19 to 11 830.68) | 19 837.47 (16 596.49 to 22 441.73) | 89.42% (85.38% to 93.59%) | −4.85% (−6.64% to −2.98%) |
| Endocrine, metabolic, blood, and immune disorders | 11 | 12 | 11 022.44 (7513.64 to 15 340.32) | 18 000.31 (12 249.60 to 24 962.91) | 63.31% (59.14% to 67.48%) | −4.64% (−6.09% to −3.38%) |
| Other gynecological diseases | 12 | 13 | 10 812.95 (7041.93 to 15 340.80) | 16 382.52 (10 628.96 to 23 352.28) | 51.51% (48.55% to 54.4%) | −9.37% (−11.11% to −7.59%) |
| Schizophrenia | 14 | 14 | 9131.34 (6692.14 to 11 637.63) | 15 107.25 (11 003.87 to 19 206.79) | 65.44% (62.36% to 68.86%) | −0.56% (−1.57% to 0.38%) |
| Ischemic stroke | 18 | 15 | 6499.45 (4626.50 to 8367.19) | 13 128.53 (9349.92 to 16 930.38) | 101.99% (97.41% to 106.95%) | 0.07% (−1.76% to 1.95%) |

(*Continued*)

**Table 2-10. Continued**

| Diseases and injuries | YLD rank (for total number) | | Total No. of YLD, in thousands (95% UI) | | Percent change, 1990–2019 (95% UI) | |
|---|---|---|---|---|---|---|
| | 1990 | 2019 | 1990 | 2019 | Total No. of YLDs | Age-standardized YLD rate |
| Osteoarthritis knee | 25 | 16 | 5184.78 (2569.34 to 10565.52) | 11534.02 (5719.12 to 23489.98) | 122.46% (120.76% to 124.08%) | 7.8% (7.1% to 8.44%) |
| Diarrheal diseases | 16 | 17 | 8035.21 (5544.86 to 11122.17) | 11030.29 (7631.54 to 15146.75) | 37.27% (33.79% to 41.16%) | −2.63% (−4.19% to −1.02%) |
| Alcohol use disorders | 17 | 18 | 7875.53 (5287.35 to 11122.36) | 10732.01 (7253.40 to 15212.46) | 36.27% (31.35% to 41.08%) | −15.49% (−16.83% to −14.07%) |
| Asthma | 15 | 19 | 8832.45 (5776.18 to 13071.58) | 10196.26 (6654.65 to 15061.36) | 15.44% (12.66% to 18.69%) | −23.4% (−26.63% to −20.2%) |
| Neonatal PTB | 26 | 20 | 5054.73 (3854.95 to 6433.30) | 9673.88 (7598.43 to 12021.19) | 91.38% (75.26% to 106.94%) | 43.44% (31.94% to 54.79%) |

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Disease; PTB, preterm birth; UI, uncertainty interval; and YLD, year of life lived with disability or injury.

Source: Data derived from GBD Study 2019. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[106]

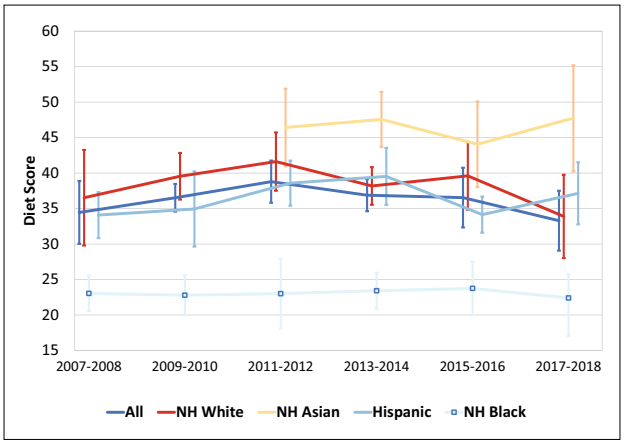



**Chart 2-1. Trends in age-adjusted mean scores (95% CI) for the diet component of CVH among US adults ≥20 years of age, NHANES 2007 to 2008 through 2017 to 2018.**

Dietary estimates were available only through data up to the 2017 to 2018 NHANES cycle at the time of this report.

CI indicates confidence interval; CVH, cardiovascular health; NH, non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

Source: Unpublished American Heart Association tabulation using NHANES.[82]

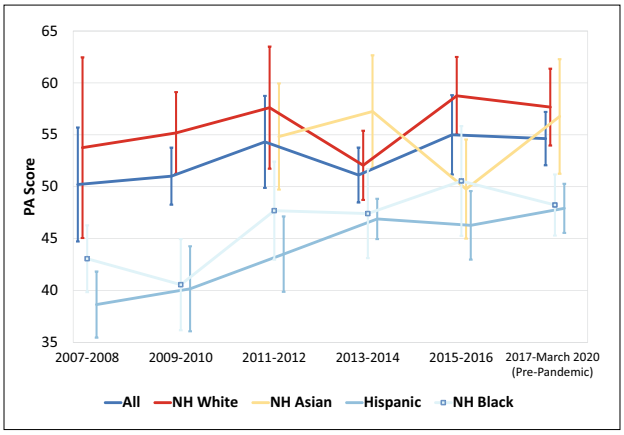



**Chart 2-2. Trends in age-adjusted mean scores (95% CI) for the PA component of CVH among US adults ≥20 years of age, NHANES 2007 to 2008 through 2017 to March 2020.**

CI indicates confidence interval; CVH, cardiovascular health; NH, non-Hispanic; NHANES, National Health and Nutrition Examination Survey; and PA, physical activity.

Source: Unpublished American Heart Association tabulation using NHANES.[82]

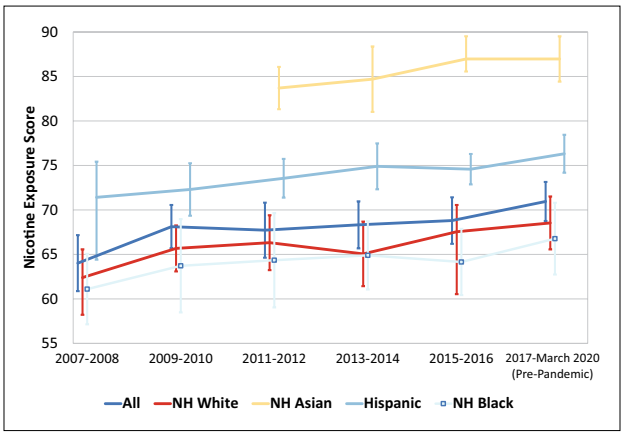



**Chart 2-3. Trends in age-adjusted mean scores (95% CI) for the nicotine exposure component of CVH among US adults ≥20 years of age, NHANES 2007 to 2008 through 2017 to March 2020.**

CI indicates confidence interval; CVH, cardiovascular health; NH, non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

Source: Unpublished American Heart Association tabulation using NHANES.[82]

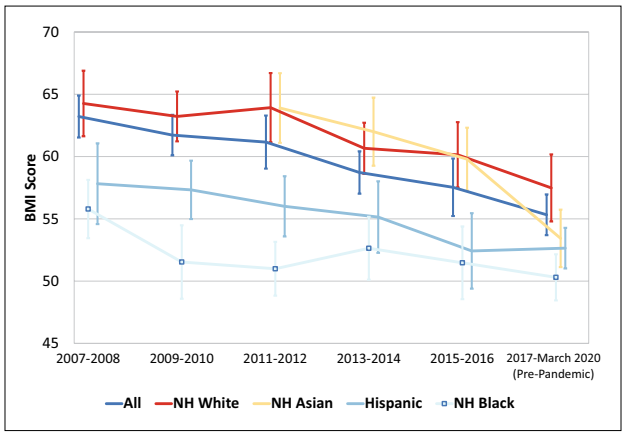



**Chart 2-5. Trends in age-adjusted mean scores (95% CI) for the BMI component of CVH among US adults ≥20 years of age, NHANES 2007 to 2008 through 2017 to March 2020.**

BMI indicates body mass index; CI, confidence interval; CVH, cardiovascular health; NH, non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

Source: Unpublished American Heart Association tabulation using NHANES.[82]

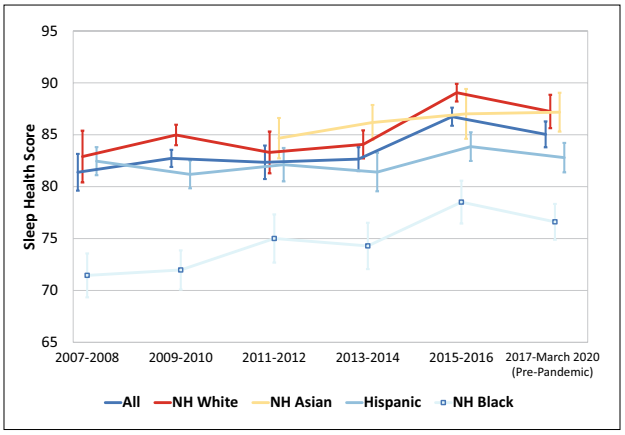



**Chart 2-4. Trends in age-adjusted mean scores (95% CI) for the sleep health component of CVH among US adults ≥20 years of age, NHANES 2007 to 2008 through 2017 to March 2020.**

CI indicates confidence interval; CVH, cardiovascular health; NH, non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

Source: Unpublished American Heart Association tabulation using NHANES.[82]

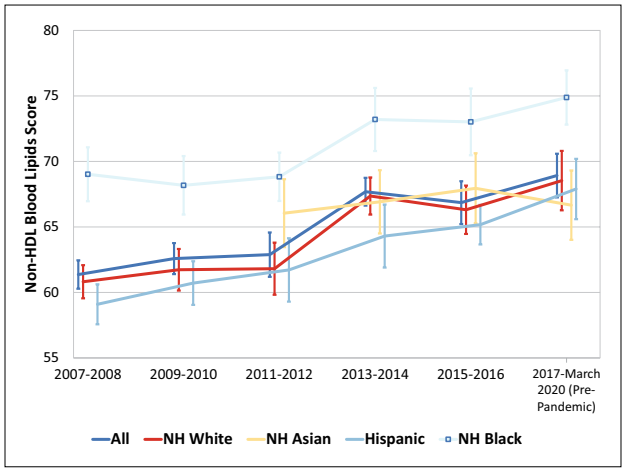



**Chart 2-6. Trends in age-adjusted mean scores (95% CI) for the non-HDL blood lipids component of CVH among US adults ≥20 years of age, NHANES 2007 to 2008 through 2017 to March 2020.**

CI indicates confidence interval; CVH, cardiovascular health; HDL, high-density lipoprotein; NH, non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

Source: Unpublished American Heart Association tabulation using NHANES.[82]

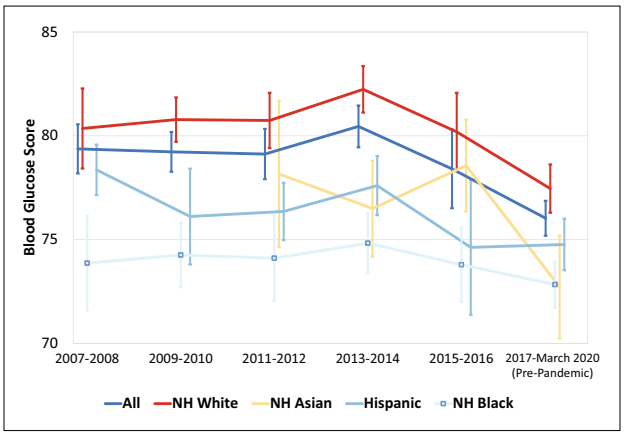



**Chart 2-7. Trends in age-adjusted mean scores (95% CI) for the blood glucose component of CVH among US adults ≥20 years of age, NHANES 2007 to 2008 through 2017 to March 2020.**

CI indicates confidence interval; CVH, cardiovascular health; NH, non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

Source: Unpublished American Heart Association tabulation using NHANES.[82]

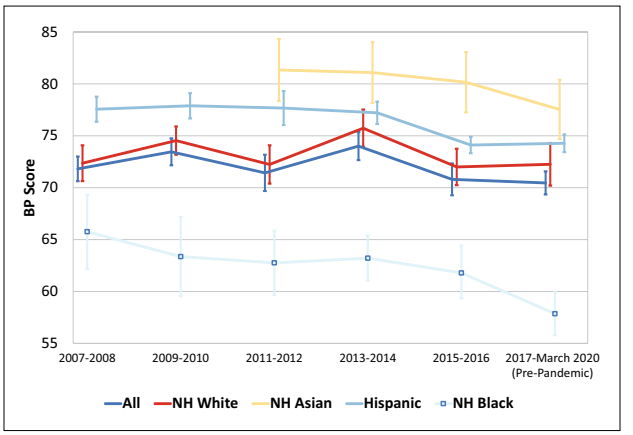



**Chart 2-8. Trends in age-adjusted mean scores (95% CI) for the BP component of CVH among US adults ≥20 years of age, NHANES 2007 to 2008 through 2017 to March 2020.**

BP indicates blood pressure; CI, confidence interval; CVH, cardiovascular health; NH, non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

Source: Unpublished American Heart Association tabulation using NHANES.[82]

## REFERENCES


1. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, Greenlund K, Daniels S, Nichol G, Tomaselli GF, et al; on behalf of the American Heart Association Strategic Planning Task Force and Statistics Committee. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. *Circulation*. 2010;121:586–613. doi: 10.1161/CIRCULATIONAHA.109.192703
2. Lloyd-Jones DM, Allen NB, Anderson CAM, Black T, Brewer LC, Foraker RE, Grandner MA, Lavretsky H, Perak AM, Sharma G, et al; on behalf of the American Heart Association. Life's Essential 8: updating and enhancing the American Heart Association's construct of cardiovascular health: a presidential advisory from the American Heart Association. *Circulation*. 2022;146:e18–e43. doi: 10.1161/CIR.0000000000001078
3. Shay CM, Gooding HS, Murillo R, Foraker R. Understanding and improving cardiovascular health: an update on the American Heart Association's concept of cardiovascular health. *Prog Cardiovasc Dis*. 2015;58:41–49. doi: 10.1016/j.pcad.2015.05.003
4. González HM, Tarraf W, Rodriguez CJ, Gallo LC, Sacco RL, Talavera GA, Heiss G, Kizer JR, Hernandez R, Davis S, et al. Cardiovascular health among diverse Hispanics/Latinos: Hispanic Community Health Study/Study of Latinos (HCHS/SOL) results. *Am Heart J*. 2016;176:134–144. doi: 10.1016/j.ahj.2016.02.008
5. Spahillari A, Talegawkar S, Correa A, Carr JJ, Terry JG, Lima J, Freedman JE, Das S, Kociol R, de Ferranti S, et al. Ideal cardiovascular health, cardiovascular remodeling, and heart failure in Blacks: the Jackson Heart Study. *Circ Heart Fail*. 2017;10:e003682. doi: 10.1161/CIRCHEARTFAILURE.116.003682
6. Oyenuga AO, Folsom AR, Cheng S, Tanaka H, Meyer ML. Greater adherence to Life's Simple 7 is associated with less arterial stiffness: the Atherosclerosis Risk in Communities (ARIC) study. *Am J Hypertens*. 2019;32:769–776. doi: 10.1093/ajh/hpz057
7. Isiozor NM, Kunutsor SK, Voutilainen A, Kurl S, Kauhanen J, Laukkanen JA. Association between ideal cardiovascular health and risk of sudden cardiac death and all-cause mortality among middle-aged men in Finland. *Eur J Prev Cardiol*. 2021;28:294–300.
8. Díez-Espino J, Buil-Cosiales P, Babio N, Toledo E, Corella D, Ros E, Fitó M, Gómez-Gracia E, Estruch R, Fiol M, et al. Impact of Life's Simple 7 on the incidence of major cardiovascular events in high-risk Spanish adults in the PREDIMED study cohort. *Rev Esp Cardiol (Engl Ed)*. 2020;73:205–211. doi: 10.1016/j.rec.2019.05.010
9. Gao B, Wang F, Zhu M, Wang J, Zhou M, Zhang L, Zhao M. Cardiovascular health metrics and all-cause mortality and mortality from major non-communicable chronic diseases among Chinese adult population. *Int J Cardiol*. 2020;313:123–128. doi: 10.1016/j.ijcard.2020.04.048
10. Younus A, Aneni EC, Spatz ES, Osondu CU, Roberson L, Ogunmoroti O, Malik R, Ali SS, Aziz M, Feldman T, et al. A Systematic review of the prevalence and outcomes of ideal cardiovascular health in US and non-US populations. *Mayo Clin Proc*. 2016;91:649–670. doi: 10.1016/j.mayocp.2016.01.019
11. Wang T, Lu J, Su Q, Chen Y, Bi Y, Mu Y, Chen L, Hu R, Tang X, Yu X, et al; for the 4C Study Group. Ideal cardiovascular health metrics and major cardiovascular events in patients with prediabetes and diabetes. *JAMA Cardiol*. 2019;4:874–883. doi: 10.1001/jamacardio.2019.2499
12. Talegawkar SA, Jin Y, Kandula NR, Kanaya AM. Cardiovascular health metrics among South Asian adults in the United States: prevalence and associations with subclinical atherosclerosis. *Prev Med*. 2017;96:79–84. doi: 10.1016/j.ypmed.2016.12.017
13. Kim S, Chang Y, Cho J, Hong YS, Zhao D, Kang J, Jung HS, Yun KE, Guallar E, Ryu S, et al. Life's Simple 7 cardiovascular health metrics and progression of coronary artery calcium in a low-risk population. *Arterioscler Thromb Vasc Biol*. 2019;39:826–833. doi: 10.1161/ATVBAHA.118.311821
14. Brenn T. Survival to age 90 in men: the Tromso Study 1974-2018. *Int J Environ Res Public Health*. 2019;16:2028. doi: 10.3390/ijerph16112028
15. Szlejf C, Suemoto CK, Santos IS, Brunoni AR, Nunes MA, Viana MC, Barreto SM, Lotufo PA, Bensenor IM. Poorer cardiovascular health is associated with psychiatric comorbidity: results from the ELSA-Brasil Study. *Int J Cardiol*. 2019;274:358–365. doi: 10.1016/j.ijcard.2018.06.037
16. Dong Y, Hao G, Wang Z, Wang X, Chen Z, Zhang L. Ideal cardiovascular health status and risk of cardiovascular disease or all-cause mortality in Chinese middle-aged population. *Angiology*. 2019;70:523–529. doi: 10.1177/0003319718813448
17. Uijl A, Koudstaal S, Vaartjes I, Boer JMA, Verschuren WMM, van der Schouw YT, Asselbergs FW, Hoes AW, Sluijs I. Risk for heart failure: the opportunity for prevention with the American Heart Association's Life's Simple 7. *JACC Heart Fail*. 2019;7:637–647. doi: 10.1016/j.jchf.2019.03.009
18. Wu S, Xu Y, Zheng R, Lu J, Li M, Chen L, Huo Y, Xu M, Wang T, Zhao Z, et al. Hypertension DEfined by 2017 ACC/AHA Guideline, Ideal Cardiovascular Health Metrics, and Risk of Cardiovascular Disease: a nationwide prospective cohort study. *Lancet Reg Health West Pac*. 2022;20:100350. doi: 10.1016/j.lanwpc.2021.100350
19. Del Brutto OH, Mera RM, Recalde BY, Rumbea DA, Sedler MJ. Life's Simple 7 and all-cause mortality: a population-based prospective cohort study in

middle-aged and older adults of Amerindian ancestry living in rural Ecuador. *Prev Med Rep*. 2022;25:101668. doi: 10.1016/j.pmedr.2021.101668
20. Han L, You D, Ma W, Astell-Burt T, Feng X, Duan S, Qi L. National trends in American Heart Association revised Life's Simple 7 metrics associated with risk of mortality among US adults. *JAMA Netw Open*. 2019;2:e1913131. doi: 10.1001/jamanetworkopen.2019.13131
21. Yang Q, Cogswell ME, Flanders WD, Hong Y, Zhang Z, Loustalot F, Gillespie C, Merritt R, Hu FB. Trends in cardiovascular health metrics and associations with all-cause and CVD mortality among US adults. *JAMA*. 2012;307:1273–1283. doi: 10.1001/jama.2012.339
22. Folsom AR, Yatsuya H, Nettleton JA, Lutsey PL, Cushman M, Rosamond WD; ARIC Study Investigators. Community prevalence of ideal cardiovascular health, by the American Heart Association definition, and relationship with cardiovascular disease incidence. *J Am Coll Cardiol*. 2011;57:1690–1696. doi: 10.1016/j.jacc.2010.11.041
23. Tsao CW, Aday AW, Almarzooq ZI, Anderson CAM, Arora P, Avery CL, Baker-Smith CM, Beaton AZ, Boehme AK, Buxton AE, et al; on behalf of the American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics–2023 update: a report from the American Heart Association [published corrections appear in *Circulation*. 2023;147:e622 and *Circulation*. 2023;148:e4]. *Circulation*. 2023;147:e93–e621. doi: 10.1161/CIR.0000000000001123
24. Kulshreshtha A, Vaccarino V, Judd SE, Howard VJ, McClellan WM, Muntner P, Hong Y, Safford MM, Goyal A, Cushman M. Life's Simple 7 and risk of incident stroke: the Reasons for Geographic and Racial Differences in Stroke study. *Stroke*. 2013;44:1909–1914. doi: 10.1161/STROKEAHA.111.000352
25. Cao Z, Li S, Yang H, Xu C, Zhang Y, Yang X, Yan T, Liu T, Wang Y. Associations of behaviors, biological phenotypes and cardiovascular health with risks of stroke and stroke subtypes: a prospective cohort study. *EClinicalMedicine*. 2021;33:100791. doi: 10.1016/j.eclinm.2021.100791
26. Nguyen ATH, Saeed A, Bambs CE, Swanson J, Emechebe N, Mansuri F, Talreja K, Reis SE, Kip KE. Usefulness of the American Heart Association's ideal cardiovascular health measure to predict long-term major adverse cardiovascular events (from the Heart SCORE study). *Am J Cardiol*. 2021;138:20–25. doi: 10.1016/j.amjcard.2020.10.019
27. Bundy JD, Zhu Z, Ning H, Zhong VW, Paluch AE, Wilkins JT, Lloyd-Jones DM, Whelton PK, He J, Allen NB. Estimated impact of achieving optimal cardiovascular health among US adults on cardiovascular disease events. *J Am Heart Assoc*. 2021;10:e019681. doi: 10.1161/JAHA.120.019681
28. Perak AM, Ning H, Khan SS, Bundy JD, Allen NB, Lewis CE, Jacobs DR Jr, Van Horn LV, Lloyd-Jones DM. Associations of late adolescent or young adult cardiovascular health with premature cardiovascular disease and mortality. *J Am Coll Cardiol*. 2020;76:2695–2707. doi: 10.1016/j.jacc.2020.10.002
29. Corlin L, Short MI, Vasan RS, Xanthakis V. Association of the duration of ideal cardiovascular health through adulthood with cardiometabolic outcomes and mortality in the Framingham Offspring Study. *JAMA Cardiol*. 2020;5:549–556. doi: 10.1001/jamacardio.2020.0109
30. Gaye B, Tajeu GS, Vasan RS, Lassale C, Allen NB, Singh-Manoux A, Jouven X. Association of changes in cardiovascular health metrics and risk of subsequent cardiovascular disease and mortality. *J Am Heart Assoc*. 2020;9:e017458. doi: 10.1161/JAHA.120.017458
31. Yang PS, Jang E, Yu HT, Kim TH, Pak HN, Lee MH, Joung B. Changes in cardiovascular risk factors and cardiovascular events in the elderly population. *J Am Heart Assoc*. 2021;10:e019482. doi: 10.1161/JAHA.120.019482
32. Muchira JM, Gona PN, Mogos MF, Stuart-Shor E, Leveille SG, Piano MR, Hayman LL. Parental cardiovascular health predicts time to onset of cardiovascular disease in offspring. *Eur J Prev Cardiol*. 2022;29:883–891. doi: 10.1093/eurjpc/zwaa072
33. Perak AM, Lancki N, Kuang A, Labarthe DR, Allen NB, Shah SH, Lowe LP, Grobman WA, Lawrence JM, Lloyd-Jones DM, et al; HAPO Follow-Up Study Cooperative Research Group. Associations of maternal cardiovascular health in pregnancy with offspring cardiovascular health in early adolescence. *JAMA*. 2021;325:658–668. doi: 10.1001/jama.2021.0247
34. Wilkins JT, Ning H, Berry J, Zhao L, Dyer AR, Lloyd-Jones DM. Lifetime risk and years lived free of total cardiovascular disease. *JAMA*. 2012;308:1795–1801. doi: 10.1001/jama.2012.14312
35. Wang L, Song L, Li D, Zhou Z, Chen S, Yang Y, Hu Y, Wang Y, Wu S, Tian Y. Ideal cardiovascular health metric and its change with lifetime risk of cardiovascular diseases: a prospective cohort study. *J Am Heart Assoc*. 2021;10:e022502. doi: 10.1161/JAHA.121.022502
36. Xu C, Zhang P, Cao Z. Cardiovascular health and healthy longevity in people with and without cardiometabolic disease: a prospective cohort study. *EClinicalMedicine*. 2022;45:101329. doi: 10.1016/j.eclinm.2022.101329
37. Zhang N, Yang Y, Wang A, Cao Y, Li J, Yang Y, Zhang K, Zhang W, Wu S, Wang Z, et al. Association of ideal cardiovascular health metrics and cognitive functioning: the APAC study. *Eur J Neurol*. 2016;23:1447–1454. doi: 10.1111/ene.13056
38. Peloso GM, Beiser AS, Satizabal CL, Xanthakis V, Vasan RS, Pase MP, Destefano AL, Seshadri S. Cardiovascular health, genetic risk, and risk of dementia in the Framingham Heart Study. *Neurology*. 2020;95:e1341–e1350. doi: 10.1212/WNL.0000000000010306
39. Sabia S, Fayosse A, Dumurgier J, Schnitzler A, Empana JP, Ebmeier KP, Dugravot A, Kivimaki M, Singh-Manoux A. Association of ideal cardiovascular health at age 50 with incidence of dementia: 25 year follow-up of Whitehall II cohort study. *BMJ*. 2019;366:l4414. doi: 10.1136/bmj.l4414
40. Liang Y, Ngandu T, Laatikainen T, Soininen H, Tuomilehto J, Kivipelto M, Qiu C. Cardiovascular health metrics from mid- to late-life and risk of dementia: a population-based cohort study in Finland. *PLoS Med*. 2020;17:e1003474. doi: 10.1371/journal.pmed.1003474
41. Climie RE, Tafflet M, van Sloten T, de Lauzon-Guillain B, Bernard JY, Dargent-Molina P, Plancoulaine S, Lioret S, Jouven X, Charles MA, et al. Cardiovascular health at age 5 years: distribution, determinants, and association with neurodevelopment. *Front Pediatr*. 2022;10:827525. doi: 10.3389/fped.2022.827525
42. Zhang Z, Jackson S, Merritt R, Gillespie C, Yang Q. Association between cardiovascular health metrics and depression among U.S. adults: National Health and Nutrition Examination Survey, 2007-2014. *Ann Epidemiol*. 2019;31:49–56.e2. doi: 10.1016/j.annepidem.2018.12.005
43. Brunoni AR, Szlejf C, Suemoto CK, Santos IS, Goulart AC, Viana MC, Koyanagi A, Barreto SM, Moreno AB, Carvalho AF, et al. Association between ideal cardiovascular health and depression incidence: a longitudinal analysis of ELSA-Brasil. *Acta Psychiatr Scand*. 2019;140:552–562. doi: 10.1111/acps.13109
44. Ogunmoroti O, Osibogun O, Spatz ES, Okunrintemi V, Mathews L, Ndumele CE, Michos ED. A systematic review of the bidirectional relationship between depressive symptoms and cardiovascular health. *Prev Med*. 2022;154:106891. doi: 10.1016/j.ypmed.2021.106891
45. He YM, Chen WL, Kao TW, Wu LW, Yang HF, Peng TC. Relationship between ideal cardiovascular health and incident proteinuria: a 5 year retrospective cohort study. *Nutrients*. 2022;14:4040. doi: 10.3390/nu14194040
46. Ogunmoroti O, Allen NB, Cushman M, Michos ED, Rundek T, Rana JS, Blankstein R, Blumenthal RS, Blaha MJ, Veledar E, et al. Association between Life's Simple 7 and noncardiovascular disease: the Multi-Ethnic Study of Atherosclerosis. *J Am Heart Assoc*. 2016;5:e003954. doi: 10.1161/JAHA.116.003954
47. Fan W, Lee H, Lee A, Kieu C, Wong ND. Association of lung function and chronic obstructive pulmonary disease with American Heart Association's Life's Simple 7 cardiovascular health metrics. *Respir Med*. 2017;131:85–93. doi: 10.1016/j.rmed.2017.08.001
48. Lee JH, Yang PS, Yu HT, Kim TH, Jang E, Uhm JS, Pak HN, Lee MH, Joung B. Association of cardiovascular health and incident atrial fibrillation in elderly population. *Heart*. 2021;107:1206–1212. doi: 10.1136/heartjnl-2020-318858
49. Garg PK, O'Neal WT, Chen LY, Loehr LR, Sotoodehnia N, Soliman EZ, Alonso A. American Heart Association's Life Simple 7 and risk of atrial fibrillation in a population without known cardiovascular disease: the ARIC (Atherosclerosis Risk in Communities) study. *J Am Heart Assoc*. 2018;7:e008424. doi: 10.1161/JAHA.117.008424
50. Osibogun O, Ogunmoroti O, Spatz ES, Fashanu OE, Michos ED. Ideal cardiovascular health and resting heart rate in the Multi-Ethnic Study of Atherosclerosis. *Prev Med*. 2020;130:105890. doi: 10.1016/j.ypmed.2019.105890
51. DeCoste LR, Wang N, Palmisano JN, Mendez J, Hoffmann U, Benjamin EJ, Long MT. Adherence to ideal cardiovascular health metrics is associated with reduced odds of hepatic steatosis. *Hepatol Commun*. 2021;5:74–82. doi: 10.1002/hep4.1614
52. De La Cruz N, Shabaneh O, Appiah D. The association of ideal cardiovascular health and ocular diseases among US adults. *Am J Med*. 2021;134:252–259.e1. doi: 10.1016/j.amjmed.2020.06.004
53. Palta P, Griswold M, Ranadive R, Bandeen-Roche K, Folsom AR, Petruski-Ivleva N, Burgard S, Kucharska-Newton A, Windham BG. Midlife cardiovascular health and robust versus frail late-life status: the Atherosclerosis Risk in Communities (ARIC) study. *J Gerontol A Biol Sci Med Sci*. 2022;77:1222–1229. doi: 10.1093/gerona/glab310

54. Caleyachetty R, Echouffo-Tcheugui JB, Muennig P, Zhu W, Muntner P, Shimbo D. Association between cumulative social risk and ideal cardiovascular health in US adults: NHANES 1999-2006. *Int J Cardiol*. 2015;191:296–300. doi: 10.1016/j.ijcard.2015.05.007
55. Lassale C, Cene CW, Asselin A, Sims M, Jouven X, Gaye B. Sociodemographic determinants of change in cardiovascular health in middle adulthood in a bi-racial cohort. *Atherosclerosis*. 2022;346:98–108. doi: 10.1016/j.atherosclerosis.2022.01.006
56. Johnson AE, Herbert BM, Stokes N, Brooks MM, Needham BL, Magnani JW. Educational attainment, race, and ethnicity as predictors for ideal cardiovascular health: from the National Health and Nutrition Examination Survey. *J Am Heart Assoc*. 2022;11:e023438. doi: 10.1161/JAHA.121.023438
57. Acquah I, Hagan K, Javed Z, Taha MB, Valero-Elizondo J, Nwana N, Yahya T, Sharma G, Gulati M, Hammoud A, et al. Social determinants of cardiovascular risk, subclinical cardiovascular disease, and cardiovascular events. *J Am Heart Assoc*. 2023;12:e025581. doi: 10.1161/JAHA.122.025581
58. Hawes MR, Roth KB, Wang X, Stefancic A, Weatherly C, Cabassa LJ. Ideal cardiovascular health in racially and ethnically diverse people with serious mental illness. *J Health Care Poor Underserved*. 2020;31:1669–1692. doi: 10.1353/hpu.2020.0126
59. Zheng Y, Wen X, Bian J, Zhao J, Lipkind HS, Hu H. Racial, ethnic, and geographic disparities in cardiovascular health among women of childbearing age in the United States. *J Am Heart Assoc*. 2021;10:e020138. doi: 10.1161/JAHA.120.020138
60. Jankovic J, Mandic-Rajcevic S, Davidovic M, Jankovic S. Demographic and socioeconomic inequalities in ideal cardiovascular health: a systematic review and meta-analysis. *PLoS One*. 2021;16:e0255959. doi: 10.1371/journal.pone.0255959
61. Mujahid MS, Moore LV, Petito LC, Kershaw KN, Watson K, Diez Roux AV. Neighborhoods and racial/ethnic differences in ideal cardiovascular health (the Multi-Ethnic Study of Atherosclerosis). *Health Place*. 2017;44:61–69. doi: 10.1016/j.healthplace.2017.01.005
62. Ko YA, Shen J, Kim JH, Topel M, Mujahid M, Taylor H, Quyyumi A, Sims M, Vaccarino V, Baltrus P, et al. Identifying neighbourhood and individual resilience profiles for cardiovascular health: a cross-sectional study of Blacks living in the Atlanta metropolitan area. *BMJ Open*. 2021;11:e041435. doi: 10.1136/bmjopen-2020-041435
63. Piedra LM, Andrade FCD, Hernandez R, Perreira KM, Gallo LC, Gonzalez HM, Gonzalez S, Cai J, Chen J, Castaneda SF, et al. Association of subjective social status with Life's Simple 7s cardiovascular health index among Hispanic/Latino people: results from the HCHS/SOL. *J Am Heart Assoc*. 2021;10:e012704. doi: 10.1161/JAHA.119.012704
64. Diaz CL, Shah NS, Lloyd-Jones DM, Khan SS. State of the nation's cardiovascular health and targeting health equity in the United States: a narrative review. *JAMA Cardiol*. 2021;6:963–970. doi: 10.1001/jamacardio.2021.1137
65. Lloyd-Jones DM, Elkind M, Albert MA. American Heart Association's 2024 Impact Goal: every person deserves the opportunity for a full, healthy life. *Circulation*. 2021;144:e277–e279. doi: 10.1161/CIRCULATIONAHA.121.057617
66. Angell SY, McConnell MV, Anderson CAM, Bibbins-Domingo K, Boyle DS, Capewell S, Ezzati M, de Ferranti S, Gaskin DJ, Goetzel RZ, et al. The American Heart Association 2030 Impact Goal: a presidential advisory from the American Heart Association. *Circulation*. 2020;141:e120–e138. doi: 10.1161/CIR.0000000000000758
67. Willis BL, DeFina LF, Bachmann JM, Franzini L, Shay CM, Gao A, Leonard D, Berry JD. Association of ideal cardiovascular health and long-term healthcare costs. *Am J Prev Med*. 2015;49:678–685. doi: 10.1016/j.amepre.2015.03.034
68. Osondu CU, Aneni EC, Valero-Elizondo J, Salami JA, Rouseff M, Das S, Guzman H, Younus A, Ogunmoroti O, Feldman T, et al. Favorable cardiovascular health is associated with lower health care expenditures and resource utilization in a large US employee population: the Baptist Health South Florida Employee Study. *Mayo Clin Proc*. 2017;92:512–524. doi: 10.1016/j.mayocp.2016.12.026
69. Lloyd-Jones DM, Ning H, Labarthe D, Brewer L, Sharma G, Rosamond W, Foraker RE, Black T, Grandner MA, Allen NB, et al. Status of cardiovascular health in US adults and children using the American Heart Association's new "Life's Essential 8" metrics: prevalence estimates from the National Health and Nutrition Examination Survey (NHANES), 2013-2018. *Circulation*. 2022;146:822–835. doi: 10.1161/circulationaha.122.060911
70. Shetty NS, Parcha V, Patel N, Yadav I, Basetty C, Li C, Pandey A, Kalra R, Li P, Arora G, et al. AHA Life's Essential 8 and ideal cardiovascular health among young adults. *Am J Prev Cardiol*. 2023;13:100452. doi: 10.1016/j.ajpc.2022.100452
71. Ma H, Wang X, Xue Q, Li X, Liang Z, Heianza Y, Franco OH, Qi L. Cardiovascular health and life expectancy among adults in the United States. *Circulation*. 2023;147:1137–1146. doi: 10.1161/CIRCULATIONAHA.122.062457
72. Sun J, Li Y, Zhao M, Yu X, Zhang C, Magnussen CG, Xi B. Association of the American Heart Association's new "Life's Essential 8" with all-cause and cardiovascular disease-specific mortality: prospective cohort study. *BMC Med*. 2023;21:116. doi: 10.1186/s12916-023-02824-8
73. Yi J, Wang L, Guo X, Ren X. Association of Life's Essential 8 with all-cause and cardiovascular mortality among US adults: a prospective cohort study from the NHANES 2005-2014. *Nutr Metab Cardiovasc Dis*. 2023;33:1134–1143. doi: 10.1016/j.numecd.2023.01.021
74. Petermann-Rocha F, Deo S, Celis-Morales C, Ho FK, Bahuguna P, McAllister D, Sattar N, Pell JP. An opportunity for prevention: associations between the Life's Essential 8 score and cardiovascular incidence using prospective data from UK Biobank. *Curr Probl Cardiol*. 2023;48:101540. doi: 10.1016/j.cpcardiol.2022.101540
75. Wang X, Ma H, Li X, Heianza Y, Manson JE, Franco OH, Qi L. Association of cardiovascular health with life expectancy free of cardiovascular disease, diabetes, cancer, and dementia in UK adults. *JAMA Intern Med*. 2023;183:340–349. doi: 10.1001/jamainternmed.2023.0015
76. Zhang Y, Yang R, Hou Y, Chen Y, Li S, Wang Y, Yang H. Association of cardiovascular health with diabetic complications, all-cause mortality, and life expectancy among people with type 2 diabetes. *Diabetol Metab Syndr*. 2022;14:158. doi: 10.1186/s13098-022-00934-6
77. Sun Y, Yu Y, Zhang K, Yu B, Yu Y, Wang Y, Wang B, Tan X, Wang Y, Lu Y, et al. Association between Life's Essential 8 score and risk of premature mortality in people with and without type 2 diabetes: a prospective cohort study. *Diabetes Metab Res Rev*. 2023;39:e3636. doi: 10.1002/dmrr.3636
78. Isiozor NM, Kunutsor SK, Voutilainen A, Laukkanen JA. Life's Essential 8 and the risk of cardiovascular disease death and all-cause mortality in Finnish men. *Eur J Prev Cardiol*. 2023;30:658–667. doi: 10.1093/eurjpc/zwad040
79. Xing A, Tian X, Wang Y, Chen S, Xu Q, Xia X, Zhang Y, Zhang X, Wang A, Wu S. "Life's Essential 8" cardiovascular health with premature cardiovascular disease and all-cause mortality in young adults: the Kailuan prospective cohort study. *Eur J Prev Cardiol*. 2023;30:593–600. doi: 10.1093/eurjpc/zwad033
80. Jin C, Li J, Liu F, Li X, Hui Y, Chen S, Li F, Wang G, Liang F, Lu X, et al. Life's Essential 8 and 10-year and lifetime risk of atherosclerotic cardiovascular disease in China. *Am J Prev Med*. 2023;64:927–935. doi: 10.1016/j.amepre.2023.01.009
81. Perng W, Aris IM, Slopen N, Younoszai N, Swanson V, Mueller NT, Sauder KA, Dabelea D. Application of Life's Essential 8 to assess cardiovascular health during early childhood. *Ann Epidemiol*. 2023;80:16–24. doi: 10.1016/j.annepidem.2023.02.004
82. Centers for Disease Control and Prevention and National Center for Health Statistics. National Health and Nutrition Examination Survey (NHANES) public use data files. Accessed April 1, 2023. https://cdc.gov/nchs/nhanes/
83. Centers for Disease Control and Prevention. Trends in COVID-19 cases and deaths in the United States, by county-level population factors: COVID data tracker. Accessed May 5, 2023. https://covid.cdc.gov/covid-data-tracker/#datatracker-home
84. Arias E, Tejada-Vera B, Kochanek KD, Ahmad FB. Provisional life expectancy estimates for 2021. *Vital Statistics Rapid Release*. 2022. Centers for Disease Control and Prevention. Accessed October 18, 2023. https://cdc.gov/nchs/data/vsrr/vsrr023.pdf
85. Baumgart M, Snyder HM, Carrillo MC, Fazio S, Kim H, Johns H. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: a population-based perspective. *Alzheimers Dement*. 2015;11:718–726. doi: 10.1016/j.jalz.2015.05.016
86. Wu S, An S, Li W, Lichtenstein AH, Gao J, Kris-Etherton PM, Wu Y, Jin C, Huang S, Hu FB, et al. Association of trajectory of cardiovascular health score and incident cardiovascular disease. *JAMA Netw Open*. 2019;2:e194758. doi: 10.1001/jamanetworkopen.2019.4758
87. Dong C, Rundek T, Wright CB, Anwar Z, Elkind MS, Sacco RL. Ideal cardiovascular health predicts lower risks of myocardial infarction, stroke, and vascular death across Whites, Blacks, and Hispanics: the Northern Manhattan Study. *Circulation*. 2012;125:2975–2984. doi: 10.1161/CIRCULATIONAHA.111.081083
88. Rebholz CM, Anderson CA, Grams ME, Bazzano LA, Crews DC, Chang AR, Coresh J, Appel LJ. Relationship of the American Heart Association's

Impact Goals (Life's Simple 7) with risk of chronic kidney disease: results from the Atherosclerosis Risk in Communities (ARIC) cohort study. *J Am Heart Assoc*. 2016;5:e003192. doi: 10.1161/JAHA.116.003192

89. Joseph JJ, Bennett A, Echouffo Tcheugui JB, Effoe VS, Odei JB, Hidalgo B, Dulin A, Safford MM, Cummings DM, Cushman M, et al. Ideal cardiovascular health, glycaemic status and incident type 2 diabetes mellitus: the REasons for Geographic And Racial Differences in Stroke (REGARDS) study. *Diabetologia*. 2019;62:426–437. doi: 10.1007/s00125-018-4792-y
90. Effoe VS, Carnethon MR, Echouffo-Tcheugui JB, Chen H, Joseph JJ, Norwood AF, Bertoni AG. The American Heart Association ideal cardiovascular health and incident type 2 diabetes mellitus among Blacks: the Jackson Heart Study. *J Am Heart Assoc*. 2017;6:e005008. doi: 10.1161/JAHA.116.005008
91. Foraker RE, Abdel-Rasoul M, Kuller LH, Jackson RD, Van Horn L, Seguin RA, Safford MM, Wallace RB, Kucharska-Newton AM, Robinson JG, et al. Cardiovascular health and incident cardiovascular disease and cancer: the Women's Health Initiative. *Am J Prev Med*. 2016;50:236–240. doi: 10.1016/j.amepre.2015.07.039
92. Rasmussen-Torvik LJ, Shay CM, Abramson JG, Friedrich CA, Nettleton JA, Prizment AE, Folsom AR. Ideal cardiovascular health is inversely associated with incident cancer: the Atherosclerosis Risk in Communities study. *Circulation*. 2013;127:1270–1275. doi: 10.1161/CIRCULATIONAHA.112.001183
93. Gorelick PB, Furie KL, Iadecola C, Smith EE, Waddy SP, Lloyd-Jones DM, Bae HJ, Bauman MA, Dichgans M, Duncan PW, et al; on behalf of the American Heart Association/American Stroke Association. Defining optimal brain health in adults: a presidential advisory from the American Heart Association/American Stroke Association. *Stroke*. 2017;48:e284–e303. doi: 10.1161/STR.0000000000000148
94. Mellen PB, Gao SK, Vitolins MZ, Goff DC Jr. Deteriorating dietary habits among adults with hypertension: DASH dietary accordance, NHANES 1988-1994 and 1999-2004. *Arch Intern Med*. 2008;168:308–314. doi: 10.1001/archinternmed.2007.119
95. Gao S. *Diet and Exercise: Behavioral Management of Hypertension and Diabetes* [dissertation]. Seattle: University of Washington; 2006.
96. Cerwinske LA, Rasmussen HE, Lipson S, Volgman AS, Tangney CC. Evaluation of a dietary screener: the Mediterranean Eating Pattern for Americans tool. *J Hum Nutr Diet*. 2017;30:596–603. doi: 10.1111/jhn.12451
97. National Health and Nutrition Examination Survey. Physical activity and physical fitness: PAQ-K. 2019. Accessed May 5, 2023. https://wwwn.cdc.gov/nchs/data/nhanes/2019-2020/questionnaires/PAQ_K.pdf
98. National Health and Nutrition Examination Survey. Smoking and tobacco use: SMQ. 2015. Accessed May 5, 2023. https://wwwn.cdc.gov/nchs/data/nhanes/2015-2016/questionnaires/SMQ_I.pdf
99. Raghuveer G, White DA, Hayman LL, Woo JG, Villafane J, Celermajer D, Ward KD, de Ferranti SD, Zachariah J; on behalf of the American Heart Association Committee on Atherosclerosis, Hypertension, and Obesity in the Young of the Council on Cardiovascular Disease in the Young; Behavior Change for Improving Health Factors Committee of the Council on Lifestyle and Cardiometabolic Health and Council on Epidemiology and Prevention; and Stroke Council. Cardiovascular consequences of childhood secondhand tobacco smoke exposure: prevailing evidence, burden, and racial and socioeconomic disparities: a scientific statement from the American Heart Association [published correction appears in *Circulation*. 2016;134:e366]. *Circulation*. 2016;134:e336–e359. doi: 10.1161/CIR.0000000000000443
100. American Academy of Pediatrics. Healthy sleep habits: how many hours does your child need? 2016. Accessed May 5, 2023. https://healthychildren.org/English/healthy-living/sleep/Pages/healthy-sleep-habits-how-many-hours-does-your-child-need.aspx
101. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol [published corrections appear in *Circulation*. 2019;139:e1182–e1186622 and *Circulation*. 2023;148:e5]. *Circulation*. 2019;139:e1082–e1143. doi: 10.1161/CIR.0000000000000625
102. American Diabetes Association. Practice guidelines resources. Accessed May 5, 2023. https://professional.diabetes.org/content-page/practice-guidelines-resources
103. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published correction appears in *Hypertension*. 2018;71:e140–e144]. *Hypertension*. 2018;71:e13–e115. doi: 10.1161/HYP.0000000000000065
104. Stierman B, Afful J, Carroll M, Chen T, Davy O, Fink S, Fryar C, Gu Q, Hales C, Hughes J, et al. National Health and Nutrition Examination Survey 2017-March 2020 prepandemic data files: development of files and prevalence estimates for selected health outcomes. *Natl Health Stat Reports*. 2021;158. Accessed April 1, 2023. https://stacks.cdc.gov/view/cdc/106273
105. GBD Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. 2020;396:1223–1249. doi: 10.1016/S0140-6736(20)30752-2
106. GBD Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. 2020;396:1204–1222. doi: 10.1016/S0140-6736(20)30925-9

# 3. SMOKING/TOBACCO USE

*See Table 3-1 and Charts 3-1 through 3-4*

Click here to return to the Table of Contents
Click here to return to the Abbreviations

Tobacco use is one of the leading preventable causes of death in the United States and globally. Cigarette smoking, the most common form of tobacco use, is a major risk factor for CVD, including stroke.[1] The AHA has identified combustible tobacco use or inhaled nicotine delivery system use (e-cigarettes or vaping) and secondhand smoke exposure to have adverse effects on CVH in Life's Essential 8.[2] Unless otherwise stated, throughout the rest of this chapter, we report tobacco use and smoking estimates from the NYTS[3] for adolescents and from the NHIS[4] for adults (≥18 years of age) because these data sources have more recent data. As a survey of middle and high school students, the NYTS may not be generalizable to youth who are not enrolled in school; however, in 2016, 97% of youth 10 to 17 years of age were enrolled in school, which indicates that the results of the NYTS are likely broadly applicable to US youth.[5]

Other forms of tobacco use are becoming increasingly common. E-cigarette use, which involves inhalation of a vaporized liquid that includes nicotine, solvents, and flavoring (vaping), has risen dramatically, particularly among young adults and high school–aged children. The variety of e-cigarette–related and nicotine products has increased exponentially, giving rise to the more general term electronic nicotine delivery systems.[6] A notable evolution in electronic nicotine delivery systems technology and marketing has occurred recently with the advent of pod mods, small rechargeable devices that deliver high levels of nicotine from nicotine salts in loose-leaf tobacco.[7] Use of cigars, cigarillos, filtered cigars, and smokeless and hookah (ie, water pipe) tobacco also has become increasingly common in recent years. Thus, each section here addresses the most recent statistical estimates for combustible cigarettes, electronic nicotine delivery systems, and other forms of tobacco use if such estimates are available.

The 2024 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2024. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

## Prevalence

### *Youth*

*(See Chart 3-1)*

- Prevalence of cigarette use in the past 30 days for middle and high school students by sex and race and ethnicity in 2022 is shown in Chart 3-1.
- In 2022[3]:
  - 33.9% (95% CI, 31.5%–36.3%) of high school students (corresponding to 5.2 million users) and 13.1% (95% CI, 11.7%–14.7%) of middle school students (corresponding to 1.6 million users) reported ever use of any tobacco product.
  - Nearly 1 in 9 (11.3%; corresponding to 3.1 million users) middle and high school students reported current (past 30-day) use of any tobacco product: 16.5% (95% CI, 14.6%–18.5%) of high school students (corresponding to 2.5 million users) and 4.5% (95% CI, 3.7%–5.5%) of middle school students (corresponding to 530 000 users).
  - Of all high school students, 2.0% (95% CI, 1.7%–2.5%; corresponding to 310 000 users), and of all middle school students, 1.0% (95% CI, 0.6%–1.5%; corresponding to 110 000 users), smoked cigarettes in the past 30 days.
  - 2.8% (95% CI, 2.2%–3.5%) of high school students (410 000 users) and 0.6% (95% CI, 0.4%–0.9%) of middle school students (70 000 users) used cigars—the most commonly used combustible tobacco product—in the past 30 days.
  - 1.6% (95% CI, 1.3%–2.1%) of high school students (240 000 users) and 0.7% (95% CI, 0.5%–1.0%) of middle school students (80 000) used smokeless tobacco in the past 30 days.
  - 1.5% (95% CI, 1.2%–1.9%) of high school students (180 000 users) and 0.5% (95% CI, 0.4%–0.7%) of middle school students (50 000 users) used hookah in the past 30 days.
- Of youth who smoked cigarettes in the past 30 days in 2021, 18.9% (95% CI, 13.6%–25.7%) of middle and high school students (corresponding to 70 000 users) reported smoking cigarettes on 20 to 30 days of the past 30 days.[8]
- In 2022, tobacco use within the past month for middle and high school students varied by race, ethnicity, sexual identity, and transgender status:
  - The highest prevalence of tobacco product use was reported among NH American Indian or Alaska Native youth (13.5% [95% CI, 9.9%–18.2%]) compared with 13.0% (95% CI, 10.3%–16.2%) in NH multiracial youth, 12.4% (95% CI, 10.2%–14.8%) in NH White youth, 11.5% (95% CI, 9.2%–14.3%) in NH Black or African American youth; 11.1% (95% CI, 9.7%–12.8%) in Hispanic youth; and 3.1% (95% CI, 1.9%–18.2%) in NH Asian youth.

- The prevalence of past 30-day cigarette use was comparable among NH White youth (1.8% [95% CI, 1.4%–2.3%]) and Hispanic youth (1.8% [95% CI, 1.3%–2.5%]) compared with NH multiracial youth (2.3% [95% CI, 1.4%–3.9%]). For cigars, the respective percentages were 1.8% (95% CI, 1.3%–2.5%), 1.7% (95% CI, 1.3%–2.3%), and 2.2% (95% CI, 1.3%–3.7%), with the highest prevalence among NH Black youth (3.3% [95% CI, 2.3%–4.7%]). For smokeless tobacco use, the prevalence among NH White youth was 1.5% (95% CI, 1.2%–2.0%) compared with 1.2% (95% CI, 0.8%–1.7%) in Hispanic youth. For hookah use, the prevalence was highest among NH Black youth (2.3% [95% CI, 1.7%–3.1%]) compared with 0.7% (95% CI, 0.5%–1.0%) in NH White youth, 1.5% (95% CI, 1.1%–2.1%) in Hispanic youth, and 1.0% (95% CI, 0.6%–1.6%) in NH multiracial youth.[9]
  - Tobacco product use was highest among those who identified as lesbian, gay, or bisexual (16.0%) and transgender (16.6%) compared with heterosexual youth (9.7%).
- The percentage of high school (14.1% or 2 140 000 users) and middle school (3.3% or 380 000 users) students who used e-cigarettes in the past 30 days exceeded the proportion using cigarettes in the past 30 days in 2022 (Chart 3-1).

### Adults

#### (See Charts 3-2 and 3-3)

- According to the NHIS 2021 data, among adults ≥18 years of age[4]:
  - 11.5% (95% CI, 11.1%–12.0%) of adults reported cigarette use every day or some days.
  - 13.1% (95% CI, 12.4%–13.9%) of males and 10.1% (95% CI, 9.5%–10.7%) of females reported cigarette use every day or some days.
  - 5.3% of those 18 to 24 years of age, 12.6% of those 25 to 44 years of age, 14.9% of those 45 to 64 years of age, and 8.3% of those ≥65 years of age reported cigarette use every day or some days.
  - 11.7% of NH Black adults, 5.4% of NH Asian adults, 7.7% of Hispanic adults, and 11.7% of NH White adults reported cigarette use every day or some days. Prevalence rates were statistically unreliable for NH American Indian and Alaska Native adults.
  - By income-to-poverty ratio (income level), reported cigarette use every day or some days was 18.3% of people with low (0–1.99) income compared with 12.3% of those with middle (2.00–3.99) income and 6.7% of those with high (≥4.00) income.
  - In adults ≥25 years of age, the percentage reporting current cigarette use was 20.1% for those with <12 years of education, 30.7% in those with a General Educational Development high school equivalency, 17.1% among those with a high school diploma, 16.1% among those with some college, 13.7% among those with an associate's degree, and 5.3% among those with an undergraduate degree compared with 3.2% among those with a graduate degree.
  - 16.8% of those divorced, separated, or widowed; 10.9% of those who were single, never married, or not living with partner; and 10.4% of those married or living with a partner reported cigarette use every day or some days.
  - 15.3% of lesbian/gay/bisexual individuals were current smokers compared with 11.4% of heterosexual/straight individuals.
  - By region, the prevalence of current cigarette smokers was highest in the Midwest (14.0%) and South (12.4%) and lowest in the Northeast (10.4%) and West (8.9%).
- According to data from BRFSS 2021, the state with the highest age-adjusted percentage of current cigarette smokers was West Virginia (23.6%). The state with the lowest age-adjusted percentage of current cigarette smokers was Utah (7.2%; Chart 3-2).[10]
- In 2021, smoking prevalence was higher among adults ≥18 years of age who reported having a disability or activity limitation (18.5%) than among those reporting no disability or limitation (10.9%).[4]
- Among individuals who reported cigarette use every day or some days, 28.1% reported having serious psychological stress compared with 10.9% who reported no serious psychological distress; 19.4% were ever told by a health care professional that they had depression compared with 9.9% who had never been told that they had depression.[4]
- Among females who gave birth in 2017, 6.9% smoked cigarettes during pregnancy. Smoking prevalence during pregnancy was greatest for females 20 to 24 years of age (9.9%), followed by females 15 to 19 years of age (8.3%) and 25 to 29 years of age (7.9%).[11] Rates were highest among NH American Indian or Alaska Native females (15%) and lowest in NH Asian females (1%). With respect to differences by education, cigarette smoking prevalence was highest among females who completed high school (12.2%) and lowest among females with a master's degree and higher (0.3%).
- E-cigarette prevalence in 2021 is shown in Chart 3-3. Comparing current e-cigarette prevalence across the 50 states shows that the lowest age-adjusted prevalence was observed in Vermont (1.4%) and the highest prevalence was observed in Tennessee (4.2%).[10]

## Incidence

- Because 2021 NSDUH estimates are based on multimode data collection, including in-person and web interviews, and estimates from 2019 or earlier are based on in-person data collection only, 2021 estimates cannot be compared with estimates from 2019 or earlier. According to the 2021 NSDUH[12]:
  - ≈1.19 million people ≥12 years of age had smoked cigarettes for the first time within the past 12 months (2019 NSDUH; Table 4.2B). Of new smokers in 2021, 362 000 were 12 to 17 years of age, 446 000 were 18 to 20 years of age; 259 000 were 21 to 25 years of age; and 120 000 were ≥26 years of age when they first smoked cigarettes.
  - Overall, for underage individuals (12–20 years of age), use of tobacco products in the past month was 5.4% (2.1 million) compared with 21.8% (52.6 million) individuals of legal age for tobacco (≥21 years of age; 2021 NSDUH; Table 2.1A and 2.1B).
  - Among underage individuals (12 to 20 years of age), 1.3 million smoked cigarettes in the past month, of whom 253 000 were daily smokers, compared with 42.3 million individuals of legal age for tobacco (≥21 years of age), of whom 26.8 million were daily smokers (2021 NSDUH; Table 2.1A).
- According to data from the PATH study between 2013 and 2016, in youth 12 to 15 years of age, use of an e-cigarette was independently associated with new ever use of combustible cigarettes (OR, 4.09 [95% CI, 2.97–5.63]) and past 30-day use (OR, 2.75 [95% CI, 1.60–4.73]) at 2 years of follow-up. For youth who tried another non–e-cigarette tobacco product, a similar strength of association for cigarette use at 2 years was observed.[13]

## Lifetime Risk

### *Youth*

- Per NSDUH data for individuals 12 to 17 years of age, overall, the lifetime use of tobacco products was 9.4%, with lifetime cigarette use of 6.9% (2021NSDUH; Tables 2.1B and 2.4B).[12]
  - The lifetime use of tobacco products among adolescents 12 to 17 years of age varied by the following:
    - Sex: Lifetime use was higher among males (9.7%) than females (9.0%; 2021 NSDUH; Table 2.13B).
    - Race and ethnicity: Lifetime use was highest among NH White adolescents (11.6%), Hispanic or Latino adolescents (8.2%), NH Black adolescents (4.9%), and NH Asian adolescents (2.4%; 2021 NSDUH; Table 2.13B).

### *Adults*

- According to 2021 NSDUH data, the lifetime use of tobacco products in individuals ≥18 years of age was 61.7%. Lifetime cigarette use during the same year was 55.8% (2021 NSDUH; Table 2.1B). Similar to the patterns in youth, lifetime risk of tobacco products varied by demographic factors (2021 NSDUH; Table 2.13B)[12]:
  - Sex: Lifetime use was higher in males (69.2%) than females (54.6%).
  - Race and ethnicity: Lifetime use was highest in American Indian or Alaska Native adults (68.5%) and NH White adults (69.6%), followed by Hispanic or Latino adults (49.0%), NH Black adults (51.2%), and NH Asian adults (34.4%).
- In 2021, the lifetime use of smokeless tobacco for adults ≥18 years of age was 15% (2021 NSDUH; Table 2.19B).[12]

## Secular Trends

### *Youth*

#### *(See Chart 3-4)*

- According to data from MTF (8th, 10th, and 12th grades combined), the percentage of adolescents who reported smoking cigarettes in the past month was 2.3% in 2021 and 2.1% in 2022.[14] Data from NSDUH (12–17 years of age) show the percentage of adolescents who reported smoking cigarettes in the past month was 1.4% in 2020 and 1.5% in 2021.[15]

### *Adults*

- Since the US Surgeon General's first report on the health dangers of smoking, age-adjusted prevalence of smoking among adults has declined, from 51% of males smoking in 1965 to 15.6% in 2018 and from 34% of females in 1965 to 12.0% in 2018, according to NHIS data.[16] The decline in smoking, along with other factors (including improved treatment and reductions in the prevalence of risk factors such as uncontrolled hypertension and high cholesterol), is a contributing factor to secular declines in the CHD death rate.[17]
- On the basis of NHIS data between 2020 and 2021, the prevalence of cigarette smoking decreased (from 12.5% to 11.5%), whereas the prevalence of e-cigarette use increased (from 3.7% to 4.5%). In 2021, 18.7% (46 million) of US adults reported currently using any commercial tobacco product, including cigarettes (11.5%), e-cigarettes (4.5%), cigars (3.5%), smokeless tobacco (2.1%), and pipes (including hookah; 0.9%).[4]

- According to data from the BRFSS, the overall prevalence of e-cigarette use nonsignificantly increased from 4.3% to 4.8% ($P$=0.18) between 2016 and 2018 in US adults. Increases in e-cigarette use over this period were significant for middle-aged adults 45 to 54 years of age (from 3.9% in 2016 to 5.2% in 2018; $P$=0.004), females (from 3.3% in 2016 to 4.3% in 2018; $P$<0.001), and former smokers (from 5.2% in 2016 to 7.9% in 2018; $P$=0.02).[18]

## CVH Impact

- A 2010 report of the US Surgeon General on how tobacco causes disease summarized an extensive body of literature on smoking and CVD and the mechanisms through which smoking is thought to cause CVD.[19] There is a sharp increase in CVD risk with low levels of exposure to cigarette smoke (even among individuals who smoke <5 cigarettes per day), including secondhand smoke, and a less rapid further increase in risk as the number of cigarettes per day increases. Similar health risks for CHD events were reported in a systematic review of regular cigar smoking.[20]
- Smoking is an independent risk factor for CHD and appears to have a multiplicative effect with the other major risk factors for CHD: high serum levels of lipids, untreated hypertension, and diabetes.[19]
- In a contemporary cohort study of 551 338 adults, self-reported smoking was associated with a higher risk of all-cause mortality (HR, 2.80 [95% CI, 2.73–2.88]).[21] Associations were similar for both males and females but differed by race (Hispanic race, 2.01 [95% CI, 1.84–2.18]; NH Black, 2.19 [95% CI, 2.06–2.33]; NH White, 3.00 [95% CI, 2.91–3.10]; and other NH race and ethnicity, 2.16 [95% CI, 1.88–2.47]).
- Among the US Black population, cigarette use is associated with elevated measures of subclinical PAD in a dose-dependent manner whereby those who self-reported smoking ≥20 cigarettes per day and higher pack-years had higher odds of subclinical PAD compared with those who self-reported smoking 1 to 19 cigarettes per day. Current smokers had an increased adjusted odds of ABI <1 (OR, 2.2 [95% CI, 1.5–3.3]) compared with never-smokers.[22]
- A meta-analysis of 75 cohort studies (≈2.4 million individuals) demonstrated a 25% greater risk for CHD in female smokers than in male smokers (RR, 1.25 [95% CI, 1.12–1.39]).[23]
- Cigarette smoking is a risk factor for both ischemic stroke and SAH in adjusted analyses (RR, 1.9 [95% CI, 1.7–2.2] and 2.9 [95% CI, 2.5–3.5] for smokers versus nonsmokers, respectively) and has a synergistic effect on other stroke risk factors such as oral contraceptive use.[24]
- A meta-analysis comparing pooled data of ≈3.8 million smokers and nonsmokers found a similar risk of stroke associated with current smoking in females and males (RR, 1.06 [95% CI, 0.99–1.13]).[25]
- Current smokers have a 2 to 4 times increased risk of stroke compared with nonsmokers or those who have quit for >10 years.[24,26] Among JHS participants without a history of stroke (N=4410), risk of stroke was higher among current smokers compared with individuals who never smoked (HR, 2.48 [95% CI, 1.60–3.83]).[27]
- A meta-analysis of 26 studies reported that compared with never smoking, current smoking (RR, 1.75 [95% CI, 1.54–1.99]) and former smoking (RR, 1.16 [95% CI, 1.08–1.24]) were associated with an increased risk of HF.[28] In MESA, compared with never smoking, current smoking was associated with an adjusted doubling in incident HF (HR, 2.05 [95% CI, 1.36–3.09]). The increased risk was similar for HFpEF (HR, 2.51) and HFrEF (HR, 2.58).[29]
- Short-term exposure to hookah smoking is associated with a significant increase in BP and heart rate and changes in cardiac function and blood flow, similar to those associated with cigarette smoking.[30] The short-term vascular impairment associated with hookah smoking is masked by the high levels of carbon monoxide––a vasodilator molecule—released from the charcoal briquettes used to heat the flavored tobacco product.[31] In a recent meta-analysis of 42 studies, compared with nonsmokers, hookah smokers had significantly lower HDL-C (−3.39 mg/dL [95% CI, −5.13 to −1.65]; $P$<0.001) and higher LDL-C (+8.77 mg/dL [95% CI, 0.55–17.0]; $P$=0.04), triglycerides (+30.6 mg/dL [95% CI, 14.4–46.7]; $P$<0.001), and fasting glucose (+4.66 mg/dL [95% CI, 0.53–8.80]; $P$=0.03).[32] The long-term effects of hookah smoking remain unclear.
- The long-term CVD risks associated with e-cigarette use are not known because of a lack of longitudinal data.[33,34] However, e-cigarette vaping has been linked to elevated levels of preclinical biomarkers associated with cardiovascular injury such as markers for sympathetic activation, oxidative stress, inflammation, thrombosis, and vascular dysfunction.[35] In addition, daily e-cigarette use is independently associated with MI (OR, 1.79 [95% CI, 1.20–2.66]) and dual use of e-cigarettes and combustible cigarettes was associated with CVD, as a composite of self-reported CHD, MI, or stroke, compared with current combustible cigarettes users who never used e-cigarette (OR, 1.36 [95% CI, 1.18–1.56]).[36,37] Similar to e-cigarette vaping and despite the absence of tobacco combustion, flavored electronic hookah vaping has been shown to acutely impair endothelial function, likely mediated by oxidative stress.[38]

- Dual use of e-cigarettes and combustible cigarettes was associated with significantly higher odds of CVD (OR, 1.36 [95% CI, 1.18–1.56]) compared with exclusive combustible cigarette use.[37] The association of dual use (relative to exclusive cigarette use) with CVD was 1.57 (95% CI, 1.18–2.07) for daily e-cigarette users and 1.31 (95% CI, 1.13–1.53) for occasional e-cigarette users.
- In a pooled analysis of data collected from 10 randomized trials (N=2564), smokers had a higher risk of death or HF hospitalization (HR, 1.49 [95% CI, 1.09–2.02]), as well as reinfarction (HR, 1.97 [95% CI, 1.17–3.33]), after primary PCI in STEMI.[39]
- In a 2-sample mendelian randomization study that examined the causal effect of 12 lifestyle risk factors on the risk of stroke, genetically predicted lifetime smoking was associated with ischemic (OR, 1.23 [95% CI, 1.10–1.39]) and large-artery (OR, 1.72 [95% CI, 1.26–2.36]) stroke.[40] In another mendelian randomization study, genetic liability to smoking was associated with increased risk of PAD (OR, 2.13 [95% CI, 1.78–2.56]; $P=3.6\times10^{-16}$), CAD (OR, 1.48 [95% CI, 1.25–1.75]; $P=4.4\times10^{-6}$), and stroke (OR, 1.40 [95% CI, 1.02–1.92]; $P=0.04$).[41]

## Family History and Genetics

- Genetic variation contributes to smoking initiation, smoking regularity, nicotine dependence, and smoking cessation, among other smoking traits. Twin studies have estimated heritability as large as 70% for the transition from regular smoking to nicotine dependence[42] and ≈50% for other smoking measures.[43,44] A much smaller fraction (8.6%) of variation in nicotine dependence is explained by genetic variation in commonly occurring SNPs,[45] although genetic variation explains higher proportions of phenotypic variance for smoking initiation (18%) and smoking cessation (12%).[46]
- GWASs have identified loci associated with smoking initiation, heaviness of smoking, smoking regularity, and smoking cessation. In analyses of up to 1.2 million participants, common and rare variants in 298 independent loci were identified.[47] Highlights of this study include identification of novel associations between ≥1 smoking phenotypes with central nervous system–expressed nicotinic receptor genes. Loci underlying reward-related learning and memory systems, particularly the neurotransmitter glutamate, also were identified for smoking initiation phenotypes.
- Genetic loci underlying nicotine dependence also have been identified; a GWAS of >58 000 smokers of European and African ancestry identified 5 genome-wide significant loci, including 2 loci unique to nicotine dependence at *NAGI2/GNAI1* and *TENM2*.[45]
- GRSs for age at smoking initiation, number of cigarettes per day, smoking cessation, and smoking initiation explain ≈1% to 4% of phenotypic variation.[47]
- The genetic architecture of smoking shares similarities with alcohol dependence,[48] CAD,[49] and schizophrenia.[50]

## Smoking Prevention

Tobacco 21 legislation was signed into law on December 20, 2019, increasing the federal minimum age for sale of tobacco products from 18 to 21 years.[51]

- Such legislation may reduce the rates of smoking during adolescence—a time during which the majority of smokers start smoking—by limiting access because most people who buy cigarettes for adolescents are <21 years of age.
  - For instance, investigators used repeated cross-sectional, statewide surveys of adolescents in Minnesota in 2016 and 2019 across a range of tobacco products (including any tobacco, cigarettes, cigars, e-cigarettes, hookah, chewing tobacco, flavored tobacco, and multiple products).[52] Eighth and ninth grade students exposed to Tobacco 21 laws had significantly lower odds of tobacco use than unexposed students in using the following: any tobacco (aOR, 0.80 [95% CI, 0.74–0.87]), cigarettes (aOR, 0.81 [95% CI, 0.67–0.99]), e-cigarettes (aOR, 0.78 [95% CI, 0.71–0.85]), flavored tobacco (aOR, 0.79 [95% CI, 0.70–0.89]), and dual/polytobacco (aOR, 0.77 [95% CI, 0.65–0.92]).
  - In Massachusetts, investigators examined the associations between county-level Tobacco 21 laws and adolescent cigarette and e-cigarette use. Increasing Tobacco 21 laws were significantly ($P=0.01$) associated with decreases in cigarette use only among adolescents 18 years of age.[53]
  - Another study using BRFSS 2011 to 2016 data before the federal legislation found that metropolitan and micropolitan statistical areas with local Tobacco 21 policies yielded significant reductions in smoking among youth 18 to 20 years of age.[54]
- Before the federal minimum age of sale increase, 19 states (Hawaii, California, New Jersey, Oregon, Maine, Massachusetts, Illinois, Virginia, Delaware, Arkansas, Texas, Vermont, Connecticut, Maryland, Ohio, New York, Washington, Pennsylvania, and Utah), Washington, DC, and at least 470 localities (including New York City, NY; Chicago, IL; San Antonio, TX; Boston, MA; Cleveland, OH; and both Kansas City, KS, and Kansas City, MO) passed legislation setting the minimum age for the purchase of tobacco to 21 years.[55]

## Awareness, Treatment, and Control

### *Smoking Cessation*

- According to NHIS 2021 data, 66.5% of adult ever-smokers had stopped smoking; the quit rate has increased 11 percentage points since 2012 (55.1%).[4]
  - Between 2011 and 2017, according to BRFSS surveys, quit attempts varied by state, with quit attempts increasing in 4 states (Kansas, Louisiana, Virginia, and West Virginia), declining in 2 states (New York and Tennessee), and not changing significantly in 44 states. In 2017, the quit attempts over the past year were highest in Guam (72.3%) and lowest in Wisconsin (58.6%), with a median of 65.4%.[56]
  - According to NHIS 2021 data,[4] among all smokers, approximately two-thirds (66.5%) of adult ever-smokers reported having quit smoking, with rates being lower among NH Black (53.7%) than NH White (67.9%) individuals; individuals who are single, never married, or not living with a partner (51.6%) than married or living with a partner (71.1%); those with low income level (income-to-poverty ratio, 0–1.99; 46.1%) than high income level (income-to-poverty ratio ≥4.00, 72.5%); lesbian, gay, or bisexual (61.3%) than heterosexual or straight individuals (66.9%); and those with serious psychological stress (45.3%) than those without serious psychological stress (67.7%).
- According to cross-sectional data from the Population Survey Tobacco Use Supplement, past-year quit smoking attempts slightly declined from 2014 to 2015 (52.9%) to 2018 to 2019 (51.3%), with only 7.5% reporting sustained cessation.[57]
- Data from clinical settings suggest wide variation in counseling practices related to smoking cessation. In a study based on national registry data, only 1 in 3 smokers who visited a cardiology practice received smoking cessation assistance.[58]
- According to cross-sectional MEPS data from 2006 to 2015, receiving advice to quit increased over time from 60.2% in 2006 to 2007 to 64.9% in 2014 to 2015. In addition, in 2014 to 2015, use of prescription smoking cessation medicine was significantly lower among NH Black (OR, 0.51 [95% CI, 0.38–0.69]), NH Asian (OR, 0.31 [95% CI, 0.10–0.93]), and Hispanic (OR, 0.53 [95% CI, 0.36–0.78]) individuals compared with White individuals. Use of prescription smoking cessation medicine was also significantly lower among those without health insurance (OR, 0.58 [95% CI, 0.41–0.83]) and higher among females (OR, 1.28 [95% CI, 1.10–1.52]).[59] In 2014 to 2015, receipt of doctor's advice to quit among US adult smokers was significantly lower in NH Black (59.7% [95% CI, 56.1%–63.1%]) and Hispanic (57.9% [95% CI, 53.5%–62.2%]) individuals compared with NH White individuals (66.6% [95% CI, 64.1%–69.1%]).
- Smoking cessation reduces the risk of cardiovascular morbidity and mortality for smokers with and without CHD.
  - In several studies, a dose-response relationship has been seen among current smokers between the number of cigarettes smoked per day and CVD incidence.[60,61]
  - Quitting smoking at any age significantly lowers mortality from smoking-related diseases, and the risk declines with the time since quitting smoking.[1] Cessation appears to have both short-term (weeks to months) and long-term (years) benefits for lowering CVD risk. Compared with those who continued to smoke, those who quit had lower risks of recurrent major atherosclerotic cardiovascular events—a composite of stroke, MI and cardiovascular mortality (aHR, 0.66 [95% CI, 0.49–0.88]).[62]
  - Smokers who quit smoking at 25 to 34 years of age gained 10 years of life compared with those who continued to smoke. Those 35 to 44 years of age gained 9 years, those 45 to 54 years of age gained 6 years, and those 55 to 64 years of age gained 4 years of life, on average, compared with those who continued to smoke.[60]
  - Among those with a cumulative smoking history of at least 20 pack-years, individuals who quit smoking had a significantly lower risk of CVD within 5 years of smoking cessation compared with current smokers (HR, 0.61 [95% CI, 0.49–0.76]). However, former smokers' CVD risks remained significantly higher than risks for never-smokers beyond 5 years, and possibly for 25 years, after smoking cessation.[63]
- Among 726 smokers included in the Wisconsin Smokers Health Study, smoking cessation was associated with less progression of carotid plaque (mean change, 0.093 mm [SD, 0.0094]) but not IMT.[64]
- Cessation medications (including sustained-release bupropion, varenicline, nicotine gum, lozenge, nasal spray, and patch) are effective for helping smokers quit.[65,66]
- EVITA was an RCT that examined the efficacy of varenicline versus placebo for smoking cessation among smokers who were hospitalized for ACS. At 24 weeks, rates of smoking abstinence and reduction were significantly higher among patients randomized to varenicline. The abstinence rates at 24 weeks were higher in the varenicline (47.3%) than the placebo (32.5%) group ($P$=0.012; number needed to treat, 6.8). Continuous abstinence rates and reduction rates (≥50% of daily cigarette

consumption) were also higher in the varenicline group.[67]
- The EAGLES trial[68] demonstrated the efficacy and safety of 12 weeks of varenicline, bupropion, or a nicotine patch in motivated-to-quit patients who smoked with major depressive disorder, bipolar disorder, anxiety disorders, posttraumatic stress disorder, obsessive-compulsive disorder, social phobia, psychotic disorders including schizophrenia and schizoaffective disorders, and borderline personality disorder. Of note, these participants were all clinically stable from a psychiatric perspective and were believed not to be at high risk for self-injury.[68]
- Extended use of a nicotine patch (24 compared with 8 weeks) has been demonstrated to be safe and efficacious for abstinence (OR, 1.70 [95% CI, 1.03–2.81]; $P$=0.04) in randomized clinical trials.[69]
- An RCT demonstrated the effectiveness of individual- and group-oriented financial incentives for tobacco abstinence (abstinence rate range, 9.4%–16.0% with different incentives group versus 6.0% for usual care; $P$<0.05 for all comparisons) through at least 12 months of follow-up.[70]
- In addition to medications, smoke-free policies, increases in tobacco prices, cessation advice from health care professionals, quit lines, and other counseling have contributed to smoking cessation.[71,72]
- Mass media antismoking campaigns such as the CDC's Tips campaign (Tips From Former Smokers) have been shown to reduce smoking-attributable morbidity and mortality and are cost-effective. Investigators estimated that the Tips campaign cost about $48 million, saved ≈179 099 QALYs, and prevented ≈17 000 premature deaths in the United States.[73]
- Despite states having collected $25.6 billion in 2012 from the 1998 Tobacco Master Settlement Agreement and tobacco taxes, <2% of those funds are spent on tobacco prevention and cessation programs.[74]
- A randomized trial of e-cigarettes and behavioral support compared with nicotine-replacement therapy and behavioral support in adults attending the UK National Health Service stop-smoking services found that 1-year cigarette abstinence rates were 18% in the e-cigarette group compared with 9.9% in the nicotine-replacement therapy group (RR, 1.83 [95% CI, 1.30–2.58]; $P$<0.001). However, among participants abstinent at 1 year, in the nicotine-replacement therapy group, only 9% were still using nicotine-replacement therapy, whereas 80% of those in the e-cigarette group were still using e-cigarettes.[75]
- In a meta-analysis of 55 observational studies and 9 RCTs, e-cigarettes were not associated with increased smoking cessation, but e-cigarette provision was associated with increased smoking cessation.[76]
- In a double-blind, 2×2 factorial randomized clinical trial, patients were randomized to 1 of 4 medication groups: varenicline monotherapy for 12 weeks, varenicline plus nicotine patch for 12 weeks, varenicline monotherapy for 24 weeks, or varenicline plus nicotine patch for 24 weeks.[77] Results demonstrated that there were no significant differences in 7-day point prevalence abstinence at 52 weeks among those treated with combined varenicline plus nicotine patch therapy versus varenicline monotherapy or among those treated for 24 weeks versus 12 weeks.
- An RCT comparing combined treatment with varenicline and nicotine patch with placebo and nicotine patch for smoking cessation among smokers who drink heavily showed that combination treatment led to higher smoking cessation rates (44% versus 27.9%; $P$=0.04) and a lower likelihood of relapse (HR, 0.62 [95% CI, 0.40-0.96]; $P$=0.03).[78]
- In a multisite RCT of patients who were not ready to quit smoking, investigators showed that patients could be engaged in a brief abstinence game called Take a Break.[79] In this group, there was a 2-fold higher rates of cessation compared with the nicotine replacement therapy group (OR, 1.92 [95% CI, 1.01-3.68]).

## Mortality

- According to the 2020 Surgeon General's report on smoking cessation, >480 000 Americans die as a result of cigarette smoking and >41 000 die of secondhand smoke exposure each year, ≈1 in 5 deaths annually.
- Of risk factors evaluated by the US Burden of Disease Collaborators, tobacco use was the second leading risk factor for death in the United States and the leading cause of DALYs, accounting for 11% of DALYs, in 2016.[80] Overall mortality among US smokers is 3 times higher than that for never-smokers.[60]
- On average, on the basis of 2016 data, male smokers die 12 years earlier than male never-smokers, and female smokers die 11 years earlier than female never-smokers.[17,81]
- Recent analyses from multiple cycles of the Tobacco Use Supplements to the Current Population Survey (1992–1993, 1995–1996, 1998–1999, 2000, 2001–2002, 2003, 2006–2007, or 2010–2011) show that current daily (HR, 2.32 [95% CI, 2.25–2.38]) and lifelong nondaily (HR, 1.82 [95% CI, 1.65–2.01]) cigarette smokers had higher all-cause mortality risks compared with never-smokers.[82]
- Harmonized tobacco use data from adult participants in the 1991, 1992, 1998, 2000, 2005, and

2010 NHIS show that daily smokeless tobacco use (HR, 1.41 [95% CI, 1.20–1.66]) and daily cigar smoking (HR, 1.52 [95% CI, 1.12–2.08]) were associated with a higher mortality risk compared with no tobacco use.[83]

- Increased CVD mortality risks exist among daily (HR, 1.47 [95% CI, 1.40–1.54]) and nondaily (HR, 1.24 [95% CI, 1.11–1.39]) cigarette smokers compared with never tobacco smokers[84] and persist for older (≥60 years of age) smokers as well. A meta-analysis of 25 studies comparing CVD risks in 503 905 cohort participants ≥60 years of age reported an HR for cardiovascular mortality of 2.07 (95% CI, 1.82–2.36) compared with never-smokers and 1.37 (95% CI, 1.25–1.49) compared with former smokers.[85]
- In a sample of Native American individuals (SHS), among whom the prevalence of tobacco use is highest in the United States, the PAR for total mortality rate was 18.4% for males and 10.9% for females.[86]
- Since the first report on the dangers of smoking was issued by the US Surgeon General in 1964, tobacco control efforts have contributed to a reduction of 8 million premature smoking-attributable deaths.[87]
- If current smoking trends continue, 5.6 million US children will die of smoking prematurely during adulthood.[19]
- A mendelian randomization study using UK Biobank data reported that current smokers had a higher risk of hospitalization (OR, 1.80 [95% CI, 1.26–2.29]) and mortality (smoking 1–9 cigarettes/d: OR, 2.14 [95% CI, 0.87–5.24]; 10-19 cigarettes/d: OR, 5.91 [95% CI, 3.66–9.54]; ≥20 cigarettes/d: OR, 6.11 [95% CI, 3.59–10.42]).[88]

## E-Cigarettes and Vaping Products (See Charts 3-1 and 3-3)

- Electronic nicotine delivery systems are battery-operated devices that deliver nicotine, flavors, and other chemicals to the user in an aerosol without any combustion. Although e-cigarettes—the most common form of electronic nicotine delivery systems—were introduced in the United States only around 2007, there are currently >450 e-cigarette brands and vaping products on the market, with sales in the United States showing dramatic increases from 2015 ($304 million) through 2018 ($2 billion).[89–91] Juul came on the market in 2015 and has rapidly became one of the most popular vaping products sold in the United States.[92] The popularity of Juul likely relates to several factors, including its slim and modern design, appealing flavors, and intensity of nicotine delivery, which approximates the experience of combustible cigarettes.[93] Besides e-cigarettes and Juul, electronic hookahs (ie, electronic water pipes) are a newer category of vaping devices patented by Philip Morris in 2019.[94,95] Unlike e-cigarettes and Juul, electronic hookahs are used through traditional water pipes, allowing the flavored aerosol to pass through the water-filled bowl before being inhaled.[96] The popularity of electronic hookahs is driven in part by unsubstantiated claims that the presence of water "filters out toxins," rendering electronic hookahs as healthier tobacco alternatives.[97,98]
- E-cigarette use has become prevalent among never-smokers. In 2016, an estimated 1.9 million tobacco users exclusively used e-cigarettes in the United States. Of these exclusive e-cigarette users, 60% were <25 years of age.[99]
- Current e-cigarette user prevalence for 2017 in the United States is shown in Chart 3-3.
- The 2022 NYTS was fully conducted amid the unprecedented COVID-19 pandemic using an online survey—administered during January 18 until May 31—with nearly all students (99.3%) completing it on a school campus. Because of methodological changes, including differences in survey administration and data collection procedures, estimates from the 2022 NYTS are not to be compared with previous waves. According to the 2022 NYTS data[3]:
  - E-cigarettes were the most commonly used tobacco products in youth: Ever use of e-cigarettes was reported by 8.5% of middle school (1.0 million) and 28.9% of high school (4.4 million) students. In the past 30 days, 3.3% of middle school (380 000) and 14.1% of high school (2.1 million) students reported current e-cigarette use (Chart 3-1).
  - Among high school students, rates of current use were slightly higher among females (15.4%) than males (12.8%) and most pronounced among NH White students (16.9%). In middle school students, current use rates among females were 4.1% compared with 2.5% among males, with higher rates among NH multiracial (6.0%) compared with NH White (2.8 %) students.
  - Among current e-cigarette users, 84.9% (85.5% high school users and 81.5% of middle school users) used flavored e-cigarettes, with fruit (69.1%) being the most common flavor type used compared with candy, desserts, or other sweets (38.3%); mint (29.4%); and menthol (26.6%).[100]
  - Among both middle and high school current e-cigarette users, the most commonly used e-cigarette device type was disposables, followed by prefilled or refillable pods or cartridges and tanks or mod systems.[100]

- According to multiple annual data sets from NYTS data, the proportion among adolescent current tobacco users who reported first tobacco product used was e-cigarettes increased from 27.2% in 2014 to 78.3% in 2019 and remained at 77.0% in 2021.[101]
- According to the NYTS data between 2011 and 2020, current exclusive use of e-cigarettes increased significantly at an annual percentage change of 226.8% from 2011 to 2014 and 14.6% from 2014 to 2020, whereas exclusive use of any tobacco product—including cigarettes, cigars, hookahs, and smokeless tobacco—decreased significantly.[102] Among high school students, current exclusive e-cigarette use increased at an annual percentage change of 336.6% during 2011 to 2014 and 15.7% during 2014 to 2020; among middle school students, use increased at an annual percentage change of 10.4% during 2014 to 2020.
- Frequent use of e-cigarettes among high school students who were current e-cigarette users increased from 27.7% in 2018 to 34.2% in 2019. In middle school students, the percentage frequently using e-cigarettes among current users increased from 16.2% in 2018 to 18.0% in 2019.[5,8]
- In 2021, 70.3% of US middle and high school students were exposed to e-cigarette marketing (advertisements or promotions).[103] Among adolescents and young adults, a systematic review suggested an association between exposure to e-cigarette advertisement and lower harm perceptions of e-cigarettes, intention to use e-cigarettes, and e-cigarettes trial.[104]
- In 2021, the prevalence of current e-cigarette use in adults, defined as use every day or on some days, was 4.5% according to data from the NHIS. The prevalence of current e-cigarette use was highest among males (5.1%); individuals 18 to 24 years of age (11.0%); lesbian, gay, or bisexual individuals (13.2%); and those reporting serious psychological distress (10.4%).[4]
- According to data from BRFSS 2016 to 2018, current use of e-cigarettes in adults ≥18 years of age was higher in sex- and gender-underrepresented individuals.[105,106] Data from 2017 and 2018 show that the prevalence of current e-cigarette use among sex- and gender-underrepresented adults was 13.0% (95% CI, 12.0%–14.2%) versus 4.8% (95% CI, 4.6%–4.9%) among heterosexual individuals.[105] In 2016, with respect to sexual orientation, 9.0% of bisexual and 7.0% of lesbian/gay individuals were current e-cigarette users compared with 4.6% of heterosexual people. Individuals who were transgender (8.7%) were current e-cigarette users at a higher rate than cisgender individuals (4.7%). Across US states, the highest prevalence of current e-cigarette use was observed in Oklahoma (7.0%) and the lowest in South Dakota (3.1%).[106]
- Limited data exist on the prevalence of other electronic nicotine delivery devices besides e-cigarettes. According to nationally representative data from the PATH study, in 2014 to 2015, 7.7% of youth 12 to 17 years of age reported ever electronic hookah use.[107] Among adults >18 years of age, 4.6% reported ever electronic hookah use, and 26.8% of them reported current use.
- E-cigarettes contain lower levels of most tobacco-related toxic constituents compared with traditional cigarettes,[108] including volatile organic compounds.[109,110] According to nationally representative data from the PATH study (2013-2014), there was a significant reduction in urine concentrations of tobacco-specific nitrosamines [including 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol], polycyclic aromatic hydrocarbons, and volatile organic compounds, when study participants transitioned from exclusive cigarette to exclusive e-cigarette use, with a 92% decrease in 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (from 168.4 [95% CI, 102.3–277.1] to 12.9 [95% CI, 6.4–25.7] pg/mg creatinine; $P<0.001$).[111] However, nicotine levels have been found to be consistent across long-term cigarette and long-term e-cigarette users.[35,112]
- E-cigarette use has a significant cross-sectional association with a less favorable perception of physical and mental health and with depression.[113,114]
- According to the BRFSS 2016 and 2017, e-cigarettes are associated with a 39% increased odds of self-reported asthma (OR, 1.39 [95% CI, 1.15–1.68]) and self-reported chronic obstructive pulmonary disease (OR, 1.75 [95% CI, 1.25–2.45]) among never users of combustible cigarette.[115,116] There is a dose-response relationship such that higher frequency of e-cigarette use was associated with more asthma or chronic obstructive pulmonary disease.
- An outbreak of e-cigarette or vaping product use–associated lung injury peaked in September 2019 after increasing rapidly between June and August 2019. Surveillance data and product testing indicate that tetrahydrocannabinol-containing e-cigarettes or vaping products are linked to most e-cigarette– or vaping product use–associated lung injury cases. In particular, vitamin E acetate, an additive in some tetrahydrocannabinol-containing e-cigarettes or vaping, has been identified as the primary source of risk, although exposure to other e-cigarette– or vaping-related toxicants may also play a role. As of February 18, 2020, a total of 2807 hospitalized e-cigarette or vaping product use–associated lung injury cases or deaths occurred in the United States.[117]

- Effective August 8, 2016, the FDA's Deeming Rule prohibited sale of e-cigarettes to individuals <18 years of age.[118]
- In January 2020, the FDA issued a policy prioritizing enforcement against the development and distribution of certain unauthorized flavored e-cigarette products such as fruit and mint flavors (ie, any flavors other than tobacco and menthol).[119] This policy, however, applies only to cartridge- or pod-based e-cigarette products, defined as "any small, enclosed unit (sealed or unsealed) designed to fit within or operate as part of an electronic nicotine delivery system."[120] Products that would be exempted from this prohibition include self-contained, customizable, or disposable products.
- According to data from the BRFSS 2016 and 2017, e-cigarette use among adults is associated with state-level regulations and policies on e-cigarettes: OR of 0.90 (95% CI, 0.83–0.98) for laws prohibiting e-cigarette use in indoor areas; OR of 0.90 (95% CI, 0.85–0.95) for laws requiring retailers to purchase a license to sell e-cigarettes; OR of 1.04 (95% CI, 0.99–1.09) for laws prohibiting self-service displays of e-cigarettes; OR of 0.86 (95% CI, 0.74–0.99) for laws prohibiting sales of tobacco products, including e-cigarettes, to people <21 years of age; and OR of 0.89 (95% CI, 0.83–0.96) for laws applying taxes to e-cigarettes.[121]

## Secondhand Smoke

- Data from the US Surgeon General on the consequences of secondhand smoke indicate the following:
  - Nonsmokers who are exposed to secondhand smoke at home or at work have a 25% to 30% increased risk of developing CHD.[19]
  - Exposure to secondhand smoke increases the RR of stroke by 20% to 30% and is associated with increased mortality (adjusted mortality rate ratio, 2.11) after a stroke.[122]
- A meta-analysis of 23 prospective and 17 case-control studies of cardiovascular risks associated with secondhand smoke exposure demonstrated an 18%, 23%, 23%, and 29% increased RR for total mortality, total CVD, CHD, and stroke, respectively, in those exposed to secondhand smoke.[123]
- A meta-analysis of 24 studies demonstrated that secondhand smoke can increase risks for PTB by 20%.[124]
- A study using the Framingham Offspring cohort found that there was an 18% increase in AF among offspring for every 1–cigarette pack/d increase in parental smoking. In addition, offspring with parents who smoked had 1.34 (95% CI, 1.17–1.54) times the odds of smoking compared with offspring with nonsmoking parents.[125]
- As of December 31, 2022, 17 states (California, Colorado, Connecticut, Delaware, Hawaii, Massachusetts, Minnesota, New Jersey, New Mexico, New York, North Dakota, Ohio, Oregon, Rhode Island, South Dakota, Utah, and Vermont), the District of Columbia, and Puerto Rico have passed comprehensive smoke-free indoor air laws that include e-cigarettes. These laws prohibit smoking and the use of e-cigarettes in indoor areas of private worksites, restaurants, and bars.[126]
- Pooled data from 17 studies in North America, Europe, and Australia suggest that smoke-free legislation can reduce the incidence of acute coronary events by 10% (RR, 0.90 [95% CI, 0.86–0.94]).[127]
- The percentage of the US nonsmoking population with serum cotinine ≥0.05 ng/mL (which indicates exposure to secondhand smoke) declined from 52.5% in 1999 to 2000 to 24.7% in 2017 to 2018, with declines occurring for both children and adults. During 2017 to 2018, the percentage of nonsmokers with detectable serum cotinine was 38.2% for those 3 to 11 years of age, 33.2% for those 12 to 19 years of age, and 21.2% for those ≥20 years of age. The percentage was higher for NH Black individuals (48.0%) than for NH White individuals (22.0%) and Mexican American individuals (16.6%). People living below the poverty level (44.7%) had higher rates of secondhand smoke exposure than their counterparts (21.3% of those living above the poverty level; NHANES).[128,129]

## Cost

According to the Surgeon General's 50th anniversary report on the health consequences of smoking, the estimated annual cost attributable to smoking from 2009 to 2012 was between $289 and $332.5 billion: Direct medical care for adults accounted for $132.5 to $175.9 billion; lost productivity attributable to premature death accounted for $151 billion (estimated from 2005–2009); and lost productivity resulting from secondhand smoke accounted for $5.6 billion (in 2006).[17]

- In the United States, cigarette smoking was associated with 8.7% of annual aggregated health care spending from 2006 to 2010, which represented roughly $170 billion/y, 60% of which was paid by public programs (eg, Medicare and Medicaid).[130]
- According to the CDC and Federal Trade Commission, the tobacco industry spends about $9.06 billion on cigarette and smokeless tobacco advertising annually, equivalent to $25 million/d.[131] In 2018, total US e-cigarette advertising expenditures (including print, radio, television, internet, and outdoors) were estimated to be $110 million, which increased remarkably from $48 million in 2017.[132]
- In 2018, 216.9 billion cigarettes were sold by major manufacturers in the United States, which

represents a 5.3% decrease (12.2 billion units) from 2017.[133]

- Cigarette prices in the United States increased steeply between the early 1970s and 2018, in large part because of excise taxes on tobacco products. The increase in cigarette prices appeared to be larger than general inflation: Per pack in 1970, the average cost was $0.38 and tax was $0.18, whereas in 2018, the average cost was $6.90 and average tax was $2.82.[134]
- From 2012 through 2016, e-cigarette sales significantly increased while national e-cigarette prices significantly decreased,[134] with total e-cigarette unit sales exponentially increasing nearly 300% from 2016 through 2019.[135] Together, these trends highlight the rapidly changing landscape of the US e-cigarette marketplace.[134]
- Despite the morbidity and mortality resulting from tobacco use, Dieleman et al[136] estimated that tobacco interventions were among the bottom third of health care expenditures of the 154 health conditions they analyzed. They estimated that in 2019 the United States spent $1.9 billion (95% CI, $1.5–$2.3 billion) on tobacco interventions, the majority (75.6%) on individuals 20 to 64 years of age. Almost half of the funding (48.5%) for the intervention came from public insurance.

## Global Burden of Tobacco Use (See Table 3-1 and Chart 3-4)

- Of 204 countries and territories in 2021, Oceania and east Asia had the highest mortality rates attributable to tobacco. Mortality rates were lowest in Andean Latin America (Chart 3-4). In 2021, tobacco caused 7.43 (95% UI, 3.38-11.74) million deaths, with 5.77 (95% UI, 2.42-9.34) million among males and 1.66 (95% UI, 0.85-2.56) million among females (Table 3-1).[137]
- GBD investigators estimated that in 2019 tobacco was the second leading risk of mortality (high SBP was number 1), and tobacco ranked third in DALYs globally.[138]
- Worldwide, ≈80% of tobacco users live in low- and middle-income countries.[139]
- The WHO estimated that the economic cost of smoking-attributable diseases accounted for US $422 billion in 2012, which represented ≈5.7% of global health expenditures.[140] The total economic costs, including both health expenditures and lost productivity, amounted to approximately US $1436 billion, which was roughly equal to 1.8% of the world's annual gross domestic product. The WHO further estimated that 40% of the expenditures were in developing countries.
- To help combat the global problem of tobacco exposure, in 2003, the WHO adopted the Framework Convention on Tobacco Control treaty. From this emerged a set of evidence-based policies with the goal of reducing the demand for tobacco titled MPOWER. MPOWER policies outline the following strategies for nations to reduce tobacco use: (1) monitor tobacco use and prevention policies; (2) protect individuals from tobacco smoke; (3) offer to help with tobacco cessation; (4) warn about tobacco-related dangers; (5) enforce bans on tobacco advertising; (6) raise taxes on tobacco; and (7) reduce the sale of cigarettes. More than half of all nations have implemented at least 1 MPOWER policy.[106,141] In 2018, population cost coverage (either partial or full) for quit interventions increased to 78% in middle-income countries and to 97% in high-income countries; 5 billion people are now covered by at least 1 MPOWER measure. However, only 23 countries offered comprehensive cessation support in the same year.[142]
- The CDC examined data from 28 countries in the 2008 to 2016 Global Adult Tobacco Survey and reported that the median prevalence of tobacco smoking was 22.5% with wide heterogeneity (3.9% in Nigeria to 38.2% in Greece). Among current smokers, quit attempts over the prior 12 months also varied with a median of 42.5% (range, 14.4% in China to 59.6% in Senegal). Knowledge that smoking causes heart attacks (median, 83.6%; range, 38.7% in China–95.5% in Turkey) and stroke (median 73.6%; range, 27.2% in China–89.2% in Romania) varied widely across countries.[143]

**Table 3-1. Deaths Caused by Tobacco Worldwide by Sex, 2021**

| | Both sexes (95% UI) | Males (95% UI) | Females (95% UI) |
|---|---|---|---|
| Total number of deaths (millions), 2021 | 7.43 (3.38 to 11.74) | 5.77 (2.42 to 9.34) | 1.66 (0.85 to 2.56) |
| Percent change in total number, 1990–2021 | 29.51 (9.02 to 46.54) | 34.93 (15.22 to 50.68) | 13.59 (−7.63 to 39.06) |
| Percent change in total number, 2010–2021 | 11.94 (3.21 to 19.16) | 13.15 (3.75 to 22.86) | 7.90 (−1.76 to 16.76) |
| Mortality rate per 100 000, age standardized, 2021 | 87.03 (39.75 to 137.50) | 149.02 (62.60 to 241.81) | 35.69 (18.16 to 55.13) |
| Percent change in rate, age standardized, 1990–2021 | −42.56 (−48.99 to −37.38) | −41.75 (−48.45 to −36.22) | −49.70 (−55.71 to −42.06) |

(*Continued*)

**Table 3-1. Continued**

| | Both sexes (95% UI) | Males (95% UI) | Females (95% UI) |
|---|---|---|---|
| Percent change in rate, age standardized, 2010–2021 | −19.00 (−24.70 to −13.75) | −18.49 (−24.63 to −11.50) | −22.63 (−28.38 to −16.64) |
| PAF, all ages, 2021, % | 10.74 (4.95 to 16.75) | 15.07 (6.31 to 23.78) | 5.37 (2.81 to 8.30) |
| Percent change in PAF, all ages, 1990–2021 | −13.26 (−25.69 to −3.38) | −12.45 (−23.09 to −3.68) | −20.97 (−33.85 to −2.75) |
| Percent change in PAF, all ages, 2010–2021 | −14.13 (−18.99 to −9.49) | −14.31 (−19.19 to −9.94) | −15.93 (−21.57 to −9.82) |

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Disease; PAF, population attributable fraction; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[137]

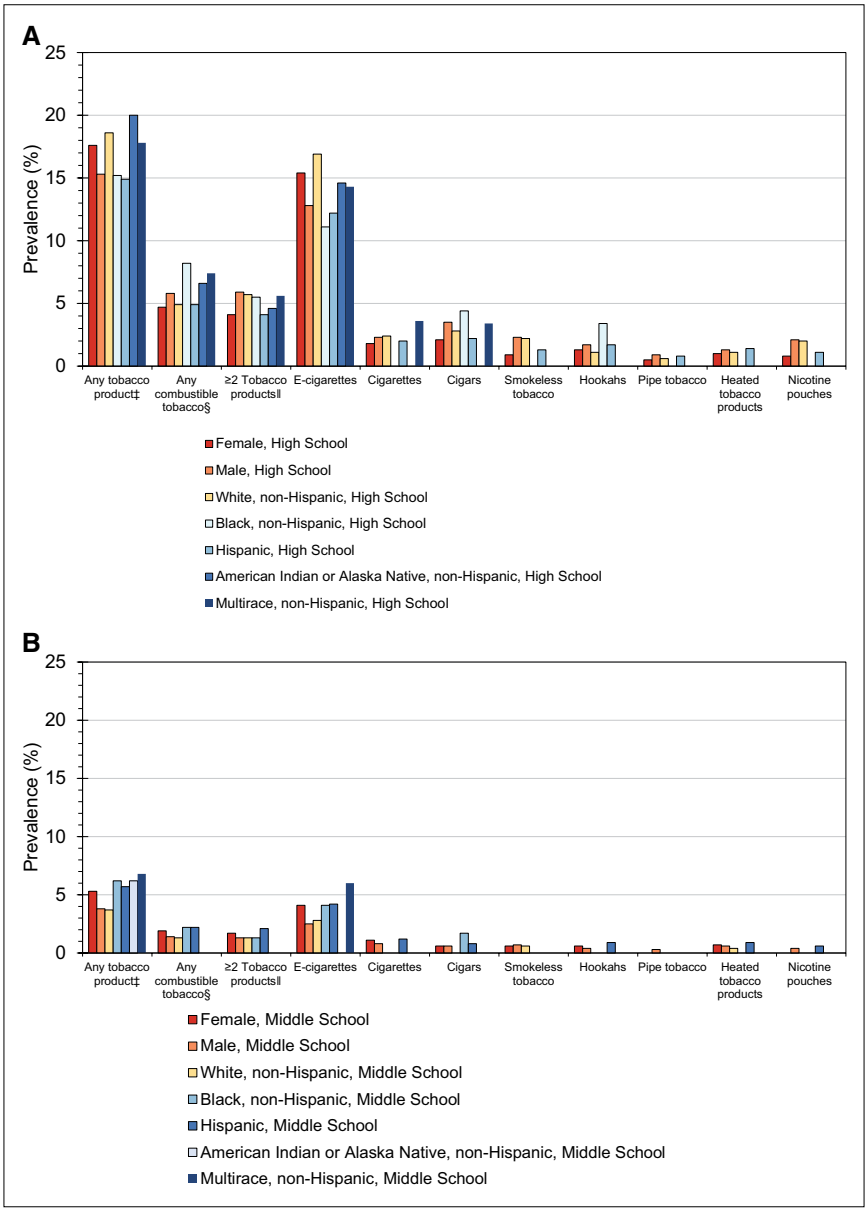



**Chart 3-1. Prevalence (percent) of tobacco use in the United States in the past 30 days by product,* school level, sex, and race and ethnicity† (NYTS, 2022).**

**A**, High school students. **B**, Middle school students. E-cigarette indicates electronic cigarette; and NYTS, National Youth Tobacco Survey.

*Past 30-day use of e-cigarettes was determined by asking "During the past 30 days, on how many days did you use e-cigarettes?" Past 30-day use of cigarettes was determined by asking "During the past 30 days, on how many days did you smoke cigarettes?" Past 30-day use of cigars was determined by asking "During the past 30 days, on how many days did you smoke cigars, cigarillos, or little cigars?" Smokeless tobacco was defined as use of chewing tobacco, snuff, dip, snus, or dissolvable tobacco products. Past 30-day use of smokeless tobacco was (*Continued*)

**Chart 3-1. Continued.** determined by asking the following question: "During the past 30 days, on how many days did you use chewing tobacco, snuff, dip, snus, or dissolvable products?" Responses from these questions were combined to derive overall smokeless tobacco use. Past 30-day use of hookahs was determined by asking "During the past 30 days, on how many days did you smoke tobacco in a hookah or water pipe?" Past 30-day use of pipe tobacco (not hookahs) was determined by asking "In the past 30 days, on how many days did you smoke pipes filled with tobacco?" Past 30-day use of heated tobacco products was determined by asking
"During the past 30 days, on how many days did you use a 'heated tobacco product'?" Past 30-day use of nicotine pouches was determined by asking "During the past 30 days, on how many days did you use a 'nicotine pouch'?" Because of missing data on the past 30-day use questions, denominators for each tobacco product might be different.
†Black people, White people, and people of other race are non-Hispanic; Hispanic people could be of any race. Non-Hispanic people who selected >1 race were classified as multiracial.
‡In 2022, any tobacco product use was defined as use of any tobacco product (e-cigarettes, cigarettes, cigars [cigars, cigarillos, or little cigars], smokeless tobacco [chewing tobacco, snuff, or dip, snus, or dissolvable tobacco products], hookahs, pipe tobacco, nicotine pouches, bidis [small brown cigarettes wrapped in a leaf], or heated tobacco products) on ≥1 day during the past 30 days.
§Any combustible tobacco product use was defined as use of cigarettes, cigars (cigars, cigarillos, or little cigars), hookahs, pipe tobacco, or bidis on ≥1 days during the past 30 days.
‖In 2022, multiple tobacco product use was defined as use of ≥2 tobacco products (e-cigarettes, cigarettes, cigars [cigars, cigarillos, or little cigars], smokeless tobacco [chewing tobacco, snuff, or dip, snus, or dissolvable tobacco products], hookahs, pipe tobacco, nicotine pouches, bidis, or heated tobacco products) on ≥1 days during the past 30 days.
Source: Data derived from Park-Lee et al.[3]

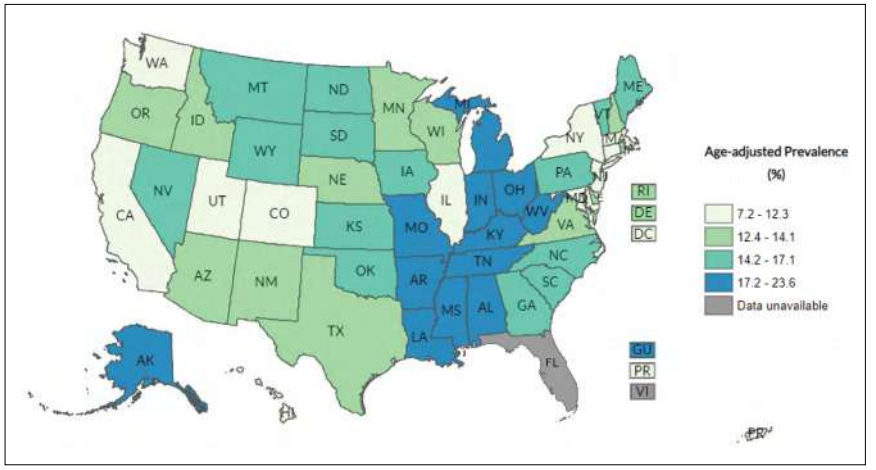



**Chart 3-2. Age-adjusted prevalence (percent) of current cigarette smoking for US adults by state (BRFSS, 2021).**
White space between the map and legend has been removed. Icons and drop-down menus for interactive tools have been removed.
BRFSS indicates Behavior Risk Factor Surveillance System.
Source: BRFSS prevalence and trends data.[10]

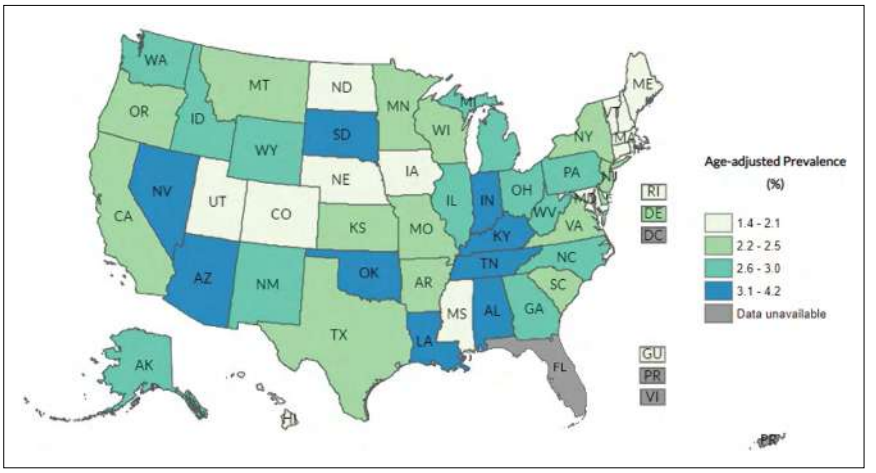



**Chart 3-3. Prevalence (age-adjusted) of current electronic cigarette use, United States (BRFSS, 2021).**
White space between the map and legend has been removed. Icons and drop-down menus for interactive tools have been removed.
BRFSS indicates Behavior Risk Factor Surveillance System.
Source: BRFSS prevalence and trends data.[10]

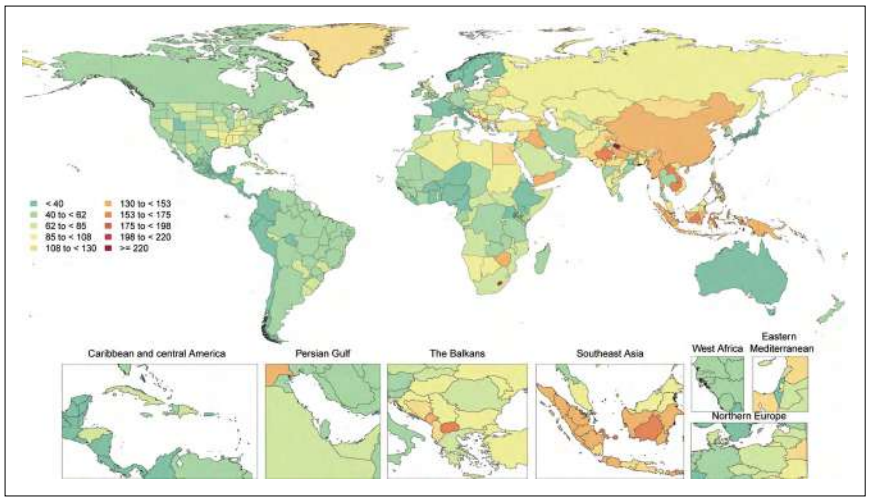



**Chart 3-4. Age-standardized global mortality rates attributable to tobacco per 100 000, both sexes, 2021.**
During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.
GBD indicates Global Burden of Disease.
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[137]

## REFERENCES


1. Thun MJ, Carter BD, Feskanich D, Freedman ND, Prentice R, Lopez AD, Hartge P, Gapstur SM. 50-Year trends in smoking-related mortality in the United States. *N Engl J Med*. 2013;368:351–364. doi: 10.1056/nejmsa1211127
2. Lloyd-Jones DM, Allen NB, Anderson CAM, Black T, Brewer LC, Foraker RE, Grandner MA, Lavretsky H, Perak AM, Sharma G, et al; on behalf of the American Heart Association. Life's Essential 8: updating and enhancing the American Heart Association's construct of cardiovascular health: a presidential advisory from the American Heart Association. *Circulation*. 2022;146:e18–e43. doi: 10.1161/CIR.0000000000001078
3. Park-Lee E, Ren C, Cooper M, Cornelius M, Jamal A, Cullen KA. Tobacco product use among middle and high school students–United States, 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71:1429–1435. doi: 10.15585/mmwr.mm7145a1
4. Cornelius ME, Loretan CG, Jamal A, Davis Lynn BC, Mayer M, Alcantara IC, Neff L. Tobacco product use among adults–United States, 2021. *MMWR Morb Mortal Wkly Rep*. 2023;72:475–483. doi: 10.15585/mmwr.mm7218a1
5. Gentzke AS, Creamer M, Cullen KA, Ambrose BK, Willis G, Jamal A, King BA. Vital signs: tobacco product use among middle and high school students–United States, 2011–2018. *MMWR Morb Mortal Wkly Rep*. 2019;68:157–164. doi: 10.15585/mmwr.mm6806e1
6. Centers for Disease Control and Prevention (CDC). Electronic nicotine delivery systems key facts. 2019. Accessed March 26, 2023. https://chronicdata.cdc.gov/Policy/Electronic-Nicotine-Delivery-Systems-Key-Facts-Inf/nwhw-m4ki
7. Barrington-Trimis JL, Leventhal AM. Adolescents' use of "pod mod" e-cigarettes: urgent concerns. *N Engl J Med*. 2018;379:1099–1102. doi: 10.1056/NEJMp1805758
8. Wang TW, Gentzke AS, Creamer MR, Cullen KA, Holder-Hayes E, Sawdey MD, Anic GM, Portnoy DB, Hu S, Homa DM, et al. Tobacco product use and associated factors among middle and high school students–United States, 2019. *MMWR Surveill Summ*. 2019;68:1–22. doi: 10.15585/mmwr.ss6812a1
9. Gentzke AS, Wang TW, Jamal A, Park-Lee E, Ren C, Cullen KA, Neff L. Tobacco product use among middle and high school students–United States, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69:1881–1888. doi: 10.15585/mmwr.mm6950a1
10. Centers for Disease Control and Prevention and National Center for Chronic Disease Prevention and Health Promotion. Behavioral Risk Factor Surveillance System (BRFSS): BRFSS prevalence & trends data. Accessed March 27, 2023. https://cdc.gov/brfss/brfssprevalence/
11. Azagba S, Manzione L, Shan L, King J. Trends in smoking during pregnancy by socioeconomic characteristics in the United States, 2010-2017. *BMC Pregnancy Childbirth*. 2020;20:52. doi: 10.1186/s12884-020-2748-y
12. Center for Behavioral Statistics and Quality and Substance Abuse and Mental Health Services Administration. Results from the 2021 National Survey on Drug Use and Health: detailed tables. 2023. Accessed April 9, 2023. http://samhsa.gov/data/report/2021-nsduh-detailed-tables
13. Berry KM, Fetterman JL, Benjamin EJ, Bhatnagar A, Barrington-Trimis JL, Leventhal AM, Stokes A. Association of electronic cigarette use with subsequent initiation of tobacco cigarettes in US youths. *JAMA Netw Open*. 2019;2:e187794. doi: 10.1001/jamanetworkopen.2018.7794
14. Johnston LD, Miech RA, Patrick ME, O'Malley PM, Schulenberg JE, Bachman J; Institute for Social Research. Monitoring the future: national survey results on drug use 1975-2022: overview, key findings on adolescent drug use 2023. Accessed May 17, 2023. https://monitoringthefuture.org/wp-content/uploads/2023/01/mtfoverview2022.pdf
15. *Key Substance Use and Mental Health Indicators in the United States: Results From the 2021 National Survey on Drug Use and Health*. Center for Behavioral Health Statistics and Quality and Substance Abuse and Mental Health Services Administration; 2022. HHS Publication No. PEP22-07-01-005, NSDUH Series H-57.
16. Creamer MR, Wang TW, Babb S, Cullen KA, Day H, Willis G, Jamal A, Neff L. Tobacco product use and cessation indicators among adults–United States, 2018. *MMWR Morb Mortal Wkly Rep*. 2019;68:1013–1019. doi: 10.15585/mmwr.mm6845a2
17. National Center for Chronic Disease Prevention and Health Promotion and Office on Smoking and Health. *The Health Consequences of Smoking-50 Years of Progress: A Report of the Surgeon General*. US Department of Health and Human Services, Centers for Disease Control and Prevention; 2014.
18. Al Rifai M, Merchant AT, Nambi V, Jia X, Gulati M, Valero-Elizondo J, Nasir K, Ballantyne CM, Virani SS. Temporal trends in e-cigarette use among U.S. adults: Behavioral Risk Factor Surveillance System, 2016 to 2018. *Am J Med*. 2020;133:e508–e511. doi: 10.1016/j.amjmed.2019.12.020
19. US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion and Office on Smoking and Health. *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General*. Centers for Disease Control and Prevention; 2010.
20. Chang CM, Corey CG, Rostron BL, Apelberg BJ. Systematic review of cigar smoking and all cause and smoking related mortality. *BMC Public Health*. 2015;15:390. doi: 10.1186/s12889-015-1617-5
21. Thomson B, Emberson J, Lacey B, Lewington S, Peto R, Jemal A, Islami F. Association between smoking, smoking cessation, and mortality by race, ethnicity, and sex among US adults. *JAMA Netw Open*. 2022;5:e2231480. doi: 10.1001/jamanetworkopen.2022.31480
22. Clark D 3rd, Cain LR, Blaha MJ, DeFilippis AP, Mentz RJ, Kamimura D, White WB, Butler KR, Robertson RM, Bhatnagar A, et al. Cigarette smoking and subclinical peripheral arterial disease in Blacks of the Jackson Heart Study. *J Am Heart Assoc*. 2019;8:e010674. doi: 10.1161/JAHA.118.010674
23. Huxley RR, Woodward M. Cigarette smoking as a risk factor for coronary heart disease in women compared with men: a systematic review and meta-analysis of prospective cohort studies. *Lancet*. 2011;378:1297–1305. doi: 10.1016/S0140-6736(11)60781-2

24. Meschia JF, Bushnell C, Boden-Albala B, Braun LT, Bravata DM, Chaturvedi S, Creager MA, Eckel RH, Elkind MS, Fornage M, et al; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, Council on Functional Genomics and Translational Biology, and Council on Hypertension. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45:3754–3832. doi: 10.1161/STR.0000000000000046
25. Peters SA, Huxley RR, Woodward M. Smoking as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 81 cohorts, including 3,980,359 individuals and 42,401 strokes. *Stroke*. 2013;44:2821–2828. doi: 10.1161/STROKEAHA.113.002342
26. Shah RS, Cole JW. Smoking and stroke: the more you smoke the more you stroke. *Expert Rev Cardiovasc Ther*. 2010;8:917–932. doi: 10.1586/erc.10.56
27. Oshunbade AA, Yimer WK, Valle KA, Clark D 3rd, Kamimura D, White WB, DeFilippis AP, Blaha MJ, Benjamin EJ, O'Brien EC, et al. Cigarette smoking and incident stroke in Blacks of the Jackson Heart Study. *J Am Heart Assoc*. 2020;9:e014990. doi: 10.1161/JAHA.119.014990
28. Aune D, Schlesinger S, Norat T, Riboli E. Tobacco smoking and the risk of heart failure: a systematic review and meta-analysis of prospective studies. *Eur J Prev Cardiol*. 2019;26:279–288. doi: 10.1177/2047487318806658
29. Watson M, Dardari Z, Kianoush S, Hall ME, DeFilippis AP, Keith RJ, Benjamin EJ, Rodriguez CJ, Bhatnagar A, Lima JA, et al. Relation between cigarette smoking and heart failure (from the Multiethnic Study of Atherosclerosis). *Am J Cardiol*. 2019;123:1972–1977. doi: 10.1016/j.amjcard.2019.03.015
30. Bhatnagar A, Maziak W, Eissenberg T, Ward KD, Thurston G, King BA, Sutfin EL, Cobb CO, Griffiths M, Goldstein LB, et al; on behalf of the American Heart Association Behavioral Change for Improving Health Factors Committee of the Council on Lifestyle and Cardiometabolic Health and Council on Epidemiology and Prevention; Council on Cardiovascular and Stroke Nursing; Council on Quality of Care and Outcomes Research; and Stroke Council. Water pipe (hookah) smoking and cardiovascular disease risk: a scientific statement from the American Heart Association. *Circulation*. 2019;139:e917–e936. doi: 10.1161/CIR.0000000000000671
31. Rezk-Hanna M, Mosenifar Z, Benowitz NL, Rader F, Rashid M, Davoren K, Moy NB, Doering L, Robbins W, Sarna L, et al. High carbon monoxide levels from charcoal combustion mask acute endothelial dysfunction induced by hookah (waterpipe) smoking in young adults. *Circulation*. 2019;139:2215–2224. doi: 10.1161/CIRCULATIONAHA.118.037375
32. Al Ali R, Vukadinović D, Maziak W, Katmeh L, Schwarz V, Mahfoud F, Laufs U, Böhm M. Cardiovascular effects of waterpipe smoking: a systematic review and meta-analysis. *Rev Cardiovasc Med*. 2020;21:453–468. doi: 10.31083/j.rcm.2020.03.135
33. Bhatnagar A, Whitsel LP, Ribisl KM, Bullen C, Chaloupka F, Piano MR, Robertson RM, McAuley T, Goff D, Benowitz N; on behalf of the American Heart Association Advocacy Coordinating Committee, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Quality of Care and Outcomes Research. Electronic cigarettes: a policy statement from the American Heart Association. *Circulation*. 2014;130:1418–1436. doi: 10.1161/CIR.0000000000000107
34. Bhatnagar A. E-cigarettes and cardiovascular disease risk: evaluation of evidence, policy implications, and recommendations. *Curr Cardiovasc Risk Rep*. 2016;10:24.
35. Middlekauff HR. Cardiovascular impact of electronic-cigarette use. *Trends Cardiovasc Med*. 2020;30:133–140. doi: 10.1016/j.tcm.2019.04.006
36. Alzahrani T, Pena I, Temesgen N, Glantz SA. Association between electronic cigarette use and myocardial infarction. *Am J Prev Med*. 2018;55:455–461. doi: 10.1016/j.amepre.2018.05.004
37. Osei AD, Mirbolouk M, Orimoloye OA, Dzaye O, Uddin SMI, Benjamin EJ, Hall ME, DeFilippis AP, Stokes A, Bhatnagar A, et al. Association between e-cigarette use and cardiovascular disease among never and current combustible-cigarette smokers. *Am J Med*. 2019;132:949–954.e2. doi: 10.1016/j.amjmed.2019.02.016
38. Rezk-Hanna M, Seals DR, Rossman MJ, Gupta R, Nettle CO, Means A, Dobrin D, Cheng CW, Brecht ML, Mosenifar Z, et al. Ascorbic acid prevents vascular endothelial dysfunction induced by electronic hookah (waterpipe) vaping. *J Am Heart Assoc*. 2021;10:e019271. doi: 10.1161/JAHA.120.019271
39. Redfors B, Furer A, Selker HP, Thiele H, Patel MR, Chen S, Udelson JE, Ohman EM, Eitel I, Granger CB, et al. Effect of smoking on outcomes of primary PCI in patients with STEMI. *J Am Coll Cardiol*. 2020;75:1743–1754. doi: 10.1016/j.jacc.2020.02.045
40. Harshfield EL, Georgakis MK, Malik R, Dichgans M, Markus HS. Modifiable lifestyle factors and risk of stroke: a mendelian randomization analysis. *Stroke*. 2021;52:931–936. doi: 10.1161/STROKEAHA.120.031710
41. Levin MG, Klarin D, Assimes TL, Freiberg MS, Ingelsson E, Lynch J, Natarajan P, O'Donnell C, Rader DJ, Tsao PS, et al; VA Million Veteran Program. Genetics of smoking and risk of atherosclerotic cardiovascular diseases: a mendelian randomization study. *JAMA Netw Open*. 2021;4:e2034461. doi: 10.1001/jamanetworkopen.2020.34461
42. Sullivan PF, Kendler KS. The genetic epidemiology of smoking. *Nicotine Tob Res*. 1999;1(suppl 2):S51–S57. doi: 10.1080/14622299050011811
43. Swan GE, Carmelli D, Rosenman RH, Fabsitz RR, Christian JC. Smoking and alcohol consumption in adult male twins: genetic heritability and shared environmental influences. *J Subst Abuse*. 1990;2:39–50. doi: 10.1016/s0899-3289(05)80044-6
44. Kaprio J. Genetic epidemiology of smoking behavior and nicotine dependence. *COPD*. 2009;6:304–306. doi: 10.1080/15412550903049165
45. Quach BC, Bray MJ, Gaddis NC, Liu M, Palviainen T, Minica CC, Zellers S, Sherva R, Aliev F, Nothnagel M, et al. Expanding the genetic architecture of nicotine dependence and its shared genetics with multiple traits. *Nat Commun*. 2020;11:5562. doi: 10.1038/s41467-020-19265-z
46. Evans LM, Jang S, Hancock DB, Ehringer MA, Otto JM, Vrieze SI, Keller MC. Genetic architecture of four smoking behaviors using partitioned SNP heritability. *Addiction*. 2021;116:2498–2508. doi: 10.1111/add.15450
47. Liu M, Jiang Y, Wedow R, Li Y, Brazel DM, Chen F, Datta G, Davila-Velderrain J, McGuire D, Tian C, et al. Association studies of up to 1.2 million individuals yield new insights into the genetic etiology of tobacco and alcohol use. *Nat Genet*. 2019;51:237–244. doi: 10.1038/s41588-018-0307-5
48. Walters RK, Polimanti R, Johnson EC, McClintick JN, Adams MJ, Adkins AE, Aliev F, Bacanu SA, Batzler A, Bertelsen S, et al. Transancestral GWAS of alcohol dependence reveals common genetic underpinnings with psychiatric disorders. *Nat Neurosci*. 2018;21:1656–1669. doi: 10.1038/s41593-018-0275-1
49. Nikpay M, Goel A, Won HH, Hall LM, Willenborg C, Kanoni S, Saleheen D, Kyriakou T, Nelson CP, Hopewell JC, et al. A comprehensive 1,000 Genomes-based genome-wide association meta-analysis of coronary artery disease. *Nat Genet*. 2015;47:1121–1130. doi: 10.1038/ng.3396
50. Song W, Lin GN, Yu S, Zhao M. Genome-wide identification of the shared genetic basis of cannabis and cigarette smoking and schizophrenia implicates *NCAM1* and neuronal abnormality. *Psychiatry Res*. 2022;310:114453. doi: 10.1016/j.psychres.2022.114453
51. US Food and Drug Administration. Tobacco 21. Accessed April 9, 2023. https://fda.gov/tobacco-products/retail-sales-tobacco-products/tobacco-21
52. Wilhelm AK, Kingsbury JH, Eisenberg ME, Shyne M, Helgertz S, Borowsky IW. Local Tobacco 21 policies are associated with lower odds of tobacco use among adolescents. *Nicotine Tob Res*. 2022;24:478–483. doi: 10.1093/ntr/ntab200
53. Hawkins SS, Kruzik C, O'Brien M, Levine Coley R. Flavoured tobacco product restrictions in Massachusetts associated with reductions in adolescent cigarette and e-cigarette use. *Tob Control*. 2021;31:576–579. doi: 10.1136/tobaccocontrol-2020-056159
54. Friedman AS, Wu RJ. Do local Tobacco-21 laws reduce smoking among 18 to 20 year-olds? *Nicotine Tob Res*. 2020;22:1195–1201. doi: 10.1093/ntr/ntz123
55. Municipal Tobacco Control Technical Assistance Program. States and localities that have raised the minimum legal sale age for tobacco products to 21. Accessed March 19, 2023. https://tobaccofreekids.org/assets/content/what_we_do/state_local_issues/sales_21/states_localities_MLSA_21.pdf
56. Walton K, Wang TW, Schauer GL, Hu S, McGruder HF, Jamal A, Babb S. State-specific prevalence of quit attempts among adult cigarette smokers–United States, 2011-2017. *MMWR Morb Mortal Wkly Rep*. 2019;68:621–626. doi: 10.15585/mmwr.mm6828a1
57. Leventhal AM, Dai H, Higgins ST. Smoking cessation prevalence and inequalities in the United States: 2014-2019. *J Natl Cancer Inst*. 2022;114:381–390. doi: 10.1093/jnci/djab208
58. Sardana M, Tang Y, Magnani JW, Ockene IS, Allison JJ, Arnold SV, Jones PG, Maddox TM, Virani SS, McManus DD. Provider-level variation in smoking cessation assistance provided in the cardiology clinics: insights from the NCDR PINNACLE Registry. *J Am Heart Assoc*. 2019;8:e011412. doi: 10.1161/JAHA.118.011307
59. Tibuakuu M, Okunrintemi V, Jirru E, Echouffo Tcheugui JB, Orimoloye OA, Mehta PK, DeFilippis AP, Blaha MJ, Michos ED. National trends in cessation counseling, prescription medication use, and associated costs among

US adult cigarette smokers. *JAMA Netw Open*. 2019;2:e194585. doi: 10.1001/jamanetworkopen.2019.4585
60. Jha P, Ramasundarahettige C, Landsman V, Rostron B, Thun M, Anderson RN, McAfee T, Peto R. 21st-Century hazards of smoking and benefits of cessation in the United States. *N Engl J Med*. 2013;368:341–350. doi: 10.1056/NEJMsa1211128
61. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, et al; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364:937–952. doi: 10.1016/S0140-6736(04)17018-9
62. van den Berg MJ, van der Graaf Y, Deckers JW, de Kanter W, Algra A, Kappelle LJ, de Borst GJ, Cramer MM, Visseren FLJ; SMART Study Group. Smoking cessation and risk of recurrent cardiovascular events and mortality after a first manifestation of arterial disease. *Am Heart J*. 2019;213:112–122. doi: 10.1016/j.ahj.2019.03.019
63. Duncan MS, Freiberg MS, Greevy RA Jr, Kundu S, Vasan RS, Tindle HA. Association of smoking cessation with subsequent risk of cardiovascular disease. *JAMA*. 2019;322:642–650. doi: 10.1001/jama.2019.10298
64. Stein JH, Smith SS, Hansen KM, Korcarz CE, Piper ME, Fiore MC, Baker TB. Longitudinal effects of smoking cessation on carotid artery atherosclerosis in contemporary smokers: the Wisconsin Smokers Health Study. *Atherosclerosis*. 2020;315:62–67. doi: 10.1016/j.atherosclerosis.2020.11.010
65. Clinical Practice Guideline Treating Tobacco Use and Dependence 2008 Update Panel, Liaisons and Staff. A clinical practice guideline for treating tobacco use and dependence: 2008 update. A U.S. Public Health Service report. *Am J Prev Med*. 2008;35:158–176. doi: 10.1016/j.amepre.2008.04.009
66. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease [published corrections appear in *Circulation*. 2019;140:e649–e650, *Circulation*. 2020;141:e60, and *Circulation*. 2020;141:e774]. *Circulation*. 2019;140:e596–e646. doi: 10.1161/CIR.0000000000000678
67. Eisenberg MJ, Windle SB, Roy N, Old W, Grondin FR, Bata I, Iskander A, Lauzon C, Srivastava N, Clarke A, et al; EVITA Investigators. Varenicline for smoking cessation in hospitalized patients with acute coronary syndrome. *Circulation*. 2016;133:21–30. doi: 10.1161/CIRCULATIONAHA.115.019634
68. Anthenelli RM, Benowitz NL, West R, St Aubin L, McRae T, Lawrence D, Ascher J, Russ C, Krishen A, Evins AE. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. *Lancet*. 2016;387:2507–2520. doi: 10.1016/S0140-6736(16)30272-0
69. Schnoll RA, Goelz PM, Veluz-Wilkins A, Blazekovic S, Powers L, Leone FT, Gariti P, Wileyto EP, Hitsman B. Long-term nicotine replacement therapy: a randomized clinical trial. *JAMA Intern Med*. 2015;175:504–511. doi: 10.1001/jamainternmed.2014.8313
70. Halpern SD, French B, Small DS, Saulsgiver K, Harhay MO, Audrain-McGovern J, Loewenstein G, Brennan TA, Asch DA, Volpp KG. Randomized trial of four financial-incentive programs for smoking cessation. *N Engl J Med*. 2015;372:2108–2117. doi: 10.1056/NEJMoa1414293
71. Babb S, Malarcher A, Schauer G, Asman K, Jamal A. Quitting smoking among adults–United States, 2000-2015. *MMWR Morb Mortal Wkly Rep*. 2017;65:1457–1464. doi: 10.15585/mmwr.mm6552a1
72. Centers for Disease Control and Prevention. Quitting smoking among adults–United States, 2001-2010. *MMWR Morb Mortal Wkly Rep*. 2011;60:1513–1519.
73. Xu X, Alexander RL Jr, Simpson SA, Goates S, Nonnemaker JM, Davis KC, McAfee T. A cost-effectiveness analysis of the first federally funded antismoking campaign. *Am J Prev Med*. 2015;48:318–325. doi: 10.1016/j.amepre.2014.10.011
74. Antman E, Arnett D, Jessup M, Sherwin C. The 50th anniversary of the US Surgeon General's report on tobacco: what we've accomplished and where we go from here. *J Am Heart Assoc*. 2014;3:e000740. doi: 10.1161/JAHA.113.000740
75. Hajek P, Phillips-Waller A, Przulj D, Pesola F, Myers Smith K, Bisal N, Li J, Parrott S, Sasieni P, Dawkins L, et al. A randomized trial of e-cigarettes versus nicotine-replacement therapy. *N Engl J Med*. 2019;380:629–637. doi: 10.1056/NEJMoa1808779
76. Wang RJ, Bhadriraju S, Glantz SA. E-cigarette use and adult cigarette smoking cessation: a meta-analysis. *Am J Public Health*. 2021;111:230–246. doi: 10.2105/AJPH.2020.305999
77. Baker TB, Piper ME, Smith SS, Bolt DM, Stein JH, Fiore MC. Effects of combined varenicline with nicotine patch and of extended treatment duration on smoking cessation: a randomized clinical trial. *JAMA*. 2021;326:1485–1493. doi: 10.1001/jama.2021.15333
78. King A, Vena A, de Wit H, Grant JE, Cao D. Effect of combination treatment with varenicline and nicotine patch on smoking cessation among smokers who drink heavily: a randomized clinical trial. *JAMA Netw Open*. 2022;5:e220951. doi: 10.1001/jamanetworkopen.2022.0951
79. Houston TK, Chen J, Amante DJ, Blok AC, Nagawa CS, Wijesundara JG, Kamberi A, Allison JJ, Person SD, Flahive J, et al. Effect of technology-assisted brief abstinence game on long-term smoking cessation in individuals not yet ready to quit: a randomized clinical trial. *JAMA Intern Med*. 2022;182:303–312. doi: 10.1001/jamainternmed.2021.7866
80. Mokdad AH, Ballestros K, Echko M, Glenn S, Olsen HE, Mullany E, Lee A, Khan AR, Ahmadi A, Ferrari AJ, et al; US Burden of Disease Collaborators. The state of US Health, 1990-2016: burden of diseases, injuries, and risk factors among US states. *JAMA*. 2018;319:1444–1472. doi: 10.1001/jama.2018.0158
81. National Center for Health Statistics, Centers for Disease Control and Prevention. National Health Interview Survey: public-use data files and documentation. Accessed March 15, 2023. https://cdc.gov/nchs/nhis/index.htm
82. Inoue-Choi M, McNeel TS, Hartge P, Caporaso NE, Graubard BI, Freedman ND. Non-daily cigarette smokers: mortality risks in the U.S. *Am J Prev Med*. 2019;56:27–37. doi: 10.1016/j.amepre.2018.06.025
83. Inoue-Choi M, Shiels MS, McNeel TS, Graubard BI, Hatsukami D, Freedman ND. Contemporary associations of exclusive cigarette, cigar, pipe, and smokeless tobacco use with overall and cause-specific mortality in the United States. *JNCI Cancer Spectr*. 2019;3:pkz036. doi: 10.1093/jncics/pkz036
84. Christensen CH, Rostron B, Cosgrove C, Altekruse SF, Hartman AM, Gibson JT, Apelberg B, Inoue-Choi M, Freedman ND. Association of cigarette, cigar, and pipe use with mortality risk in the US population. *JAMA Intern Med*. 2018;178:469–476. doi: 10.1001/jamainternmed.2017.8625
85. Mons U, Muezzinler A, Gellert C, Schottker B, Abnet CC, Bobak M, de Groot L, Freedman ND, Jansen E, Kee F, et al; CHANCES Consortium. Impact of smoking and smoking cessation on cardiovascular events and mortality among older adults: meta-analysis of individual participant data from prospective cohort studies of the CHANCES consortium. *BMJ*. 2015;350:h1551. doi: 10.1136/bmj.h1551
86. Zhang M, An Q, Yeh F, Zhang Y, Howard BV, Lee ET, Zhao J. Smoking-attributable mortality in American Indians: findings from the Strong Heart Study. *Eur J Epidemiol*. 2015;30:553–561. doi: 10.1007/s10654-015-0031-8
87. Holford TR, Meza R, Warner KE, Meernik C, Jeon J, Moolgavkar SH, Levy DT. Tobacco control and the reduction in smoking-related premature deaths in the United States, 1964-2012. *JAMA*. 2014;311:164–171. doi: 10.1001/jama.2013.285112
88. Clift AK, von Ende A, Tan PS, Sallis HM, Lindson N, Coupland CAC, Munafò MR, Aveyard P, Hippisley-Cox J, Hopewell JC. Smoking and COVID-19 outcomes: an observational and mendelian randomisation study using the UK Biobank cohort. *Thorax*. 2022;77:65–73. doi: 10.1136/thoraxjnl-2021-217080
89. Walley SC, Wilson KM, Winickoff JP, Groner J. A public health crisis: electronic cigarettes, vape, and Juul. *Pediatrics*. 2019;143:e20182741. doi: 10.1542/peds.2018-2741
90. Zhu SH, Sun JY, Bonnevie E, Cummins SE, Gamst A, Yin L, Lee M. Four hundred and sixty brands of e-cigarettes and counting: implications for product regulation. *Tob Control*. 2014;23:iii3–iii9. doi: 10.1136/tobaccocontrol-2014-051670
91. Federal Trade Commission. E-cigarette report for 2015-2018. Accessed April 9, 2023. https://ftc.gov/system/files/ftc_gov/pdf/E-Cigarette-Report-2015-2018.pdf
92. Hammond D, Wackowski OA, Reid JL, O'Connor RJ. Use of Juul e-cigarettes among youth in the United States. *Nicotine Tob Res*. 2020;22:827–832. doi: 10.1093/ntr/nty237
93. Bhatnagar A, Whitsel LP, Blaha MJ, Huffman MD, Krishan-Sarin S, Maa J, Rigotti N, Robertson RM, Warner JJ; on behalf of the American Heart Association. New and emerging tobacco products and the nicotine endgame: the role of robust regulation and comprehensive tobacco control and prevention: a presidential advisory from the American Heart Association. *Circulation*. 2019;139:e937–e958. doi: 10.1161/CIR.0000000000000669

94. Jawad M, Shihadeh A, Nakkash RT. Philip Morris patents "harm reduction" electronic waterpipe. *Tob Control*. 2020;30:473–473. doi: 10.1136/tobaccocontrol-2020-055885
95. Dube SR, Pathak S, Nyman AL, Eriksen MP. Electronic cigarette and electronic hookah: a pilot study comparing two vaping products. *Prev Med Rep*. 2015;2:953–958. doi: 10.1016/j.pmedr.2015.10.012
96. Rezk-Hanna M, Benowitz NL. Cardiovascular effects of hookah smoking: potential implications for cardiovascular risk. *Nicotine Tob Res*. 2019;21:1151–1161. doi: 10.1093/ntr/nty065
97. Cornacchione J, Wagoner KG, Wiseman KD, Kelley D, Noar SM, Smith MH, Sutfin EL. Adolescent and young adult perceptions of hookah and little cigars/cigarillos: implications for risk messages. *J Health Commun*. 2016;21:818–825. doi: 10.1080/10810730.2016.1177141
98. Griffiths M, Harmon T, Gily M. Hubble bubble trouble: the need for education about and regulation of hookah smoking. *J Public Policy Marketing*. 2011;30:119–132.
99. Mirbolouk M, Charkhchi P, Orimoloye OA, Uddin SMI, Kianoush S, Jaber R, Bhatnagar A, Benjamin EJ, Hall ME, DeFilippis AP, et al. E-cigarette use without a history of combustible cigarette smoking among U.S. adults: Behavioral Risk Factor Surveillance System, 2016. *Ann Intern Med*. 2019;170:76–79. doi: 10.7326/M18-1826
100. Cooper M, Park-Lee E, Ren C, Cornelius M, Jamal A, Cullen KA. Notes from the field: e-cigarette use among middle and high school students–United States, 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71:1283–1285. doi: 10.15585/mmwr.mm7140a3
101. Glantz S, Jeffers A, Winickoff JP. Nicotine addiction and intensity of e-cigarette use by adolescents in the US, 2014 to 2021. *JAMA Netw Open*. 2022;5:e2240671. doi: 10.1001/jamanetworkopen.2022.40671
102. Jebai R, Osibogun O, Li W, Gautam P, Bursac Z, Ward KD, Maziak W. Temporal trends in tobacco product use among US middle and high school students: National Youth Tobacco Survey, 2011-2020. *Public Health Rep*. 2022;138:483–492. doi: 10.1177/00333549221103812
103. Gentzke AS, Wang TW, Cornelius M, Park-Lee E, Ren C, Sawdey MD, Cullen KA, Loretan C, Jamal A, Homa DM. Tobacco product use and associated factors among middle and high school students–National Youth Tobacco Survey, United States, 2021. *MMWR Surveill Summ*. 2022;71:1–29. doi: 10.15585/mmwr.ss7105a1
104. Collins L, Glasser AM, Abudayyeh H, Pearson JL, Villanti AC. E-cigarette marketing and communication: how e-cigarette companies market e-cigarettes and the public engages with e-cigarette information. *Nicotine Tob Res*. 2019;21:14–24. doi: 10.1093/ntr/ntx284
105. Al Rifai M, Mirbolouk M, Jia X, Nasir K, Pickett JK, Nambi V, Ballantyne CM, Merchant AT, Blaha MJ, Virani SS. E-cigarette use and risk behaviors among lesbian, gay, bisexual, and transgender adults: the Behavioral Risk Factor Surveillance System (BRFSS) Survey. *Kans J Med*. 2020;13:318–321. doi: 10.17161/kjm.vol13.13861
106. Mirbolouk M, Charkhchi P, Kianoush S, Uddin SMI, Orimoloye OA, Jaber R, Bhatnagar A, Benjamin EJ, Hall ME, DeFilippis AP, et al. Prevalence and distribution of e-cigarette use among U.S. adults: Behavioral Risk Factor Surveillance System, 2016. *Ann Intern Med*. 2018;169:429–438. doi: 10.7326/M17-3440
107. Rezk-Hanna M, Toyama J, Ikharo E, Brecht ML, Benowitz NL. E-hookah versus e-cigarettes: Findings from wave 2 of the PATH Study (2014-2015). *Am J Prev Med*. 2019;57:e163–e173. doi: 10.1016/j.amepre.2019.05.007
108. Keith RJ, Fetterman JL, Orimoloye OA, Dardari Z, Lorkiewicz PK, Hamburg NM, DeFilippis AP, Blaha MJ, Bhatnagar A. Characterization of volatile organic compound metabolites in cigarette smokers, electronic nicotine device users, dual users, and nonusers of tobacco. *Nicotine Tob Res*. 2020;22:264–272. doi: 10.1093/ntr/ntz021
109. Eaton DL., Kwan LY, Stratton, K eds. *Public Health Consequences of E-Cigarettes*. National Academies Press; 2018.
110. Lorkiewicz P, Riggs DW, Keith RJ, Conklin DJ, Xie Z, Sutaria S, Lynch B, Srivastava S, Bhatnagar A. Comparison of urinary biomarkers of exposure in humans using electronic cigarettes, combustible cigarettes, and smokeless tobacco. *Nicotine Tob Res*. 2019;21:1228–1238. doi: 10.1093/ntr/nty089
111. Dai H, Benowitz NL, Achutan C, Farazi PA, Degarege A, Khan AS. Exposure to toxicants associated with use and transitions between cigarettes, e-cigarettes, and no tobacco. *JAMA Netw Open*. 2022;5:e2147891. doi: 10.1001/jamanetworkopen.2021.47891
112. Shahab L, Goniewicz ML, Blount BC, Brown J, McNeill A, Alwis KU, Feng J, Wang L, West R. Nicotine, carcinogen, and toxin exposure in long-term e-cigarette and nicotine replacement therapy users: a cross-sectional study. *Ann Intern Med*. 2017;166:390–400. doi: 10.7326/M16-1107
113. Al Rifai M, Mirbolouk M, Obisesan OH, Jia X, Nasir K, Merchant AT, Blaha M, Virani S. The association of electronic cigarette use and the subjective domains of physical and mental health: the Behavioral Risk Factor Surveillance System Survey. *Cureus*. 2020;12:e7088. doi: 10.7759/cureus.7088
114. Obisesan OH, Mirbolouk M, Osei AD, Orimoloye OA, Uddin SMI, Dzaye O, El Shahawy O, Al Rifai M, Bhatnagar A, Stokes A, et al. Association between e-cigarette use and depression in the Behavioral Risk Factor Surveillance System, 2016-2017. *JAMA Netw Open*. 2019;2:e1916800. doi: 10.1001/jamanetworkopen.2019.16800
115. Osei AD, Mirbolouk M, Orimoloye OA, Dzaye O, Uddin SMI, Dardari ZA, DeFilippis AP, Bhatnagar A, Blaha MJ. The association between e-cigarette use and asthma among never combustible cigarette smokers: Behavioral Risk Factor Surveillance System (BRFSS) 2016 & 2017. *BMC Pulm Med*. 2019;19:180. doi: 10.1186/s12890-019-0950-3
116. Osei AD, Mirbolouk M, Orimoloye OA, Dzaye O, Uddin SMI, Benjamin EJ, Hall ME, DeFilippis AP, Bhatnagar A, Biswal SS, et al. Association between e-cigarette use and chronic obstructive pulmonary disease by smoking status: Behavioral Risk Factor Surveillance System 2016 and 2017. *Am J Prev Med*. 2020;58:336–342. doi: 10.1016/j.amepre.2019.10.014
117. Centers for Disease Control and Prevention, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion. Outbreak of lung injury associated with the use of e-cigarette, or vaping, products. Accessed March 22, 2023. https://cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html#overview
118. Department of Health and Human Services and Food and Drug Administration. Deeming tobacco products to be subject to the Federal Food, Drug, and Cosmetic Act, as amended by the Family Smoking Prevention and Tobacco Control Act; restrictions on the sale and distribution of tobacco products and required warning statements for tobacco products. Accessed March 11, 2023. https://federalregister.gov/documents/2016/05/10/2016-10685/deeming-tobacco-products-to-be-subject-to-the-federal-food-drug-and-cosmetic-act-as-amended-by-the
119. US Food and Drug Administration. FDA finalizes enforcement policy on unauthorized flavored cartridge-based e-cigarettes that appeal to children, including fruit and mint. Accessed April 11, 2023. https://fda.gov/news-events/press-announcements/fda-finalizes-enforcement-policy-unauthorized-flavored-cartridge-based-e-cigarettes-appeal-children
120. US Department of Health and Human Services, Food and Drug Administration. Enforcement priorities for electronic nicotine delivery systems (ENDS) and other deemed products on the market without premarket authorization (revised). Accessed April 8. 2023. https://fda.gov/media/133880/download
121. Du Y, Liu B, Xu G, Rong S, Sun Y, Wu Y, Snetselaar LG, Wallace RB, Bao W. Association of electronic cigarette regulations with electronic cigarette use among adults in the United States. *JAMA Netw Open*. 2020;3:e1920255. doi: 10.1001/jamanetworkopen.2019.20255
122. Lin MP, Ovbiagele B, Markovic D, Towfighi A. Association of secondhand smoke with stroke outcomes. *Stroke*. 2016;47:2828–2835. doi: 10.1161/STROKEAHA.116.014099
123. Lv X, Sun J, Bi Y, Xu M, Lu J, Zhao L, Xu Y. Risk of all-cause mortality and cardiovascular disease associated with secondhand smoke exposure: a systematic review and meta-analysis. *Int J Cardiol*. 2015;199:106–115. doi: 10.1016/j.ijcard.2015.07.011
124. Cui H, Gong TT, Liu CX, Wu QJ. Associations between passive maternal smoking during pregnancy and preterm birth: evidence from a meta-analysis of observational studies. *PLoS One*. 2016;11:e0147848. doi: 10.1371/journal.pone.0147848
125. Groh CA, Vittinghoff E, Benjamin EJ, Dupuis J, Marcus GM. Childhood tobacco smoke exposure and risk of atrial fibrillation in adulthood. *J Am Coll Cardiol*. 2019;74:1658–1664. doi: 10.1016/j.jacc.2019.07.060
126. Centers for Disease Control and Prevention State Tobacco Activities Tracking and Evaluation (STATE) System. Smokefree indoor air laws, including e-cigarette. Accessed April 2, 2023. https://cdc.gov/statesystem/factsheets/ECigarette/EcigSFIA.html
127. Mackay DF, Irfan MO, Haw S, Pell JP. Meta-analysis of the effect of comprehensive smoke-free legislation on acute coronary events. *Heart*. 2010;96:1525–1530. doi: 10.1136/hrt.2010.199026
128. Homa DM, Neff LJ, King BA, Caraballo RS, Bunnell RE, Babb SD, Garrett BE, Sosnoff CS, Wang L; Centers for Disease Control and Prevention (CDC). Vital signs: disparities in nonsmokers' exposure to secondhand smoke–United States, 1999-2012. *MMWR Morb Mortal Wkly Rep*. 2015;64:103–108.
129. Shastri SS, Talluri R, Shete S. Disparities in secondhand smoke exposure in the United States: National Health and Nutrition Examination

Survey 2011-2018. *JAMA Intern Med*. 2021;181:134–137. doi: 10.1001/jamainternmed.2020.3975
130. Xu X, Bishop EE, Kennedy SM, Simpson SA, Pechacek TF. Annual healthcare spending attributable to cigarette smoking: an update. *Am J Prev Med*. 2015;48:326–333. doi: 10.1016/j.amepre.2014.10.012
131. Centers for Disease Control and Prevention, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion. Smoking and tobacco use fast facts. Accessed March 24, 2023. https://cdc.gov/tobacco/data_statistics/fact_sheets/fast_facts/index.htm#costs
132. Ali FRM, Marynak KL, Kim Y, Binns S, Emery SL, Gomez Y, King BA. E-cigarette advertising expenditures in the USA, 2014-2018. *Tob Control*. 2020;29:e124–e126. doi: 10.1136/tobaccocontrol-2019-055424
133. Federal Trade Commission. Federal Trade Commission cigarette report for 2018. 2019. Accessed March 24, 2023. https://ftc.gov/system/files/documents/reports/federal-trade-commission-cigarette-report-2018-smokeless-tobacco-report-2018/p114508cigarettereport2018.pdf
134. Centers for Disease Control and Prevention. The tax burden on tobacco, 1970-2018. Accessed March 24, 2023. https://chronicdata.cdc.gov/Policy/The-Tax-Burden-on-Tobacco-1970-2018/7nwe-3aj9/data
135. Ali FRM, Diaz MC, Vallone D, Tynan MA, Cordova J, Seaman EL, Trivers KF, Schillo BA, Talley B, King BA. E-cigarette unit sales, by product and flavor type–United States, 2014-2020. *MMWR Morb Mortal Wkly Rep*. 2020;69:1313–1318. doi: 10.15585/mmwr.mm6937e2
136. Dieleman JL, Cao J, Chapin A, Chen C, Li Z, Liu A, Horst C, Kaldjian A, Matyasz T, Scott KW, et al. US health care spending by payer and health condition, 1996-2016. *JAMA*. 2020;323:863–884. doi: 10.1001/jama.2020.0734
137. Global Burden of Disease Study and Institute for Health Metrics and Evaluation. University of Washington. Accessed August 2, 2023. http://ghdx.healthdata.org/
138. GBD Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. 2020;396:1223–1249.
139. WHO Media Centre. Tobacco fact sheet. 2018. Accessed March 19, 2023. http://who.int/mediacentre/factsheets/fs339/en/
140. Goodchild M, Nargis N, Tursan d'Espaignet E. Global economic cost of smoking-attributable diseases. *Tob Control*. 2018;27:58–64. doi: 10.1136/tobaccocontrol-2016-053305
141. World Health Organization. WHO Framework Convention on Tobacco Control. Accessed April 3, 2023. https://fctc.who.int/publications/i/item/9241591013
142. World Health Organization. WHO report on the global tobacco epidemic, 2019. Accessed April 3, 2023. https://who.int/publications/i/item/9789241516204
143. Ahluwalia IB, Smith T, Arrazola RA, Palipudi KM, Garcia de Quevedo I, Prasad VM, Commar A, Schotte K, Garwood PD, Armour BS. Current tobacco smoking, quit attempts, and knowledge about smoking risks among persons aged >/=15 years–Global Adult Tobacco Survey, 28 countries, 2008-2016. *MMWR Morb Mortal Wkly Rep*. 2018;67:1072–1076. doi: 10.15585/mmwr.mm6738a7

# 4. PHYSICAL ACTIVITY AND SEDENTARY BEHAVIOR

*(See Charts 4-1 through 4-9)*

Click here to return to the Table of Contents

Click here to return to the Abbreviations

PA is defined as any body movement produced by skeletal muscles that results in energy expenditure. In 1992, the AHA first published a position statement declaring that a lack of PA was a risk factor for the development of CHD.[1] Since then, an abundance of research has firmly established a lack of PA as a major risk factor for CVD (eg, CHD, stroke, PAD, HF).[2]

The 2018 Physical Activity Guidelines for Americans recommend that children and adolescents accumulate at least 60 minutes of PA daily, including aerobic and muscle- and bone-strengthening activity.[3] The guidelines recommend that adults accumulate at least 150 min/wk of moderate-intensity or 75 min/wk of vigorous-intensity aerobic activity (or an equivalent combination) and perform muscle-strengthening activities at least 2 d/wk. The 2019 CVD Primary Prevention Clinical Practice Guidelines[4] support the aerobic recommendations. For most people, examples of moderate-intensity activities include walking briskly or raking the yard, and examples of vigorous-intensity activities include jogging, carrying loads upstairs, strengthening activities, or shoveling snow. Achieving the aerobic PA guideline recommendations is one of the AHA's Life's Essential 8 components of ideal CVH for both children and adults.[5]

Globally, the 2020 WHO guidelines also recommend moderate to vigorous aerobic PA along with muscle-strengthening activities across all age groups and abilities.[6] Increasing moderate-intensity PA and replacing sedentary behavior with light-intensity PA can provide health benefits.[3,6] The WHO guidelines for PA also include recommendations for those living with a disability,[7] supporting research on wheelchair users.[8,9]

Sedentary behavior is defined as "any waking behavior characterized by an energy expenditure ≤1.5 METs while in a sitting, reclining, or lying posture."[10] Sedentary behavior is a distinct risk factor from PA, characterized by both posture (sitting, lying, or reclined) and intensity (low), and includes activities such as driving/riding in a vehicle, using a screen (eg, watching television, playing video games, using a computer), or reading. The 2018 Physical Activity Guidelines for Americans recommend adults should "move more and sit less throughout the day."[3] Globally, the WHO guidelines recommend reducing sedentary behaviors across all age groups and abilities.[6]

## Dimensions and Measurement of PA and Sedentary Behavior

PA is characterized by several dimensions (eg, frequency, duration, and intensity) and domains or types (eg, occupational, domestic, transportation, and leisure). Measurement of PA can be defined by 2 broad assessment methods: (1) self-reported methods that use questionnaires, diaries, or logs and (2) device-based methods that use wearables (eg, accelerometers). Sedentary behavior also has several dimensions (eg, frequency, duration) and domains or types (eg, driving/riding in a vehicle, using a screen, reading) that can be assessed with both self-reported and device-based methods.

## Prevalence and Secular Trends

### *Youth PA*

*(See Charts 4-1 and 4-2)*

- According to parental report, from 2020 to 2021, the nationwide percentage of youth 6 to 17 years of age who were active for ≥60 minutes every day of the week was 20.5% (95% CI, 19.8%–21.1%).[11] The percentage was higher for youth 6 to 11 years of age (26.3% [95% CI, 25.2%–27.5%]) compared with youth 12 to 17 years of age (14.8% [95% CI, 14.0%–15.6%]; Chart 4-1) and higher for males (23.7% [95% CI, 22.7%–24.8%]) compared with females (17.0% [95% CI, 16.1%–17.9%]). The percentage varied by race and ethnicity of the child: 15.4% (95% CI, 12.8%–18.4%) for NH Asian, 15.6% (95% CI, 14.0%–17.4%) for Hispanic, 18.2% (95% CI, 16.4%–20.2%) for NH Black, 23.4% (95% CI, 20.8%–26.2%) for NH other, and 23.7% (95% CI, 22.9%–24.5%)for NH White children. The percentage was higher among English-speaking households (21.5% [95% CI, 20.8%–22.2%]) compared with households with a primary language other than English (14.4% [95% CI, 12.3%–16.8%]). Considering the highest education in the household, the percentage was 20.3% (95% CI, 16.9%–24.2%) with less than a high school education, 21.7% (95% CI, 20.0%–23.5%) with a high school education or a General Educational Development, 21.3% (95% CI, 19.9%–22.7%) with some college or technical school, and 19.6% (95% CI, 18.9%–20.4%) with a college degree or higher.

The 2024 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2024. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

- The 2021 nationwide percentage of high school students who engaged in ≥60 minutes of PA on all 7 days of the week was 23.9% (95% CI, 22.8%–25.0%).[12] The percentage was lower with each higher grade, from 25.6% (95% CI, 23.7%–27.7%) in ninth grade to 20.8% (95% CI, 18.9%–23.0%) in 12th grade. The percentage was higher in males (31.7% [95% CI, 30.2%–33.2%]) than females (15.7% [95% CI, 14.1%–17.4%]). The percentage varied by race and ethnicity: American Indian/Alaska Native, 40.0% (95% CI, 22.5%–60.3%); Asian, 19.4% (95% CI, 14.6%–25.3%); Black, 19.7% (95% CI, 17.5%–22.0%); Hispanic, 18.9% (95% CI, 17.3%–20.5%); Native Hawaiian or other Pacific Islander, 23.2% (95% CI, 16.1%–32.2%); and White, 27.7% (95% CI, 25.1%–30.4%).
- The percentage of high school students who were physically active for ≥60 minutes on at least 5 d/wk decreased from 49.5% (95% CI, 47.4%–51.5%) in 2011 to 44.1% (95% CI, 41.9%–46.3%) in 2019.[13] Similarly, the percentage of high school students who were physically active for ≥60 minutes on all 7 d/wk decreased from 28.7% (95% CI, 27.1%–30.3%) in 2011 to 23.2% (95% CI, 21.9%–24.6%) in 2019.
- With regard to self-reported muscle-strengthening activities, in 2021, the percentage of high school students who participated in muscle-strengthening activities (such as push-ups, sit-ups, or weight lifting) on ≥3 d/wk was 44.9% (95% CI, 42.5%–47.2%) nationwide and was lower in the 12th grade (40.4% [95% CI, 37.6%–43.3%]) compared with the 9th grade (48.1% [95% CI, 44.8%–51.4%]).[12,14] More high school males (56.6% [95% CI, 54.4%–58.8%]) than females (32.3% [95% CI, 29.7%–35.1%]) reported participating in muscle-strengthening activities on ≥3 d/wk. The percentage varied by race and ethnicity: American Indian/Alaska Native, 54.8% (95% CI, 39.2%–69.5%); Asian, 41.7% (95% CI, 35.2%–48.5%); Black, 40.7% (95% CI, 36.1%–45.4%); Hispanic, 44.2% (95% CI, 41.9%–46.5%); Native Hawaiian or other Pacific Islander, 43.2% (95% CI, 31.6%–55.6%); and White, 47.0% (95% CI, 43.3%–50.6%).
- The percentage of high school students participating in muscle-strengthening activities on ≥3 d/wk decreased from 55.6% (95% CI, 53.6%–57.5%) in 2011 to 49.5% (95% CI, 47.6%–51.3%) in 2019.[12]
- The percentage of high school students who met guidelines for both aerobic (≥60 minutes on all 7 d/wk) and muscle-strengthening (≥3 d/wk) PA decreased from 21.9% in 2011 to 16.5% in 2019 (Chart 4-2).[12,13] These declines occurred among males, females, NH White youth, and NH Black youth but did not occur among Hispanic youth.[15]
- Wrist-worn accelerometry data from 6030 youth 3 to 19 years of age in the NHANES National Youth Fitness Survey 2012 and NHANES 2011 to 2014 indicated that the median daily total volume of PA (measured by MIMS units) peaked at 6 years of age for both males and females.[16] In contrast, the lowest median daily total volume of PA occurred at 17 years of age in males and 18 years of age in females. Generally, for both males and females, total PA volume was successively higher from 3 to 6 years of age, declined from 6 to ≈15 years of age, and then plateaued through 19 years of age.

### *Youth Physical Education Classes*

- In 2021, 19.0% (95% CI, 15.7%–22.7%) of high school students attended physical education classes in school daily (21.1% [95% CI, 17.2%–25.6%] of males and 16.7% [95% CI, 13.4%–20.6%] of females).[12] Daily physical education class attendance was higher in the ninth grade (29.0% [95% CI, 23.5%–35.2%]) than in the 12th grade (11.8% [95% CI, 8.6%–15.9%]). Daily physical education varied by race and ethnicity: American Indian/Alaska Native, 23.0% (95% CI, 14.7%–34.2%); Asian, 9.6% (95% CI, 5.7%–15.6%); Black, 19.6% (95% CI, 13.9%–27.0%); Hispanic, 21.0% (95% CI, 17.4%–25.2%); Native Hawaiian or other Pacific Islander, 15.9% (95% CI, 8.4%–28.2%); and White, 19.0% (95% CI, 15.0%–23.6%).
- Nationwide, the percentage of high school students who reported attending physical education classes at least once per week (on an average week while in school) did not change substantively between 1991 (48.9% [95% CI, 43.3%–54.6%]) and 2019 (52.2% [95% CI, 46.9%–57.4%]).[13] However, the percentage of attending physical education classes on all 5 days of the week decreased from 41.6% (95% CI, 36.0%–47.3%) in 1991 to 25.9% (95% CI, 21.5%–31.0%) in 2019.

### *Youth Organized Sports*

- According to parental report, from 2020 to 2021, the nationwide percentage of youth 6 to 17 years of age participating in a sports team or sports lessons after school or on weekends was 50.7% (95% CI, 49.8%–51.6%).[11] The percentage was similar for youth 6 to 11 years of age (50.0% [95% CI, 48.7%–51.3%]) compared with youth 12 to 17 years of age (51.4% [95% CI, 50.2%–52.7%]) but higher for males (53.4% [95% CI, 52.1%–54.6%]) compared with females (48.0% [95% CI, 46.7%–49.3%]). The percentage varied by race and ethnicity of the child: 40.1% (95% CI, 37.7%–42.5%) for Hispanic, 42.2% (95% CI, 39.8%–44.8%) for NH Black, 44.8% (95% CI, 41.4%–48.4%) for NH Asian, 54.0% (95% CI, 51.0%–57.0%) for NH other, and 58.6% (95% CI, 57.7%–59.6%) for NH White children. The percentage was higher among English-speaking households (53.9% [95% CI,

53.0%–54.8%]) compared with households with a primary language other than English (33.4% [95% CI, 30.4%–36.5%]). Considering the highest education in the household, the percentage of youth participating on a sports team was 26.1% (95% CI, 22.2%–30.5%) from households with less than high school education, 35.5% (95% CI, 33.4%–37.7%) from households with high school or a General Educational Development, 44.3% (95% CI, 42.5%–46.1%) with some college or technical school, and 64.5% (95% CI, 63.5%–65.5%) from households with a college degree or higher.

- In 2021, about half (49.1% [95% CI, 46.3%–51.8%]) of high school students played on at least 1 school or community sports team in the previous year (46.4% [95% CI, 43.4%–49.4%] of females and 52.0% [95% CI, 49.1%–55.0%] of males); this number was lower in 12th grade (43.7% [95% CI, 40.0%–47.4%]) compared with the ninth grade (53.2% [95% CI, 49.4%–57.0%]).[12] The percentage varied by race and ethnicity: American Indian/Alaska Native, 52.8% (95% CI, 41.8%–63.6%); Asian, 45.0% (95% CI, 33.7%–56.8%); Black, 47.2% (95% CI, 43.1%–51.3%); Hispanic, 39.4% (95% CI, 36.7%–42.1%); Native Hawaiian or other Pacific Islander, 50.6% (95% CI, 32.6%–68.4%); and White, 55.3% (95% CI, 51.4%–59.2%).
- The percentage of high school students playing on ≥1 team sports in the past year did not substantively change between 1999 (55.1% [95% CI, 52.7%–57.4%]) and 2019 (57.4% [95% CI, 54.3%–60.4%]).[13]
- From the 2018 to 2019 National Survey of Children's Health, sports participation was higher among youth 12 to 17 years living in metropolitan areas compared with those in nonmetropolitan areas.[17]

### *Youth Sedentary Behavior*

#### *(See Chart 4-3)*

- According to parental report, from 2020 to 2021, the nationwide percentage of youth 0 to 17 years of age spending ≥4 h/d in front of a television, computer, cell phone, or other electronic device watching programs, playing games, accessing the internet, or using social media (not including schoolwork) on most weekdays was 25.0% (95% CI, 24.3%–25.6%).[11] The percentage was higher for increasing age groups: 0 to 5 years of age (9.5% [95% CI, 8.8%–10.4%]), 6 to 11 years of age (21.8% [95% CI, 20.7%–22.9%]), and 12 to 17 years of age (42.2% [95% CI, 41.0%–43.4%]). The percentage was also higher for males (26.2% [95% CI, 25.3%–27.1%]) compared with females (23.7% [95% CI, 22.8%–24.6%]). The percentage varied by race and ethnicity of the child: 21.2% (95% CI, 20.6%–21.8%) for NH White, 25.8% (95% CI, 23.8%–27.8%) for NH other, 25.9% (95% CI, 23.5%–28.5%) for NH Asian, 27.5% (95% CI, 25.8%–29.3%) for Hispanic, and 33.6% (95% CI, 31.6%–35.7%) for NH Black children. The percentage was lower among English-speaking households (24.6% [95% CI, 24.0%–25.3%]) compared with households with a primary language other than English (27.0% [95% CI, 24.6%–29.5%]). Considering the highest education in the household, the percentage was 27.8% (95% CI, 24.5%–31.3%) with less than high school education, 28.0% (95% CI, 26.4%–29.7%) with high school or a General Educational Development, 28.3% (95% CI, 27.0%–29.6%) with some college or technical school, and 22.0% (95% CI, 21.3%–22.7%) with a college degree or higher.
- Nationwide in 2021, 75.9% (95% CI, 74.4%–77.3%) of high school students spent ≥3 h/d on an average school day in front of a television, computer, smartphone, or other electronic device watching shows or videos, playing games, accessing the internet, or using social media, not counting time spent doing schoolwork.[12] The percentage was high among both males (73.4% [95% CI, 70.4%–76.1%]) and females (78.7% [95% CI, 77.0%–80.4%]), from ninth (73.9% [95% CI, 71.4%–76.2%]) to 12th (76.6% [95% CI, 74.7%–78.5%]) grade, and across race categories: American Indian/Alaska Native, 78.8% (95% CI, 71.1%–84.9%); Asian, 75.2% (95% CI, 69.6%–80.1%); Black, 74.1% (95% CI, 69.4%–78.3%); Hispanic, 77.8% (95% CI, 74.7%–80.7%); Native Hawaiian or other Pacific Islander, 70.9% (95% CI, 57.8%–81.2%); and White, 75.6% (95% CI, 72.9%–78.1%).
- The percentage of computer, tablet, or smartphone use for activities other than schoolwork or using a computer ≥3 h/d increased from 22.1% in 2003 to 46.1% in 2019.[13]
- Nationwide in 2019, 19.8% of high school students watched television ≥3 h/d (Chart 4-3).[14] The percentage varied by race and ethnicity (highest among American Indian/Alaska Native students, followed by Black, Hispanic, White, and Asian students) and was higher among males than females. Watching television for ≥3 h/d decreased from 42.8% in 1999 to 19.8% in 2019.[13]

### *Neighborhood Environment Among Youth*

#### *(See Chart 4-4)*

- According to parental report, from 2020 to 2021, 35.5% (95% CI, 34.8%–36.2%) of neighborhoods among youth 0 to 17 years of age contained all 4 neighborhood activity-promoting features (parks, recreation centers, sidewalks, and libraries).[11]

Chart 4-4 displays the percentages for 1, 2, 3, or 4 neighborhood activity-promoting features. The percentage of children having all 4 neighborhood activity-promoting amenities did not vary substantially by age group (35.0% [95% CI, 33.8%–36.2%] 0–5 years, 35.8% [95% CI, 34.5%–37.0%] 6–11 years, and 35.8% [95% CI, 34.6%–37.1%] 12–17 years) or sex (35.9% [95% CI, 35.0%–36.9%] males, 35.1% [95% CI, 34.1%–36.2%] females). The percentage varied by race and ethnicity of the child: 33.6% (95% CI, 32.8%–34.3%) for NH White, 34.4% (95% CI, 32.5%–36.3%) for Hispanic, 39.3% (95% CI, 37.2%–41.5%) for NH Black, 41.4% (95% CI, 39.0%–43.9%) for NH other, and 45.2% (95% CI, 42.2%–48.2%) for NH Asian children. The percentage was higher among English-speaking households (36.3% [95% CI, 35.6%–37.0%]) compared with households with a primary language other than English (31.7% [95% CI, 29.3%–34.3%]). With respect to differences in highest level of education in the household, the percentage of youth living in a neighborhood with all 4 neighborhood activity-promoting features was 25.3% (95% CI, 22.0%–28.8%) in households with less than high school education, 27.1% (95% CI, 25.4%–28.8%) in households with high school degree or a General Educational Development, 30.6% (95% CI, 29.1%–32.0%) with some college or technical school, and 42.5% (95% CI, 41.6%–43.3%) with a college degree or higher.

- According to parental report, from 2020 to 2021, 4.2% (95% CI, 3.9%–4.6%) of youth 0 to 17 years of age nationwide lived with litter or garbage on the street or sidewalk, poorly kept or rundown housing, and vandalism such as broken windows and graffiti.[11]

## Adult PA

## (See Charts 4-5 through 4-8)

- According to NHIS 2020, 24.2% of adults reported meeting the aerobic Physical Activity Guidelines for Americans (≥150 min/wk of moderate PA, ≥75 min/wk of vigorous PA, or an equivalent combination) through leisure-time activities and participating in muscle-strengthening ≥2 d/wk (Chart 4-5).[18] The percentage was lower with older age and higher with higher family income for both males and females. The percentage varied by race and ethnicity for males (23.5% for Hispanic, 29.7% for NH Black, 30.2% for NH Asian, 30.5% for NH White) and females (18.0% for Hispanic, 16.5% for NH Black, 16.7% for NH Asian, 24.3% for NH White). The percentage was higher with higher urbanicity: 16.1% nonmetropolitan, 22.3% medium/small metropolitan, 26.9% large fringe metropolitan, and 27.8% large central metropolitan.[19]
- From BRFSS 2017 to 2020, the percentage of self-reported physical inactivity (not participating in any leisure-time PA) in the past month varied by state of residence, ranging from the lowest in Colorado (17.7%), Utah (18.2%), and Washington (18.4%) to the highest in Kentucky (32.5%), Mississippi (33.2%), and Puerto Rico (49.4%; Chart 4-6).[20]
- The percentage of self-reported physical inactivity among adults ≥18 years of age, overall and by sex, decreased from 1998 to 2018 (Chart 4-7).[21]
- The age-adjusted percentage of US adults who reported meeting both the aerobic and muscle-strengthening guidelines increased from 18.2% (95% CI, 17.5%–19.0%) in 2008 to 24.0% (95% CI, 23.2%–24.9%) in 2018.[22] The percentage of US adults who reported meeting the aerobic guidelines increased from 43.5% (95% CI, 42.4%–44.6%) in 2008 to 54.2% (95% CI, 53.2%–55.3%) in 2018.
- In 2018, the percentage of adults ≥25 years of age who met the 2018 guidelines for aerobic PA was higher with successively higher educational attainment category (Chart 4-8).[21] This pattern was similar for meeting recommendations for both aerobic and strengthening activities. In addition, the percentage of engaging in any activity or meeting aerobic recommendations among adults ≥18 years of age was higher among those with higher household incomes compared with those with middle or lower household incomes in NH White, NH Black, and Hispanic groups.
- According to the NHIS, the percentage of US adults meeting the minimal aerobic PA guideline was higher in a step-wise fashion from 1998 to 2000 to 2016 to 2018 for adults with diabetes (31.6% [95% CI, 29.3%–34.0%] to 43.5% [95% CI, 40.8%–46.1%]), hypertension (36.6% [95% CI, 35.5%–37.8%] to 47.6% [95% CI, 46.1%–49.0%]), CHD (33.5% [95% CI, 29.7%–37.5%] to 39.6% [95% CI, 35.6%–43.8%]), stroke (27.5% [95% CI, 20.8%–35.3%] to 41.1% [95% CI, 36.4%–45.9%]), and cancer (40.3% [95% CI, 37.8%–42.7%] to 53.1% [95% CI, 49.9%–56.3%]).[23]
- According to 1 week of wrist-worn accelerometry data from 8675 participants ≥20 years of age in NHANES 2011 to 2014, the median daily total volume of PA (measured by MIMS units) peaked at 20 years of age for males and 36 years of age for females.[16] For both males and females, total volume of PA was the lowest at 80 years of age.
- From a systematic review of 20 studies applying an intervention to increase PA, ≈70% of all studies found evidence for a positive association between

the PA-promoting attributes of the built environment (walkability, density, green space) and PA.[24]

### *Adult Sedentary Behavior*

- According to NHANES, self-reported mean daily sitting time increased by 19 min/d from 2007 to 2008 (332 min/d) to 2017 to 2018 (351 min/d).[25]
- A Nielsen report indicated that in January 2020, US adults spent on average 12 hours 21 minutes per day connected to media (eg, television, radio, smartphone, tablet, internet on a computer), which was higher than estimates from January 2018 (11 hours 6 minutes per day) and January 2019 (11 hours 27 minutes per day).[26] These habits reduce time available for PA and contribute to greater time spent in sedentary behavior.

## COVID-19 Pandemic Impact on PA

- In a nationally representative sample of 3829 US adults surveyed between March 19 and April 9, 2020, 30.4% of respondents reported less PA during the pandemic, whereas 20.3% reported more PA, 42.7% reported no change, and 6.6% reported not engaging in PA.[27] Among those reporting PA, the location of the PA was mostly inside their home (61.1%), around their neighborhood (51.1%), or at a park or public trail (16.7%).
- Longitudinal data from the Understanding America Study indicated that self-reported exercise frequency decreased between April 2020 and January 2021 and then increased from January to July 2021.[28] More restrictive state-level COVID-19 policies were inversely associated with exercise frequency between April 2020 and December 2020.
- The COVID-19 pandemic affected walking and bicycling for transportation and leisure through environmental and policy changes designed to limit or accommodate shifting users such as on roads, trails, and transit and in public parks.[29,30] The short- and long-term impacts of the environmental and policy changes on national patterns of walking and bicycling are not yet known.

## Association of PA With COVID-19 Risks

- Among 194 191 adults with a COVID-19 positive test or diagnosis between January 1, 2020, and May 31, 2021, 6.3% were hospitalized, and overall 2.8% died within 90 days of initial hospitalization.[31] At outpatient visits 2 years before the COVID-19 test or diagnosis, those who were always inactive, mostly inactive, or somewhat active had higher odds of hospitalization (aOR range, 1.43–1.91) and death (aOR range, 1.92–3.91) compared with those in the always active category.
- In a South African cohort of 65 361 adults with a COVID-19 diagnosis and PA assessed before diagnosis, 11.1% were hospitalized, 2.4% were admitted to the ICU, 1.6% were ventilated, and 1.3% died.[32] Compared with individuals with low PA, those with high PA corresponding to meeting aerobic PA guidelines had a reduced risk of hospitalization (RR, 0.66 [95% CI, 0.63–0.70]), ICU admission (RR, 0.59 [95% CI, 0.52–0.66]), ventilation (RR, 0.55 [95% CI, 0.47–0.64]), and death (RR, 0.58 [95% CI, 0.50–0.68]) resulting from COVID-19. Moderate PA was associated with lesser but still significantly attenuated risks of these outcomes.

## Genetics and Family History

- Genetic factors have been shown to contribute to the propensity to exercise. However, more work is needed to identify genetic factors that contribute to PA.[33,34]
- Variants in 9 candidate genes (*ACE*, *CASR*, *CYP19A*, *FTO*, *DRD2*, *CNR1*, *LEPR*, *MC4R*, *NPC1*) have been identified to be associated with PA or sedentary behavior. However, their replication in larger unbiased GWASs is warranted.[35]
- GWASs in >377 000 individuals have identified 10 loci associated with PA phenotypes, including *CADM2*, *EXOC4*, and *APOE*.[33]
- A GWAS of 91 105 individuals with device-measured PA identified 14 significant loci.[36] An additional 5 novel loci were reported in a GWAS for 27 device-measured PA phenotypes conducted in 88 411 individuals.[37]
- Multiethnic analysis of >20 000 individuals identified several loci associated with leisure-time PA in individuals of European and African ancestry.[38] Specifically, 4 previous loci (*GABRG3*, *CYP19A1*, *PAPSS2*, and *CASR*) were replicated. Among Black individuals, 2 variants were identified (rs116550874 and rs3792874) and among European Americans, 1 variant was identified (rs28524846) as being associated with leisure-time PA.
- A meta-analysis of 51 studies consisting of 703 901 multiancestry individuals identified 99 significant loci associated with self-reported MVPA, leisure screen time, or sedentary behavior at work.[39]

## Prevention

### *PA, Sedentary Behavior, and Cardiovascular Prevention Among Youths and Adults*

- An umbrella review of 21 systematic reviews found that greater amounts and higher intensities of PA and limiting sedentary behavior were associated with improved health outcomes (eg, cardiometabolic health, cardiorespiratory fitness, adiposity,

and cognition) among youth 5 to 17 years of age.[40] However, the evidence base available was insufficient to fully describe the dose-response relationship or whether the association varied by type or domain of PA or sedentary behavior.
- In an umbrella review of 17 meta-analyses and 1 systematic review, there was a strong inverse dose-response relationship between PA and incident hypertension.[41] PA reduced the risk of CVD progression among adults with hypertension.
- Multisession behavioral counseling among those with elevated lipid levels or BP can improve PA and reduce LDL, BP, adiposity, and cardiovascular events.[42] The US Preventive Services Task Force recommends "offering or referring adults with CVD risk factors to behavioral counseling interventions to promote a healthy diet and PA."[43]
- A narrative review indicated that breaking up time in sedentary behavior with short bouts of PA in controlled settings can improve postprandial glucose, insulin, BP, and triglycerides.[44]

### *Primary Prevention Using Self-Reported PA and Sedentary Behavior*

- A meta-analysis including 94 cohorts and >30 million participants found that higher leisure PA or combinations of nonoccupational PA were associated with a lower risk of all-cause mortality (RR, 0.69 [95% CI, 0.65–0.73]) and CVD mortality (RR, 0.71 [95% CI, 0.66–0.77]) at 8.75 marginal MET-h/wk.[45]
- In contrast, a systematic review and meta-analysis of 31 articles indicated that occupational activity was generally not associated with CVD mortality for both males and females.[46] There are multiple possible explanations for the apparent paradox between leisure-time (beneficial) and occupational (not beneficial) activity with CVD and mortality.[47,48]
- A harmonized meta-analysis that included >1 million participants across 16 studies compared the risk associated with sitting time and television viewing in physically active and inactive study participants. For inactive individuals (defined as the lowest quartile of PA), those sitting >8 h/d had a higher all-cause mortality risk than those sitting <4 h/d (HR, 1.27 [95% CI, 1.22–1.32]).[49] For active individuals (top quartile for PA), sitting time was not associated with all-cause mortality (HR, 1.04 [95% CI, 0.98–1.10]), but active people who watched television ≥5 h/d had higher mortality risk (HR, 1.15 [95% CI, 1.05–1.27]).
- With an average of 27 years of follow-up, estimates from 13 534 ARIC participants indicated that those who engaged in past-year leisure-time PA at least at median levels (≥13.2 MET-h/wk or a walk at 3 mph for 48 min/d for 5 d/wk) had a longer life expectancy free of nonfatal CHD (1.5–1.6 years), stroke (1.8 years), and HF (1.6–1.7 years) compared with those who did not engage in leisure-time PA.[50] In addition, those watching less television had longer life expectancy free of CHD, stroke, and HF of close to 1 year.
- A meta-analysis found a lower risk for all-cause (RR, 0.85 [95% CI, 0.772–0.93]) and CVD mortality (RR, 0.81 [95% CI, 0.66–1.00]) for adults undertaking any amount of resistance training compared with those who did none.[51]
- An umbrella review of 24 systematic reviews of older adults concluded that those who are physically active were at reduced risk of CVD mortality (25%–40% risk reduction), all-cause mortality (22%–35%), breast cancer (12%–17%), prostate cancer (9%–10%), and depression (17%–31%) while experiencing better quality of life, healthier aging trajectories, and improved cognitive functioning.[52]
- In a meta-analysis of 29 prospective observational studies, the RR of HF was lower among those with higher levels of total PA (RR, 0.74 [95% CI, 0.68–0.81]), leisure-time PA (RR, 0.66 [95% CI, 0.59–0.74]), and cardiorespiratory fitness (RR, 0.31 [95% CI, 0.19–0.49]).[53] Favorable associations were also found with vigorous activity, occupational activity, and walking and bicycling combined.
- A meta-analysis summarizing 10 studies found that the pooled adjusted risk of VTE was 0.87 (95% CI, 0.79–0.95) when the most physically active group was compared with the least physically active group.[54]
- According to data from the NHANES III survey, adults with poor PA (OR, 1.30 [95% CI, 1.10–1.54]) and intermediate PA (OR, 1.19 [95% CI, 1.02–1.38]) had an increased odds of subclinical myocardial injury (based on an ECG) compared with those with ideal PA.[55]
- With an average of 27 years of follow-up, estimates from 13 534 ARIC participants indicated that those who engaged in past-year leisure-time PA at least at median levels (≥13.2 MET-h/wk or a walk at 3 mph for 48 min/d for 5 d/wk) had a longer life expectancy free of nonfatal CHD (1.5–1.6 years), stroke (1.8 years), and HF (1.6–1.7 years) compared with those who did not engage in leisure-time PA.[50] In addition, those watching less television had longer life expectancy free of CHD, stroke, and HF of close to 1 year.
- A systematic review and meta-analysis based on 19 studies found that adults in the highest sedentary time category (median duration, 10.5 h/d for CVD morbidity and 10.2 h/d for CVD mortality) had a higher risk of CVD morbidity (pooled RR, 1.24 [95% CI, 1.21–1.27]) and CVD mortality (pooled RR, 1.29 [95% CI, 1.13–1.47]) compared with the

lowest category (median duration, 2.8 and 3.0 h/d, respectively).[56] This was supported by another systematic review and meta-analysis of 148 RCTs and 36 longitudinal studies that found that PA reduced the risk of CVD and sedentary behavior raised the risk of CVD.[57]

- Among participants with HF, a systematic review found that sedentary behavior was associated with an increased hazard of all-cause mortality (1.97 [95% CI, 1.60–2.44]).[58]
- A systematic review of 27 studies found that the evidence on the association of occupational sitting with CVD risk factors and outcomes was limited.[59]

### *Primary Prevention Using Device-Measured PA and Sedentary Behavior*

- In a review of 15 cohort studies, adults in the highest category of device-measured total PA, light PA, and MVPA had 67%, 40%, and 56% lower risk for mortality, respectively, compared with adults in the lowest category.[60]
- In a harmonized meta-analysis of 8 prospective studies in adults measured with accelerometry, over a median of 5.8 years of follow-up, the highest 3 quartiles of light PA (HR range, 0.38–0.60 across quartiles) and MVPA (HR range, 0.52–0.64 across quartiles) compared with the lowest quartile (least active) were associated with a lower risk of all-cause mortality.[61] Time in sedentary behavior was associated with a higher risk of all-cause mortality (HR range, 1.28–2.63 across quartiles) compared with the lowest quartile (least sedentary). In a follow-up analysis of 9 prospective studies, 30 to 40 min/d of MVPA attenuated the adverse association between sedentary behavior and mortality.[62]
- A comprehensive review found that longer time in standing across the day was associated with a lower risk of mortality.[63] However, longer time spent in work-related standing had either adverse or null associations with both subclinical and incident CVD.
- Among adults 70 years of age who wore an accelerometer for 1 week, both light PA and moderate PA were associated with a lower risk, whereas sedentary behavior was associated with a higher risk of all-cause mortality, stroke, and MI.[64]
- Among participants 40 to 79 years of age in the population-based EPIC–Norfolk Study, higher levels of accelerometer-assessed total and MVPA were associated with a lower incident CVD risk; models indicated an initial steep decrease in the HR followed by a flattening of the curve.[65] In addition, longer bouts of sedentary behavior were associated with higher hazards for all-cause mortality (1.16 [95% CI, 1.07–1.26]) but not for CVD.[66]
- Among 16 031 WHS participants ≥62 years of age, those in the highest quartile for MVPA (≤60 min/d) had a 38% (95% CI, 18%–54%) lower hazard for CVD compared with those in the lowest quartile (>120 min/d).[67] Those in the lowest quartile for sedentary behavior (<7.4 h/d) had a 33% (95% CI, 11%–49%) lower hazard of CVD compared with those in the highest quartile (≥9.5 h/d).
- In the WHI/OPACH study, every 1–h/d increase in accelerometer-assessed light-intensity PA was associated with a lower risk of CHD (HR, 0.86 [95% CI, 0.73–1.00]) and lower risk of CVD (HR, 0.92 [95% CI, 0.85–0.99]).[68] For every 1 hour of daily life movement (eg, standing and moving in a confined space), the HR for CVD was 0.86 (95% CI, 0.80–0.92).[69] Those who spent more time standing (quartile 4 versus 1: HR, 0.63 [95% CI, 0.49–0.81]) and more time standing with ambulation (quartile 4 versus 1: HR, 0.50 [95% CI, 0.35–0.71]) had a lower risk of all-cause mortality.[70]
- In an analysis of 1718 MESA participants, substituting 30 minutes of sedentary time for sleep, light PA, or MVPA was associated with a more favorable CVH score.[71]
- In the Look AHEAD trial, applying a pooled analysis on 1978 adults with overweight/obesity and type 2 diabetes, every 100–MET-min/wk increase in total MVPA was associated with a lower hazard for CVD over a 4-year period (0.97 [95% CI, 0.95–0.99]) when accelerometry was used, but no associations were observed when self-reported measures were used.[72]

### *Primary Prevention Using Device-Measured Steps*

- Step counting is recommended as an effective method for translating PA guidelines and monitoring PA levels because of its simplicity and the increased availability of step-counting devices.[73,74] Results from a systematic review revealed that for every 1000 steps taken at baseline, risk reductions ranged from 6% to 36% for all-cause mortality rate and 5% to 21% for CVD.[75]
- In a harmonized meta-analysis of 15 international cohort studies that included 47 471 adults and 3013 deaths, the HR for all-cause mortality was as follows (compared with the lowest quartile of average steps per day): quartile 2 HR, 0.60 (95% CI, 0.51–0.71), quartile 3 HR, 0.55 (95% CI, 0.49–0.62), and quartile 4 HR, 0.47 (95% CI, 0.39–0.57).[76]
- In a harmonized meta-analysis of 8 international cohort studies that included 20 152 adults and 1523 CVD events (CHD, stroke, HF), the HR for those ≥60 years of age was as follows (comparing with the lowest quartile of average steps per day): quartile 2 HR, 0.80 (95% CI, 0.69–0.93), quartile 3 HR, 0.62 (95% CI, 0.52–0.74), and quartile 4 HR, 0.51 (95% CI, 0.41–0.63).[77] For those <60 years of age, the results were as follows (comparing with the

lowest quartile of average steps per day): quartile 2 HR, 0.79 (95% CI, 0.46–1.35), quartile 3 HR, 0.90 (95% CI, 0.64–1.25), and quartile 4 HR, 0.95 (95% CI, 0.61–1.48).
- A systematic review reported favorable dose-response relationships between daily step counts and both type 2 diabetes (25% reduction in 5-year dysglycemia incidence per 2000–steps/d increase) and MetS (29% reduction in 6-year metabolic score per 2000–steps/d increase).[73]
- Among 78 500 UK Biobank participants, higher daily step count was associated with a linear mean rate of change for both CVD (−0.10 [95% CI, −0.15 to −0.06]) and all-cause mortality (−0.08 [95% CI, −0.11 to −0.06]) to 10 000 steps/d.[78]
- In the WHI/OPACH study of 4838 females without physician-diagnosed diabetes, each additional 2000–steps/d increment (as measured by 1 week of hip-worn accelerometry) was associated with a lower hazard for incident diabetes (HR, 0.88 [95% CI, 0.78–1.00]).[79]
- Among Hispanic adults in the HCHS/SOL, there was a 2% (HR, 0.98 [95% CI, 0.95–1.00]) lower risk of diabetes per 1000 steps/d over the next 6 years.[80]

### *Secondary Prevention for PA and Sedentary Behavior*

- Among 1746 adults with CAD followed up for 2 years, those who remained inactive or became inactive had a 4.9- and 2.4-fold higher risk of cardiac death, respectively, than adults who remained at least occasionally active during the follow-up period.[82]
- In a prospective cohort study of 3307 adults with CHD, adults who maintained high PA levels had a lower risk of mortality than those who remained inactive over time (HR, 0.64 [95% CI, 0.50–0.83]).[83]
- Among males after an MI, those who maintained high PA had a 39% lower risk of all-cause mortality, and those who walked for at least 30 min/d had a 29% lower risk of all-cause mortality.[84]
- In a retrospective observational study from 2014 to 2016, Medicare beneficiaries with an ICD who attended cardiac rehabilitation had a lower all-cause mortality risk (HR, 0.76 [95% CI, 0.69–0.85]) at 1 year of follow-up, and the reduced risk remained at 2 and 3 years of follow-up.[85]
- Among 705 patients with ICD or cardiac resynchronization therapy defibrillator, 63% showed improved PA over 1 year after implantation.[86] Those who improved PA over 1 year by at least 30 min/d had a lower hazard of all-cause mortality (0.45 [95% CI, 0.30–0.67]) and cardiac death (0.39 [95% CI, 0.24–0.65]) compared with those who reduced or did not change their PA.

## Estimated Population-Level Benefits of Increasing PA

- According to accelerometry data from NHANES 2003 to 2006, if US adults ≥40 years of age increased their MVPA by ≈10 min/d, an estimated 110 000 deaths per year could be prevented.[87]
- Increasing population levels of PA could increase productivity, particularly through presenteeism, and lead to substantial economic gains.[88] Engaging in at least 150 min of moderate-intensity PA per week, as per the lower limit of the range recommended by the 2020 WHO guidelines, would lead to an increase in global gross domestic product of 0.15%/y to 0.24%/y by 2050, worth up to US $314 to 446 billion per year and US $6.0 to 8.6 trillion cumulatively over the 30-year projection horizon (in 2019 prices). The results vary by country because of differences in baseline levels of PA and gross domestic product per capita.

## Global Burden

## (See Chart 4-9)

- The Global Matrix 4.0 on PA for youth 5 to 17 years of age compiles PA around the world.[89] The 2022 report summarized across 57 countries and ranked global PA with a grade D, school with a grade C+, community/environment with a grade C+, active transportation with a grade C−, and sedentary behavior with a grade D+.
- The Global Observatory for PA monitors trends in PA surveillance, policy, and research in 164 countries.[90] Compared with 2015, progress by 2020 in all 3 areas was modest. They concluded that 88.2% of the world's population lives in countries where PA capacity could be improved.
- In an analysis including 168 countries, the prevalence of inactivity was found to be highest in high-income countries (36.8% [95% CI, 35.0%–38.0%]), followed by middle-income countries (26.0% [95% CI, 22.6%–31.8%]) and then low-income countries (16.2% [95% CI, 14.2%–17.9%]). Globally, the PAR associated with inactivity for all-cause mortality rate was 9.3%, 6.8%, and 4.3% in high-, middle-, and low-income countries, respectively, with similar estimates for CVD mortality. The PAR for cardiovascular events such as CHD and stroke ranged from 3.0% in low-income countries to 6.5% in high-income countries.[91]
- A systematic review of the literature including 16 studies of wearable devices from 8 countries reported a downward trend in steps from 1995 to 2017.[92] Declines were observed in both males and females and in children, adolescents, and adults.
- In 26 high- and 34 middle-income countries between 2001 and 2016, the levels of insufficient PA were greater when there were greater income

inequalities (defined as the difference between those with the highest and lowest incomes).[93]

- In 2021, based on 204 countries and territories, mortality rates attributable to low PA were highest in southern sub-Saharan Africa, North Africa and the Middle East, Oceania, and Southeast Asia (Chart 4-9). In 2021, low PA was associated with an estimated 0.67 (95% UI, 0.27–1.08) million deaths in 2021, an increase of 100.09% (95% UI, 83.11%–121.17%) since 1990.[94]

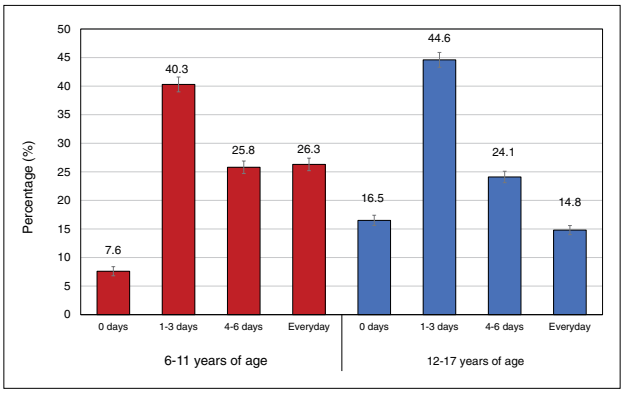



**Chart 4-1. Percentage of US youth 6 to 11 and 12 to 17 years of age who were physically active for at least 60 minutes each day, 2020 to 2021.**
Error bars represent 95% CIs.
Source: Data derived from National Survey of Children's Health.[11]

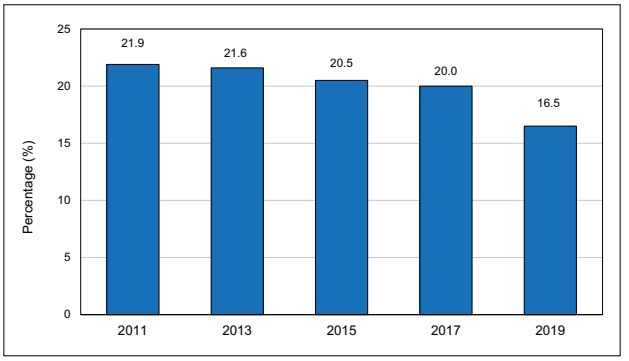



**Chart 4-2. Percentage of US youth in grades 9 through 12 who met both aerobic and muscle-strengthening PA recommendations, 2011 to 2019.**
PA indicates physical activity.
Source: Data derived from Youth Risk Behavior Survey.[12,13]

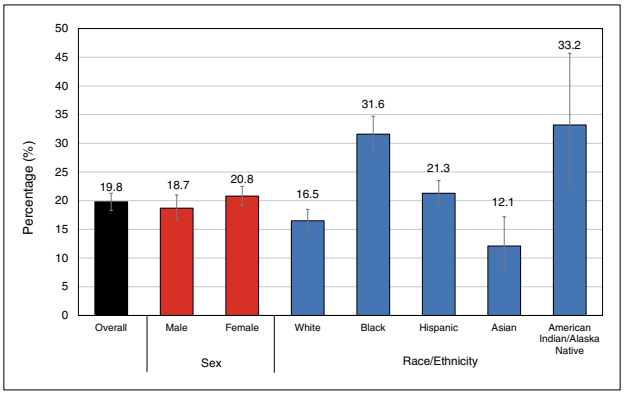



**Chart 4-3. Percentage of US students in grades 9 through 12 who watched television for ≥3 hours on an average school day, overall and by sex and race and ethnicity, 2019.**
Error bars represent 95% CIs.
Source: Data derived from Youth Risk Behavior Survey.[14]

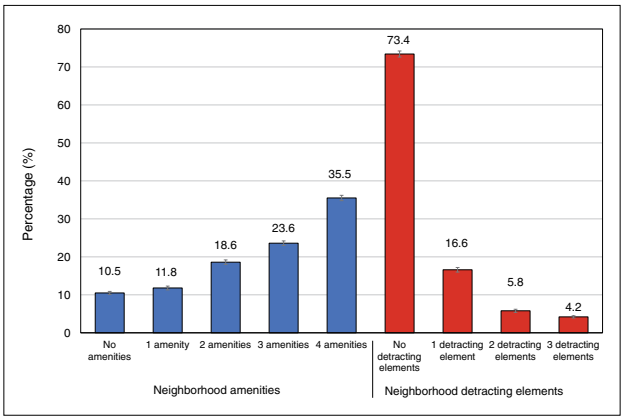



**Chart 4-4. Presence of health-promoting amenities and detracting elements in neighborhoods of US youth 0 to 17 years of age, 2020 to 2021.**
Health-promoting amenities included parks, recreation centers, sidewalks, and libraries. Health-detracting elements included litter or garbage on the street or sidewalk, poorly kept or rundown housing, and vandalism such as broken windows or graffiti.
Error bars represent 95% CIs.
Source: Data derived from National Survey of Children's Health.[11]

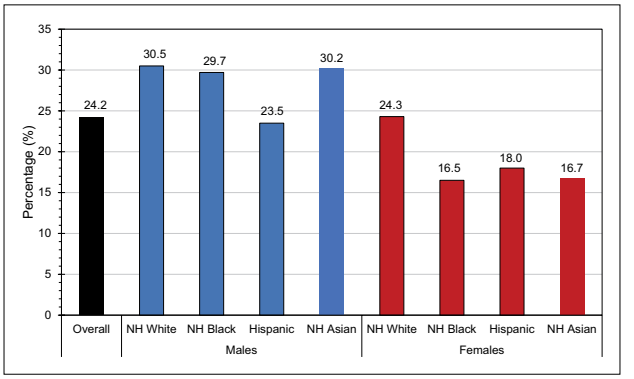



**Chart 4-5. Percentage meeting the aerobic PA guidelines among US adults ≥18 years of age, overall and by sex and race and ethnicity, 2020.**
From the 2018 Physical Activity Guidelines for Americans, the aerobic guidelines recommend engaging in moderate leisure-time physical activity for ≥150 min/wk, vigorous activity for ≥75 min/wk, or an equivalent combination. The muscle-strengthening guidelines recommend activities of moderate or greater intensity involving all major muscle groups on ≥2 d/wk.
NH indicates non-Hispanic; and PA, physical activity.
Source: Data derived from Elgaddal et al.[18]

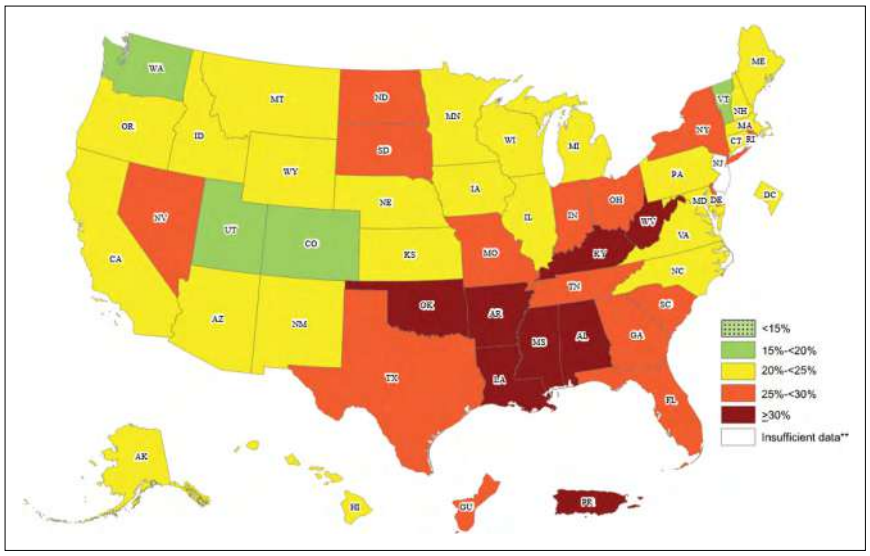



**Chart 4-6. Percentage of self-reported physical inactivity among US adults ≥18 years of age, by state and territory, 2017 to 2020.**
States in white had insufficient data, defined as a sample size <50, a relative standard error ≥30%, or no data in at least 1 year.
Source: Reprinted from Centers for Disease Control and Prevention, Behavioral Risk Factor Surveillance System.[20]

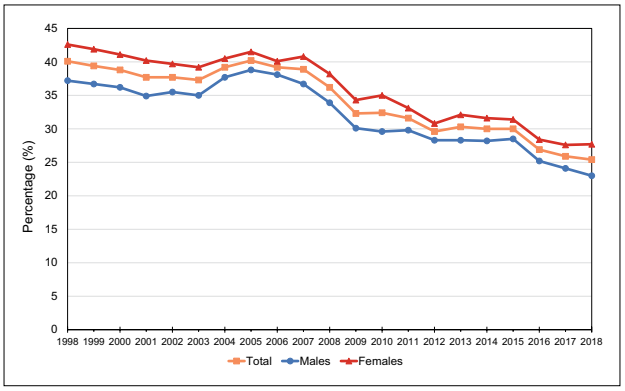



**Chart 4-7. Trends in the percentage of physical inactivity among US adults ≥18 years of age, overall and by sex, 1998 to 2018.**
Data are age adjusted to the year 2000 standard population for adults ≥18 years of age.
Physical inactivity is defined as reporting no engagement in leisure-time physical activity in bouts lasting ≥10 minutes.
Source: Data derived from the National Health Interview Survey.[21]

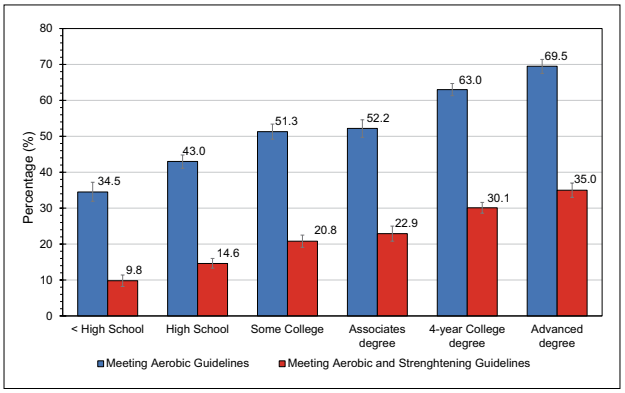



**Chart 4-8. Percentage meeting the aerobic PA guidelines among US adults ≥25 years of age, by educational attainment, 2018.**
Data are age adjusted to the year 2000 standard population for adults ≥18 years of age. The 2018 Physical Activity Guidelines for Americans[3] recommend engaging in moderate leisure-time PA for ≥150 min/wk, vigorous activity for ≥75min/wk, or an equivalent combination (eg, aerobic guideline). The 2018 Physical Activity Guidelines for Americans also recommend engaging in muscle-strengthening activities ≥2 d/wk (eg, muscle-strengthening guideline).
Error bars represent 95% CIs.
PA indicates physical activity.
Source: Data derived from the National Health Interview Survey.[21]

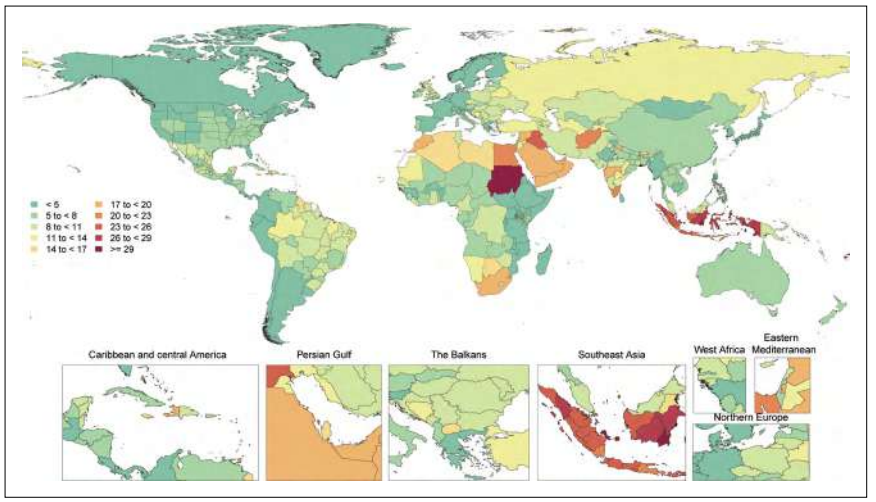



**Chart 4-9. Age-standardized global mortality rates attributable to low PA per 100 000, both sexes, 2021.**
During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.
GBD indicates Global Burden of Disease; and PA, physical activity.
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[94]

## REFERENCES


1. Fletcher GF, Blair SN, Blumenthal J, Caspersen C, Chaitman B, Epstein S, Falls H, Froelicher ES, Froelicher VF, Pina IL. Statement on exercise: benefits and recommendations for physical activity programs for all Americans: a statement for health professionals by the Committee on Exercise and Cardiac Rehabilitation of the Council on Clinical Cardiology, American Heart Association. *Circulation*. 1992;86:340–344. doi: 10.1161/01.cir.86.1.340
2. Kraus WE, Powell KE, Haskell WL, Janz KF, Campbell WW, Jakicic JM, Troiano RP, Sprow K, Torres A, Piercy KL; 2018 Physical Activity Guidelines Advisory Committee. Physical activity, all-cause and cardiovascular mortality, and cardiovascular disease. *Med Sci Sports Exerc*. 2019;51:1270–1281. doi: 10.1249/MSS.0000000000001939
3. US Department of Health and Human Services. Physical Activity Guidelines for Americans. 2nd ed. 2018. Accessed March 15, 2023. https://health.gov/sites/default/files/2019-09/Physical_Activity_Guidelines_2nd_edition.pdf
4. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease [published corrections appear in *Circulation*. 2019;140:e649–e650, *Circulation*. 2020;141:e60, and *Circulation*. 2020;141:e774]. *Circulation*. 2019;140:e596–e646. doi: 10.1161/CIR.0000000000000678
5. Lloyd-Jones DM, Allen NB, Anderson CAM, Black T, Brewer LC, Foraker RE, Grandner MA, Lavretsky H, Perak AM, Sharma G, et al; American Heart Association. Life's Essential 8: updating and enhancing the American Heart Association's construct of cardiovascular health: a presidential advisory from the American Heart Association. *Circulation*. 2022;146:e18–e43. doi: 10.1161/CIR.0000000000001078
6. Bull FC, Al-Ansari SS, Biddle S, Borodulin K, Buman MP, Cardon G, Carty C, Chaput JP, Chastin S, Chou R, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. *Br J Sports Med*. 2020;54:1451–1462. doi: 10.1136/bjsports-2020-102955
7. Carty C, van der Ploeg HP, Biddle SJH, Bull F, Willumsen J, Lee L, Kamenov K, Milton K. The first global physical activity and sedentary behavior guidelines for people living with disability. *J Phys Act Health*. 2021;18:86–93. doi: 10.1123/jpah.2020-0629
8. Selph SS, Skelly AC, Wasson N, Dettori JR, Brodt ED, Ensrud E, Elliot D, Dissinger KM, McDonagh M. Physical activity and the health of wheelchair users: a systematic review in multiple sclerosis, cerebral palsy, and spinal cord injury. *Arch Phys Med Rehabil*. 2021;102:2464–2481.e33. doi: 10.1016/j.apmr.2021.10.002
9. Gurwitz JH, Carlozzi NE, Davison KK, Evenson KR, Gaskin DJ, Lushniak B. National Institutes of Health Pathways to Prevention Workshop: physical activity and health for wheelchair users. *Arch Rehabil Res Clin Transl*. 2021;3:100163. doi: 10.1016/j.arrct.2021.100163
10. Tremblay MS, Aubert S, Barnes JD, Saunders TJ, Carson V, Latimer-Cheung AE, Chastin SFM, Altenburg TM, Chinapaw MJM; SBRN Terminology Consensus Project Participants. Sedentary Behavior Research Network (SBRN): Terminology Consensus Project process and outcome. *Int J Behav Nutr Phys Act*. 2017;14:75. doi: 10.1186/s12966-017-0525-8
11. National Center for Health Statistics and Data Resource Center for Child & Adolescent Health. National Survey of Children's Health (2016-present), Interactive Data Query (2020-2021). 2023. Accessed March 7, 2023. http://nschdata.org/browse/survey/
12. Centers for Disease Control and Prevention. 1991-2021 High School Youth Risk Behavior Survey data. Accessed May 1, 2023. http://nccd.cdc.gov/youthonline/
13. Centers for Disease Control and Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention and Division of Adolescent and School Health. Trends in the prevalence of physical activity and sedentary behaviors: national YRBS: 1999-2019. 2021. Accessed March 15, 2023. https://cdc.gov/healthyyouth/data/yrbs/pdf/trends/2019_physical_trend_yrbs.pdf
14. Centers for Disease Control and Prevention. High School Youth Risk Behavior Survey, 2019. Accessed March 15, 2023. https://cdc.gov/healthyyouth/data/yrbs/index.htm
15. Merlo C, Jones S, Michael S, Chen T, Sliwa S, Lee S, Brener N, Lee S, Park S. Dietary and physical activity behaviors among high school students: Youth Risk Behavior Survey, United States, 2019. *MMWR Suppl*. 2020;69:64–76. doi: 10.15585/mmwr.su6901a8
16. Belcher BR, Wolff-Hughes DL, Dooley EE, Staudenmayer J, Berrigan D, Eberhardt MS, Troiano RP. U.S. population-referenced percentiles for wrist-worn accelerometer-derived activity. *Med Sci Sports Exerc*. 2021;53:2455–2464. doi: 10.1249/mss.0000000000002726
17. Johnson AM, Bocarro JN, Saelens BE. Youth sport participation by metropolitan status: 2018-2019 National Survey of Children's Health (NSCH). *Res Q Exerc Sport*. 2022;1:1–10. doi: 10.1080/02701367.2022.2069662
18. Elgaddal N, Kramarow E, Reuben C. Physical activity among adults aged 18 and over: United States, 2020. *NCHS Data Brief*. 2022;443:1–8.
19. Abildso CG, Daily SM, Umstattd Meyer MR, Perry CK, Eyler A. Prevalence of meeting aerobic, muscle-strengthening, and combined physical activity guidelines during leisure time among adults, by rural-urban classification and region–United States, 2020. *MMWR Morb Mortal Wkly Rep*. 2023;72:85–89. doi: 10.15585/mmwr.mm7204a1
20. Centers for Disease Control and Prevention and Behavioral Risk Factor Surveillance System. Map: overall physical inactivity. 2022. Accessed March 15, 2023. https://cdc.gov/physicalactivity/data/inactivity-prevalence-maps/index.html
21. Centers for Disease Control and Prevention and National Center for Health Statistics. National Health Interview Survey: public-use data files and documentation. Accessed March 15, 2023. https://cdc.gov/nchs/nhis/index.htm
22. Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion and Division of Nutrition, Physical Activity, and Obesity. 2008 Physical Activity Guidelines for Americans: trends in meeting the 2008 Physical Activity Guidelines, 2008-2018. 2019. Accessed March 15, 2023. https://cdc.gov/physicalactivity/downloads/trends-in-the-prevalence-of-physical-activity-508.pdf

23. Omura JD, Hyde ET, Imperatore G, Loustalot F, Murphy L, Puckett M, Watson KB, Carlson SA. Trends in meeting the aerobic Physical Activity Guideline among adults with and without select chronic health conditions, United States, 1998-2018. *J Phys Act Health*. 2021;18:S53–S63. doi: 10.1123/jpah.2021-0178
24. McCormack GR, Patterson M, Frehlich L, Lorenzetti DL. The association between the built environment and intervention-facilitated physical activity: a narrative systematic review. *Int J Behav Nutr Phys Activity*. 2022;19:86. doi: 10.1186/s12966-022-01326-9
25. Ussery EN, Whitfield GP, Fulton JE, Galuska DA, Matthews CE, Katzmarzyk PT, Carlson SA. Trends in self-reported sitting time by physical activity levels among US adults, NHANES 2007/2008-2017/2018. *J Phys Act Health*. 2021;18:S74–S83. doi: 10.1123/jpah.2021-0221
26. Nielsen Total Audience Report. August 2020. Accessed March 15, 2023. https://nielsen.com/us/en/insights/report/2020/the-nielsen-total-audience-report-august-2020/
27. Watson KB, Whitfield GP, Huntzicker G, Omura JD, Ussery E, Chen TJ, Fanfair RN. Cross-sectional study of changes in physical activity behavior during the COVID-19 pandemic among US adults. *Int J Behav Nutr Phys Act*. 2021;18:91. doi: 10.1186/s12966-021-01161-4
28. Wijngaards I, Del Pozo Cruz B, Gebel K, Ding D. Exercise frequency during the COVID-19 pandemic: a longitudinal probability survey of the US population. *Prev Med Rep*. 2022;25:101680. doi: 10.1016/j.pmedr.2021.101680
29. Evenson KR, Naumann RB, Taylor NL, LaJeunesse S, Combs TS. Mixed method assessment of built environment and policy responses to the COVID-19 pandemic by United States municipalities focusing on walking and bicycling actions. *J Transp Health*. 2023;28:101557. doi: 10.1016/j.jth.2022.101557
30. Volenec ZM, Abraham JO, Becker AD, Dobson AP. Public parks and the pandemic: how park usage has been affected by COVID-19 policies. *PLoS One*. 2021;16:e0251799. doi: 10.1371/journal.pone.0251799
31. Young DR, Sallis JF, Baecker A, Cohen DA, Nau CL, Smith GN, Sallis RE. Associations of physical inactivity and COVID-19 outcomes among subgroups. *Am J Prev Med*. 2023;64:492–502. doi: 10.1016/j.amepre.2022.10.007
32. Steenkamp L, Saggers RT, Bandini R, Stranges S, Choi YH, Thornton JS, Hendrie S, Patel D, Rabinowitz S, Patricios J. Small steps, strong shield: directly measured, moderate physical activity in 65 361 adults is associated with significant protective effects from severe COVID-19 outcomes. *Br J Sports Med*. 2022;56:568–576. doi: 10.1136/bjsports-2021-105159
33. Klimentidis YC, Raichlen DA, Bea J, Garcia DO, Wineinger NE, Mandarino LJ, Alexander GE, Chen Z, Going SB. Genome-wide association study of habitual physical activity in over 377,000 UK Biobank participants identifies multiple variants including *CADM2* and *APOE*. *Int J Obes (Lond)*. 2018;42:1161–1176. doi: 10.1038/s41366-018-0120-3
34. Young DR, Hivert MF, Alhassan S, Camhi SM, Ferguson JF, Katzmarzyk PT, Lewis CE, Owen N, Perry CK, Siddique J, et al; on behalf of the Physical Activity Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Functional Genomics and Translational Biology; and Stroke Council. Sedentary behavior and cardiovascular morbidity and mortality: a science advisory from the American Heart Association. *Circulation*. 2016;134:e262–e279. doi: 10.1161/CIR.0000000000000440
35. Aasdahl L, Nilsen TIL, Meisingset I, Nordstoga AL, Evensen KAI, Paulsen J, Mork PJ, Skarpsno ES. Genetic variants related to physical activity or sedentary behaviour: a systematic review. *Int J Behav Nutr Phys Activity*. 2021;18:15. doi: 10.1186/s12966-020-01077-5
36. Doherty A, Smith-Byrne K, Ferreira T, Holmes MV, Holmes C, Pulit SL, Lindgren CM. GWAS identifies 14 loci for device-measured physical activity and sleep duration. *Nat Commun*. 2018;9:5257. doi: 10.1038/s41467-018-07743-4
37. Qi G, Dutta D, Leroux A, Ray D, Muschelli J, Crainiceanu C, Chatterjee N. Genome-wide association studies of 27 accelerometry-derived physical activity measurements identified novel loci and genetic mechanisms. *Genet Epidemiol*. 2022;46:122–138. doi: 10.1002/gepi.22441
38. Lin X, Chan KK, Huang YT, Luo XI, Liang L, Wilson J, Correa A, Levy D, Liu S. Genetic determinants for leisure-time physical activity. *Med Sci Sports Exerc*. 2018;50:1620–1628. doi: 10.1249/MSS.0000000000001607
39. Wang Z, Emmerich A, Pillon NJ, Moore T, Hemerich D, Cornelis MC, Mazzaferro E, Broos S, Ahluwalia TS, Bartz TM, et al; Lifelines Cohort Study. Genome-wide association analyses of physical activity and sedentary behavior provide insights into underlying mechanisms and roles in disease prevention. *Nat Genet*. 2022;54:1332–1344. doi: 10.1038/s41588-022-01165-1
40. Chaput JP, Willumsen J, Bull F, Chou R, Ekelund U, Firth J, Jago R, Ortega FB, Katzmarzyk PT. 2020 WHO guidelines on physical activity and sedentary behaviour for children and adolescents aged 5-17 years: summary of the evidence. *Int J Behav Nutr Phys Act*. 2020;17:141. doi: 10.1186/s12966-020-01037-z
41. Pescatello LS, Buchner DM, Jakicic JM, Powell KE, Kraus WE, Bloodgood B, Campbell WW, Dietz S, Dipietro L, George SM, et al; 2018 Physical Activity Guidelines Advisory Committee. Physical activity to prevent and treat hypertension: a systematic review. *Med Sci Sports Exerc*. 2019;51:1314–1323. doi: 10.1249/MSS.0000000000001943
42. O'Connor EA, Evans CV, Rushkin MC, Redmond N, Lin JS. Behavioral counseling to promote a healthy diet and physical activity for cardiovascular disease prevention in adults with cardiovascular risk factors: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2020;324:2076–2094. doi: 10.1001/jama.2020.17108
43. Krist AH, Davidson KW, Mangione CM, Barry MJ, Cabana M, Caughey AB, Donahue K, Doubeni CA, Epling JW Jr, Kubik M, et al; US Preventive Services Task Force. Behavioral counseling interventions to promote a healthy diet and physical activity for cardiovascular disease prevention in adults with cardiovascular risk factors: US Preventive Services Task Force recommendation statement. *JAMA*. 2020;324:2069–2075. doi: 10.1001/jama.2020.21749
44. Bell AC, Richards J, Zakrzewski-Fruer JK, Smith LR, Bailey DP. Sedentary behaviour: a target for the prevention and management of cardiovascular disease. *Int J Environ Res Public Health*. 2022;20:532. doi: 10.3390/ijerph20010532
45. Garcia L, Pearce M, Abbas A, Mok A, Strain T, Ali S, Crippa A, Dempsey PC, Golubic R, Kelly P, et al. Non-occupational physical activity and risk of cardiovascular disease, cancer and mortality outcomes: a dose-response meta-analysis of large prospective studies. *Br J Sports Med*. 2023;57:979–989. doi: 10.1136/bjsports-2022-105669
46. Cillekens B, Huysmans MA, Holtermann A, van Mechelen W, Straker L, Krause N, van der Beek AJ, Coenen P. Physical activity at work may not be health enhancing: a systematic review with meta-analysis on the association between occupational physical activity and cardiovascular disease mortality covering 23 studies with 655 892 participants. *Scand J Work Environ Health*. 2022;48:86–98. doi: 10.5271/sjweh.3993
47. Holtermann A, Krause N, van der Beek AJ, Straker L. The physical activity paradox: six reasons why occupational physical activity (OPA) does not confer the cardiovascular health benefits that leisure time physical activity does. *Br J Sports Med*. 2018;52:149–150. doi: 10.1136/bjsports-2017-097965
48. Cuthbertson CC, Moore CC, Evenson KR. Paradox of occupational and leisure-time physical activity associations with cardiovascular disease. *Heart*. 2023;109:656–658. doi: 10.1136/heartjnl-2022-321856
49. Ekelund U, Steene-Johannessen J, Brown WJ, Fagerland MW, Owen N, Powell KE, Bauman A, Lee IM; Lancet Physical Activity Series 2 Executive Committee. Does physical activity attenuate, or even eliminate, the detrimental association of sitting time with mortality? A harmonised meta-analysis of data from more than 1 million men and women. *Lancet*. 2016;388:1302–1310. doi: 10.1016/S0140-6736(16)30370-1
50. Cuthbertson CC, Tan X, Heiss G, Kucharska-Newton A, Nichols HB, Kubota Y, Evenson KR. Associations of leisure-time physical activity and television viewing with life expectancy free of nonfatal cardiovascular disease: the ARIC study. *J Am Heart Assoc*. 2019;8:e012657. doi: 10.1161/JAHA.119.012657
51. Shailendra P, Baldock KL, Li LSK, Bennie JA, Boyle T. Resistance training and mortality risk: a systematic review and meta-analysis. *Am J Prev Med*. 2022;63:277–285. doi: 10.1016/j.amepre.2022.03.020
52. Cunningham C, O' Sullivan R, Caserotti P, Tully MA. Consequences of physical inactivity in older adults: a systematic review of reviews and meta-analyses. *Scand J Med Sci Sports*. 2020;30:816–827. doi: 10.1111/sms.13616
53. Aune D, Schlesinger S, Leitzmann MF, Tonstad S, Norat T, Riboli E, Vatten LJ. Physical activity and the risk of heart failure: a systematic review and dose-response meta-analysis of prospective studies. *Eur J Epidemiol*. 2021;36:367–381. doi: 10.1007/s10654-020-00693-6
54. Kunutsor SK, Mäkikallio TH, Seidu S, de Araújo CGS, Dey RS, Blom AW, Laukkanen JA. Physical activity and risk of venous thromboembolism: systematic review and meta-analysis of prospective cohort studies. *Eur J Epidemiol*. 2020;35:431–442. doi: 10.1007/s10654-019-00579-2
55. German C, Ahmad MI, Li Y, Soliman EZ. Relations between physical activity, subclinical myocardial injury, and cardiovascular mortality in the general population. *Am J Cardiol*. 2020;125:205–209. doi: 10.1016/j.amjcard.2019.08.031

56. Jingjie W, Yang L, Jing Y, Ran L, Yiqing X, Zhou N. Sedentary time and its association with risk of cardiovascular diseases in adults: an updated systematic review and meta-analysis of observational studies. *BMC Public Health*. 2022;22:286. doi: 10.1186/s12889-022-12728-6
57. Liang ZD, Zhang M, Wang CZ, Yuan Y, Liang JH. Association between sedentary behavior, physical activity, and cardiovascular disease-related outcomes in adults: a meta-analysis and systematic review. *Front Public Health*. 2022;10:1018460. doi: 10.3389/fpubh.2022.1018460
58. Zhao Q, Chen C, Zhang J, Ye Y, Fan X. Sedentary behavior and health outcomes in patients with heart failure: a systematic review and meta-analysis. *Heart Fail Rev*. 2022;27:1017–1028. doi: 10.1007/s10741-021-10132-7
59. Reichel K, Prigge M, Latza U, Kurth T, Backé EM. Association of occupational sitting with cardiovascular outcomes and cardiometabolic risk factors: a systematic review with a sex-sensitive/gender-sensitive perspective. *BMJ Open*. 2022;12:e048017. doi: 10.1136/bmjopen-2020-048017
60. Ramakrishnan R, He JR, Ponsonby AL, Woodward M, Rahimi K, Blair SN, Dwyer T. Objectively measured physical activity and all cause mortality: a systematic review and meta-analysis. *Prev Med*. 2020;143:106356. doi: 10.1016/j.ypmed.2020.106356
61. Ekelund U, Tarp J, Steene-Johannessen J, Hansen BH, Jefferis B, Fagerland MW, Whincup P, Diaz KM, Hooker SP, Chernofsky A, et al. Dose-response associations between accelerometry measured physical activity and sedentary time and all cause mortality: systematic review and harmonised meta-analysis. *BMJ*. 2019;366:l4570. doi: 10.1136/bmj.l4570
62. Ekelund U, Tarp J, Fagerland MW, Johannessen JS, Hansen BH, Jefferis BJ, Whincup PH, Diaz KM, Hooker S, Howard VJ, et al. Joint associations of accelero-meter measured physical activity and sedentary time with all-cause mortality: a harmonised meta-analysis in more than 44 000 middle-aged and older individuals. *Br J Sports Med*. 2020;54:1499–1506. doi: 10.1136/bjsports-2020-103270
63. Barone Gibbs B. Association of standing with cardiovascular disease and mortality in adults. *Curr Epidemiol Rep*. 2021;Nov:1–12. doi: 10.1007/s40471-021-00276-3
64. Ballin M, Nordström P, Niklasson J, Nordström A. Associations of objectively measured physical activity and sedentary time with the risk of stroke, myocardial infarction or all-cause mortality in 70-year-old men and women: a prospective cohort study. *Sports Med*. 2021;51:339–349. doi: 10.1007/s40279-020-01356-y
65. Dempsey PC, Strain T, Khaw KT, Wareham NJ, Brage S, Wijndaele K. Prospective associations of accelerometer-measured physical activity and sedentary time with incident cardiovascular disease, cancer, and all-cause mortality. *Circulation*. 2020;141:1113–1115. doi: 10.1161/CIRCULATIONAHA.119.043030
66. Dempsey PC, Strain T, Winkler EAH, Westgate K, Rennie KL, Wareham NJ, Brage S, Wijndaele K. Association of accelerometer-measured sedentary accumulation patterns with incident cardiovascular disease, cancer, and all-cause mortality. *J Am Heart Assoc*. 2022;11:e023845. doi: 10.1161/JAHA.121.023845
67. Peter-Marske K, Evenson K, Moore C, Cuthbertson C, Howard A, Shiroma E, Buring J, Lee I. Association of accelerometer-measured physical activity and sedentary behavior with incident cardiovascular disease, myocardial infarction, and ischemic stroke: the Women's Health Study. *J Am Heart Assoc*. 2023;12:e028180. doi: 10.1161/JAHA.122.028180
68. LaCroix AZ, Bellettiere J, Rillamas-Sun E, Di C, Evenson KR, Lewis CE, Buchner DM, Stefanick ML, Lee IM, Rosenberg DE, et al; Women's Health Initiative (WHI). Association of light physical activity measured by accelerometry and incidence of coronary heart disease and cardiovascular disease in older women. *JAMA Netw Open*. 2019;2:e190419. doi: 10.1001/jamanetworkopen.2019.0419
69. Nguyen S, Bellettiere J, Wang G, Di C, Natarajan L, LaMonte MJ, LaCroix AZ. Accelerometer-derived daily life movement classified by machine learning and incidence of cardiovascular disease in older women: the OPACH study. *J Am Heart Assoc*. 2022;11:e023433. doi: 10.1161/JAHA.121.023433
70. Jain P, Bellettiere J, Glass N, LaMonte MJ, Di C, Wild RA, Evenson KR, LaCroix AZ. The relationship of accelerometer-assessed standing time with and without ambulation and mortality: the WHI OPACH study. *J Gerontol A Biol Sci Med Sci*. 2021;76:77–84. doi: 10.1093/gerona/glaa227
71. German C, Makarem N, Fanning J, Redline S, Elfassy T, McClain A, Abdalla M, Aggarwal B, Allen N, Carnethon M. Sleep, sedentary behavior, physical activity, and cardiovascular health: MESA. *Med Sci Sports Exerc*. 2021;53:724–731. doi: 10.1249/MSS.0000000000002534
72. Jakicic JM, Berkowitz RI, Bolin P, Bray GA, Clark JM, Coday M, Egan C, Evans M, Foreyt JP, Fulton JE, et al. Association between change in accelerometer-measured and self-reported physical activity and cardiovascular disease in the Look AHEAD Trial. *Diabetes Care*. 2022;45:742–749.
73. Kraus WE, Janz KF, Powell KE, Campbell WW, Jakicic JM, Troiano RP, Sprow K, Torres A, Piercy KL; 2018 Physical Activity Guidelines Advisory Committee. Daily step counts for measuring physical activity exposure and its relation to health. *Med Sci Sports Exerc*. 2019;51:1206–1212. doi: 10.1249/MSS.0000000000001932
74. 2018 Physical Activity Guidelines Advisory Committee. *2018 Physical Activity Guidelines Advisory Committee Scientific Report*. US Department of Health and Human Services; 2018.
75. Hall KS, Hyde ET, Bassett DR, Carlson SA, Carnethon MR, Ekelund U, Evenson KR, Galuska DA, Kraus WE, Lee IM, et al. Systematic review of the prospective association of daily step counts with risk of mortality, cardiovascular disease, and dysglycemia. *Int J Behav Nutr Phys Act*. 2020;17:78. doi: 10.1186/s12966-020-00978-9
76. Paluch AE, Bajpai S, Bassett DR, Carnethon MR, Ekelund U, Evenson KR, Galuska DA, Jefferis BJ, Kraus WE, Lee IM, et al; Steps for Health Collaborative. Daily steps and all-cause mortality: a meta-analysis of 15 international cohorts. *Lancet Public Health*. 2022;7:e219–e228. doi: 10.1016/S2468-2667(21)00302-9
77. Paluch AE, Bajpai S, Ballin M, Bassett DR, Buford TW, Carnethon MR, Chernofsky A, Dooley EE, Ekelund U, Evenson KR, et al; Steps for Health Collaborative. Prospective association of daily steps with cardiovascular disease: a harmonized meta-analysis. *Circulation*. 2022;147:122–131. doi: 10.1161/CIRCULATIONAHA.122.061288
78. Del Pozo Cruz B, Ahmadi MN, Lee IM, Stamatakis E. Prospective associations of daily step counts and intensity with cancer and cardiovascular disease incidence and mortality and all-cause mortality. *JAMA Intern Med*. 2022;182:1139. doi: 10.1001/jamainternmed.2022.4000
79. Garduno AC, LaCroix AZ, LaMonte MJ, Dunstan DW, Evenson KR, Wang G, Di C, Schumacher BT, Bellettiere J. Associations of daily steps and step intensity with incident diabetes in a prospective cohort study of older women: the OPACH study. *Diabetes Care*. 2022;45:339–347. doi: 10.2337/dc21-1202
80. Cuthbertson CC, Moore CC, Sotres-Alvarez D, Heiss G, Isasi CR, Mossavar-Rahmani Y, Carlson JA, Gallo LC, Llabre MM, Garcia-Bedoya OL, et al. Associations of steps per day and step intensity with the risk of diabetes: the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). *Int J Behav Nutr Phys Act*. 2022;19:46. doi: 10.1186/s12966-022-01284-2
81. Deleted in proof.
82. Lahtinen M, Toukola T, Junttila MJ, Piira OP, Lepojärvi S, Kääriäinen M, Huikuri HV, Tulppo MP, Kiviniemi AM. Effect of changes in physical activity on risk for cardiac death in patients with coronary artery disease. *Am J Cardiol*. 2018;121:143–148. doi: 10.1016/j.amjcard.2017.10.002
83. Moholdt T, Lavie CJ, Nauman J. Sustained physical activity, not weight loss, associated with improved survival in coronary heart disease. *J Am Coll Cardiol*. 2018;71:1094–1101. doi: 10.1016/j.jacc.2018.01.011
84. Al-Shaar L, Li Y, Rimm EB, Manson JE, Rosner B, Hu FB, Stampfer MJ, Willett WC. Physical activity and mortality among male survivors of myocardial infarction. *Med Sci Sports Exer*. 2020;52:1729–1736. doi: 10.1249/MSS.0000000000002309
85. Atwater BD, Li Z, Pritchard J, Greiner MA, Nabutovsky Y, Hammill BG. Early increased physical activity, cardiac rehabilitation, and survival after implantable cardioverter-defibrillator implantation. *Circ Cardiovasc Qual Outcomes*. 2021;14:e007580. doi: 10.1161/CIRCOUTCOMES.120.007580
86. Sun XR, Cheng CD, Zhou B, Zhao S, Chen KP, Hua W, Su YG, Xu W, Wang F, Fan XH, et al. Association of time-varying changes in physical activity with cardiac death and all-cause mortality after ICD or CRT-D implantation. *J Geriatr Cardiol*. 2022;19:177–188. doi: 10.11909/j.issn.1671-5411.2022.03.006
87. Saint-Maurice PF, Graubard BI, Troiano RP, Berrigan D, Galuska DA, Fulton JE, Matthews CE. Estimated number of deaths prevented through increased physical activity among US adults. *JAMA Intern Med*. 2022;182:349. doi: 10.1001/jamainternmed.2021.7755
88. Hafner M, Yerushalmi E, Stepanek M, Phillips W, Pollard J, Deshpande A, Whitmore M, Millard F, Subel S, van Stolk C. Estimating the global economic benefits of physically active populations over 30 years (2020-2050). *Br J Sports Med*. 2020;54:1482–1487. doi: 10.1136/bjsports-2020-102590
89. Aubert S, Barnes JD, Demchenko I, Hawthorne M, Abdeta C, Abi Nader P, Adsuar Sala JC, Aguilar-Farias N, Aznar S, Bakalar P, et al. Global Matrix 4.0 physical activity report card grades for children and adolescents: results

and analyses from 57 countries. *J Phys Act Health*. 2022;19:700–728. doi: 10.1123/jpah.2022-0456
90. Ramirez Varela A, Hallal PC, Mejia Grueso J, Pedisic Z, Salvo D, Nguyen A, Klepac B, Bauman A, Siefken K, Hinckson E, et al. Status and trends of physical activity surveillance, policy, and research in 164 countries: findings from the Global Observatory for Physical Activity-GoPA! 2015 and 2020 Surveys. *J Phys Act Health*. 2023;20:112–128. doi: 10.1123/jpah.2022-0464
91. Katzmarzyk PT, Friedenreich C, Shiroma EJ, Lee IM. Physical inactivity and non-communicable disease burden in low-income, middle-income and high-income countries. *Br J Sports Med*. 2022;56:101–106. doi: 10.1136/bjsports-2020-103640
92. Conger SA, Toth LP, Cretsinger C, Raustorp A, Mitas J, Inoue S, Bassett DR. Time trends in physical activity using wearable devices: a systematic review and meta-analysis of studies from 1995 to 2017. *Med Sci Sports Exerc*. 2022;54:288–298. doi: 10.1249/MSS.0000000000002794
93. Sfm C, Van Cauwenberg J, Maenhout L, Cardon G, Lambert EV, Van Dyck D. Inequality in physical activity, global trends by income inequality and gender in adults. *Int J Behav Nutr Phys Act*. 2020;17:142. doi: 10.1186/s12966-020-01039-x
94. Global Burden of Disease Study and Institute for Health Metrics and Evaluation. University of Washington. Accessed August 2, 2023. http://ghdx.healthdata.org/

# 5. NUTRITION

***See Tables 5-1 through 5-4 and Charts 5-1 through 5-3***

Click here to return to the Table of Contents

Click here to return to the Abbreviations

This chapter highlights national dietary intake and habits with a focus on key foods, nutrients, diet patterns, food systems, and other dietary factors related to cardiometabolic health. It examines current intakes, trends and changes in intakes, and estimated effects on disease to support and further stimulate efforts to monitor and equitably improve dietary habits in relation to CVH.

## Prevalence and Trends in the AHA Healthy Diet Metrics

## (See Tables 5-1 through 5-3)

On June 29, 2022, the AHA debuted Life's Essential 8, an updated algorithm for quantifying CVH.[1] This update was in response to extensive evidence that gives insights into the strengths and limitations of the original approach to quantifying CVH (Life's Simple 7). In Life's Essential 8, diet was 1 of the 4 items updated to reflect new evidence and to provide a guide to assess diet quality for adults and children at the population level (Table 5-1) and individual level (Table 5-2). At the population level, diet is assessed on the basis of DASH-style eating patterns. At the individual level, the Mediterranean Eating Pattern for Americans is used to assess and monitor CVH. A DASH-style pattern emphasizes vegetables, fruits, nuts and legumes, whole grains, and low-fat dairy and is reduced in sodium, red and processed meats, and sweetened beverages (Table 5-2). The items included in the Mediterranean Eating Pattern for Americans are shown in Table 5-3.[1] The presidential advisory to the AHA acknowledges disparities by personal and environmental factors and the need for innovation in systems and structures to correct current deleterious impacts on health.[1] A call for action is evident in the AHA science advisory focused on favorable innovation to create healthy and sustainable outcomes at every level of the food system.[2]

The first study to use the AHA's Life's Essential 8 to quantify the CVH levels of adults and children in the United States included data from 23 409 individuals 2 through 79 years of age (13 521 adults and 9888 children) participating in NHANES.[3] The adults in the study population represent 201 728 000 adults, and the children in the study represent 74 435 000 children.

This cross-sectional analysis of data from the NHANES 2013 to 2018 survey cycles revealed that 1 in 5 people in the United States has a CVH score indicative of optimal heart health and that there are differences across age and sociodemographic groups.[3] The scoring system for the AHA's Life's Essential 8 allows 100-point scores for each of the 8 metrics (0 is lowest, 100 is highest). The scores on the 8 metrics are used to generate a composite CVH score (the unweighted average of all components) that ranges from 0 to 100 points.

The mean overall CVH scores from this analysis revealed significant differences by age (range of mean values, 62.2–68.7), sex (females, 67.0; males, 62.5), and racial and ethnic group (range, 59.7–68.5).[3] Diet was among the 4 metrics with the lowest scores; the range for diet across demographic groups was 23.8 to 47.7. Among children 2 to 5 years of age, a mean diet score of 61.1 was observed. The score for children 12 to 19 years of age was 28.5.

## Dietary Habits in the United States: Current Intakes of Foods and Nutrients

### *Adults*

#### *(See Table 5-4 and Charts 5-1 and 5-2)*

The average dietary consumption by US adults of selected foods and nutrients related to cardiometabolic health based on data from NHANES 2017 to 2018 is detailed below by sex and race and ethnicity (Table 5-4):

- Consumption of whole grains was low with sex and racial variations and ranged from 0.6 (Mexican American males) to 0.9 (NH White males) serving/d. For each of these groups, <10% of adults met guidelines of ≥3 servings/d.
- Whole fruit consumption similarly showed a sex and racial difference and ranged from 1.1 (NH Black males) to 1.7 (Mexican American females) servings/d. For each of those groups except Mexican American females, <10% of adults met guidelines of ≥2 cups/d. When 100% fruit juices were included, the number of servings increased, and the proportions of adults consuming ≥2 cups/d increased.
- Nonstarchy vegetable consumption ranged from 1.5 (NH Black males) to 2.3 (NH White females) servings/d. The proportion of adults meeting guidelines of ≥2.5 cups/d was <10%.

The 2024 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2024. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

- Consumption of fish and shellfish ranged from 1.0 (NH White individuals) to 1.9 (NH Black females) servings/wk. The proportions of adults meeting guidelines of ≥2 servings/wk were ≈18% of NH White adults, ≈28% of NH Black adults, and ≈19% of Mexican American adults.
- Weekly consumption of nuts and seeds was ≈6 servings among NH White adults, ≈3 servings among NH Black adults, and ≈4 servings among Mexican American adults. Approximately 1 in 3 White adults, 1 in 5 NH Black adults, and 1 in 4 Mexican American adults met guidelines of ≥4 servings/wk.
- Consumption of processed meats was lowest among Mexican American females (1.0 servings/wk) and highest among NH White males (≈2.5 servings/wk). Between 59% (NH White males) and 87% (Mexican American females) of adults consumed ≤2 servings/wk.
- Consumption of SSBs was lowest among NH White females (6.4 servings/wk) and highest among NH Black individuals and Mexican American males (≈10 servings/wk). The proportions of adults meeting guidelines of <36 oz/wk were ≈61% for NH White adults, 48% for Mexican American adults, and 41% for NH Black adults.
- Consumption of sweets and bakery desserts ranged from 4.4 servings/wk among Mexican American females to 3.3 servings/wk among NH Black males. The majority of NH White, NH Black, and Mexican American adults consumed <2.5 servings/wk.
- The proportion of total energy intake from added sugars ranged from 11.8% for NH White males to 20.4% for NH Black females. Between 16.6% of NH Black females and 38.3% of Mexican American males consumed ≤6.5% of total energy intake from added sugars.
- Consumption of EPA and DHA ranged from 0.079 to 0.124 g/d in each sex and racial or ethnic subgroup. Fewer than 9% of US adults met the guideline of ≥0.250 g/d.
- Two-fifths to one-third of adults consumed <10% of total calories from saturated fat, and approximately one-half to two-thirds consumed <300 mg dietary cholesterol/d.
- The ratio of (PUFAs+monounsaturated fatty acids)/SFAs ranged from 1.8 in NH White males and Mexican American males to 2.6 in NH Black females. The proportion with a ratio ≥2.5 ranged from 40.6% in NH Black females to 11.2% in NH White males.
- Only ≈5% of NH White adults, ≈4% of Black adults, and ≈15% of Mexican American adults consumed ≥28 g dietary fiber/d.
- Fewer than 10% of adults consumed <2.3 g sodium/d. Estimated mean sodium intake by 24-hour urinary excretion was 4205 mg/d for males and 3039 mg/d for females in 2013 to 2014. Estimates of sodium intake by race, sex, and source are shown in Charts 5-1 and 5-2. Sodium added to food outside the home accounts for more than two-thirds of total sodium intake in the United States (Chart 5-2).[4] The average daily sodium consumption for Americans ≥1 year of age is >3400 mg, and the top 10 food categories accounted for 40% of sodium consumed.[5] These top 10 categories included prepared foods with added sodium such as deli meat sandwiches, pizza, burritos, and tacos. During 2015 to 2016, the percentage of adults in the United States with sodium intake above the chronic disease risk reduction intake level was 86.7%.[6] This is noteworthy because the chronic disease risk reduction intake for sodium was established from evidence of the beneficial effect of reducing sodium intake on CVD risk, hypertension risk, SBP, and DBP. In apparently healthy populations, when reductions in intake of sodium exceed the chronic disease risk reduction, it is expected that there will be reductions in chronic disease risk.

## Children and Teenagers

According to NHANES 2015 to 2016 data, the average dietary consumption by US children and teenagers of selected foods and nutrients related to cardiometabolic health is detailed below[7]:

- Whole grain consumption was low with an estimated average intake of 0.95 serving/d (95% CI, 0.88–1.03) among US youth 2 to 19 years of age. Youth with higher parental education had higher intake.
- Whole fruit consumption was low with an estimated average intake of 0.68 serving/d (95% CI, 0.58–0.77). The consumption pattern decreased with age. NH Asian youth and those of other races, including multiracial youth, had the highest intake of whole fruit, followed by NH White youth, other Hispanic youth, Mexican American youth, and NH Black youth. The average intake of 100% fruit juice was 0.46 serving/d (95% CI, 0.39–0.53). The consumption pattern also decreased with age. NH White youth had the lowest intake of fruit juice, followed by NH Asian youth and other races, including multiracial youth, Mexican American youth, other Hispanic youth, and NH Black youth.
- Nonstarchy vegetable consumption was low with an estimated average intake of 0.57 serving/d (95% CI, 0.53–0.62). The consumption pattern increased with age.
- Consumption of fish and shellfish was low with an estimated average intake of 0.06 serving/d (95% CI, 0.04–0.07). The consumption pattern increased with age. Hispanic youth had the highest intake of

fish and shellfish, followed by NH Asian youth and other races, including multiracial youth, NH Black youth, Mexican American youth, and NH White youth.
- Consumption of nuts and seeds was low with an estimated average intake of 0.40 serving/d (95% CI, 0.33–0.47). NH White youth had the highest intake of nuts and seeds, followed by NH Asian youth and youth of other races, including multiracial youth, other Hispanic youth, NH Black youth, and Mexican American youth. The consumption pattern of nuts and seeds increased with attainment of parental education and parental income.
- Consumption of unprocessed red meats was 0.31 serving/d (95% CI, 0.27–0.34) on average with higher intake among youth with attainment of parental education less than high school and high school graduate, and lower among youth with parental education of some college or above and college graduate or above.
- Consumption of processed meats was 0.27 serving/d (95% CI, 0.24–0.29) on average with higher intake among males and lower intake among females. NH White youth had the highest intake of processed meat, followed by NH Black youth, Mexican American youth, NH Asian youth, and those of other races, including multiracial youth and other Hispanic youth.
- Consumption of SSBs was 1.0 serving/d (95% CI, 0.89–1.11) on average among US youth. The consumption pattern of SSBs increased with age. NH Black youth had the highest intake of SSBs, followed by Mexican American youth, NH White youth, other Hispanic youth, NH Asian youth, and those of other races, including multiracial youth.
- Consumption of sweets and bakery desserts contributed to an average of 6.07% of calories (95% CI, 5.55%–6.60%) among US youth, with no significant heterogeneity across age, sex, race and ethnicity, parental education, and household income.
- Consumption of EPA and DHA was low with an estimated average intake of 0.04 g/d (95% CI, 0.03–0.05). The consumption pattern of EPA and DHA increased with age. NH Asian youth and those of other races, including multiracial youth, had the highest intake of EPA and DHA, followed by other Hispanic youth, Mexican American youth, NH White youth, and NH Black youth.
- Consumption of SFAs was ≈12.1% of calories (95% CI, 11.8%–12.4%) among US youth. Consumption of dietary cholesterol was 254 mg/d (95% CI, 244–264) with NH White youth having the lowest intake (238 mg/d [95% CI, 226–250]) and Mexican American youth having the highest intake (292 mg/d [95% CI, 275–309]).
- Consumption of dietary fiber was 15.6 g/d (95% CI, 15.1–16.0) on average among US youth, with no significant heterogeneity across age, sex, race and ethnicity, parental education, and household income.
- Consumption of sodium was 3.33 g/d (95% CI, 3.28–3.37) on average among US youth. The consumption pattern increased with age. NH Asian youth and those of other races, including multiracial youth, had the highest intake of sodium, followed by NH Black youth, Mexican American youth, and NH White youth.

## Secular Trends

In addition to individual foods and nutrients, overall dietary patterns can be useful in determining diet quality. The 2020 US Dietary Guidelines Advisory Committee summarized the evidence for benefits of healthful diet patterns on a range of cardiometabolic and other disease outcomes.[8] They concluded that the core elements of a healthy dietary pattern are (1) vegetables of all types; (2) fruits, especially whole fruits; (3) grains, of which at least half are whole grains; (4) dairy, including fat-free or low-fat milk, yogurt, and cheese or lactose-free versions and fortified soy beverages and yogurt as alternatives; (5) protein foods, including lean meats, poultry and eggs, seafood, beans, peas, lentils, nuts, seeds, and soy products; and (6) oils, including vegetable oils and oils in food such as seafood and nuts. A healthy dietary pattern is also limited in foods and beverages high in added sugars, saturated fat, sodium, and alcoholic beverages. The Dietary Guidelines for Americans are published every 5 years, and adherence to them is measured with the HEI.

Between 1999 and 2016, the average HEI-2015 score of US adults improved from 55.7 to 57.7 (difference, 2.01 [95% CI, 0.86–3.16]; $P_{trend}$<0.001).[9] This was related to improvements in the macronutrient composition, including decreases in low-quality carbohydrates (primarily added sugar) and increases in high-quality carbohydrates (primarily whole grains), plant protein (primarily whole grains and nuts), and polyunsaturated fat. However, intake of low-quality carbohydrates and saturated fat remained high. The HEI-2015 score increased more in younger compared with older adults and in those with a higher compared with a lower level of income.

Trends in diet quality among youth in the United States were characterized in a study using 9 NHANES data cycles.[7] The primary outcomes were the survey-weighted, energy-adjusted mean consumption of dietary components and proportion meeting targets of the AHA 2020 continuous diet score (range, 0–50; based on total fruits and vegetables, whole grains, fish and shellfish, SSBs, and sodium). Other outcomes were the AHA secondary score (range, 0–80; adding nuts, seeds, and legumes; processed meat; and saturated fat) and HEI 2015 score (range, 0–100). Between 1999 and 2016, the mean

HEI-2015 score in US children and adolescents 2 to 19 years of age improved from 44.6 (95% CI, 43.5–45.8) to 49.6 (95% CI, 48.5–50.8; 11.2% improvement).[7] The mean AHA primary diet score increased from 14.8 (95% CI, 14.1–15.4) to 18.8 (95% CI, 18.1–19.6; 27.0% improvement), and the mean AHA secondary score improved from 29.2 (95% CI, 28.1–30.4) to 33.0 (95% CI, 32.0–33.9; 13.0% improvement). On the basis of the AHA primary score, the estimated proportion of US children with poor dietary quality significantly decreased from 76.8% (95% CI, 72.9%–80.2%) to 56.1% (95% CI, 51.4%–60.7%); the estimated proportion with intermediate quality significantly increased from 23.2% (95% CI, 19.8%–26.9%) to 43.7% (95% CI, 39.1%–48.3%). The estimated proportion with an ideal diet significantly improved but remained low (from 0.07% to 0.25%). On the basis of the AHA secondary score, the estimated proportion of US children with poor dietary quality significantly decreased from 61.0% (95% CI, 56.5%–65.2%) to 49.1% (95% CI, 45.0%–53.3%); the estimated proportion with intermediate quality significantly increased from 39.0% (95% CI, 34.7%–43.4%) to 50.4% (95% CI, 46.3%–54.4%). The estimated proportion with an ideal diet significantly improved from 0.04% to 0.50%. The overall dietary quality improvement among US youth was attributable mainly to the increased consumption of fruits/vegetables (especially whole fruits) and whole grains, with additional increases in total dairy, total protein foods, seafood, and plant proteins and decreased consumption of SSBs and added sugar. Persistent dietary variations were identified across multiple sociodemographic groups. The mean HEI-2015 score in 2015 to 2016 was 55.0 (95% CI, 53.7–56.4) for youth 2 to 5 years of age, 49.2 (95% CI, 47.9–50.6) for youth 6 to 11 years of age, and 47.4 (95% CI, 46.0–48.8) for youth 12 to 19 years of age.

Patterns and trends in diet quality of foods from major sources, including grocery stores, restaurants, schools, and worksites, were examined in a study including children 5 to 19 years of age and adults ≥20 years of age in a serial, cross-sectional survey of data from 8 NHANES cycles from 2003 to 2018.[10] Relative to the other food sources, schools provided the best mean diet quality. More specifically, schools had the largest improvement in diet quality, with the percentage of the population having poor diet quality decreasing from 55.6% to 24.4% ($P_{trend}$<0.001).

The characteristics associated with duration of participation in WIC were examined, including household food insecurity, child diet quality, and child weight status at 5 years of age.[11] Longer duration of participation in WIC was associated with lower odds of household food insecurity (OR, 0.69 [95% CI, 0.51–0.95]), higher total dietary quality as measured by the HEI-2015 (β=0.73 [95% CI, 0.21–1.25]), and higher obesity odds (OR, 1.20 [95% CI, 1.05–1.37]) in multivariable-adjusted regression models.

### *Trends in Dietary Supplement Intake*

Use of dietary supplements is common in the United States among both adults and children despite lack of evidence to support the use of most dietary supplements in reducing the risks of CVD or death.[12] With the use of a nationally representative sample of US individuals 1 year of age or older from the NHANES 2007 to 2018, it was determined that dietary supplement use increased from 50% in 2007 to 56% in 2018.[13] The use of micronutrient-containing supplements increased from 46% in 2007 to 49% in 2018; use of single-nutrient supplements also increased (*P*<0.001). In children 1 to 18 years of age, the use of dietary supplements in any form remained stable (38%) over this time frame. However, use of micronutrient-containing supplements increased in children who experience food insecurity, in whom use increased from 24% to 31% (*P*=0.03). In adults, use of dietary supplements in any form increased (54% to 61%) and use of micronutrient-containing supplements increased (49% to 54%). Dietary supplement use increased especially in those who identify as male, NH Black, Hispanic, and low income.

## Social Determinants of Dietary Intake/Health Equity

- Societal and environmental factors independently associated with diet quality, adiposity, or weight gain include education, income, race and ethnicity, and (at least cross-sectionally) neighborhood availability of supermarkets.[14,15]
- Other local food-environment characteristics such as availability of grocery stores (ie, smaller stores than supermarkets), convenience stores, and fast-food restaurants are not consistently associated with diet quality or adiposity and could be linked to social determinants of health for CVH.[16,17]
- An analysis of the 4 major outlets where food is obtained, that is, stores, quick-serve restaurants, full-service restaurants, and schools, using 24-hour dietary recall data from 8 cycles of the NHANES showed that Americans are not consuming foods that align with the Dietary Guidelines for Americans.[18] The HEI-2015 score for schools (65/100 points) and stores (62/100 points) was significantly higher than for full-service (51/100 points) and quick-service (39/100 points) restaurants (*P*<0.0001).

## Genetics/Family History

- Genetic factors may contribute to food preferences and liking and modulate the association between dietary components and adverse CVH outcomes.[19–22] Nutrigenetics may also contribute to variation in the metabolism of specific dietary

components (such as fatty acids) across individuals or ethnic and racial groups.[23] Nutritional epigenomics stipulates that epigenetic alterations induced by environmental exposures such as diet and bioactive compounds may mediate the impact of diet on CVH outcomes.[24,25] However, there is a paucity of gene-diet interaction studies with independent replication to support personalizing dietary recommendations according to genotype.

- A recent GWAS identified 26 loci associated with dietary carbohydrate, fat, and protein intake.[22] The study noted an enrichment of genes with a higher expression in specific neurons (GABAergic, dopaminergic, and glutamatergic), indicating neural mechanisms contributing to dietary patterns.[22]
- In a randomized trial of 609 overweight/obese nondiabetic participants that compared the effects of healthy low-fat and healthy low-carbohydrate weight-loss diets, neither genotype pattern (3-SNP multilocus genotype responsiveness pattern) nor insulin secretion (30 minutes after a glucose challenge) modified the effects of diet on weight loss.[26]
- The interactions between a GRS composed of 97 BMI-associated variants and 3 diet-quality scores were examined in a pooled analysis of 30 904 participants from the Nurses' Health Study, the HPFS, and the Women's Genome Health Study. Higher diet quality was found to attenuate the association between GRS and BMI ($P$ for interaction terms <0.005 for AHEI-2010 score, Alternative Mediterranean Diet score, and DASH diet score).[27] A 10-unit increase in the GRS was associated with a 0.84-unit (95% CI, 0.72–0.96) increase in BMI for those in the highest tertile of AHEI score compared with a 1.14-unit (95% CI, 0.99–1.29) increase in BMI in those in the lowest tertile of AHEI score.
- In a study of ≈9000 females from the WHI, a GRS for LDL-C, composed of 1760 LDL-associated variants, explained 3.7% (95% CI, 0.09%–11.9%) of the variance in 1-year LDL-C changes in a dietary fat intervention arm but was not associated with changes in the control arm.[28]

## Impact on Mortality

- Nationally representative data from 37 233 US adults were analyzed to examine the association between low-carbohydrate and low-fat diets and mortality. Neither low-carbohydrate nor low-fat diets were associated with total mortality; however, diet quality and sources of macronutrients appeared to play a role in that healthy low-carbohydrate (HR, 0.91 [95% CI, 0.87–0.95]; $P$<0.001) and low-fat (HR, 0.89 [95% CI, 0.85–0.93]; $P$<0.001) diets were associated with lower mortality and unhealthy low-carbohydrate (HR, 1.07 [95% CI, 1.02–1.11]; $P$=0.01) and low-fat (HR, 1.06 [95% CI, 1.01–1.12]; $P$=0.04) diets were linked to higher mortality.[29]
- Essential to any healthy diet, higher intakes of fruit and vegetables are associated with lower mortality. Specifically, data from 66 719 females from the Nurses' Health Study (1984–2014) and 42 016 males from the HPFS (1986–2014) showed that daily intake of 5 servings of fruit and vegetables (versus 2 servings/d) was associated with lower total mortality (HR, 0.87 [95% CI, 0.85–0.90]), CVD mortality (HR, 0.88 [95% CI, 0.83–0.94]), cancer mortality (HR, 0.90 [95% CI, 0.86–0.95]), and respiratory disease mortality (HR, 0.65 [95% CI, 0.59–0.72]).[30]
- NHANES III (1988–1994) data from 3733 adults (20–90 years of age) with overweight/obese (BMI ≥25 kg/m$^2$) were analyzed to assess the relationship between the DII score and mortality.[31] DII scores of metabolically unhealthy obese/overweight individuals were associated with increased mortality risk ($HR_{\text{tertile 3 versus tertile 1}}$, 1.44 [95% CI, 1.11–1.86]; $P_{\text{trend}}$=0.008; $HR_{\text{1-SD increase}}$, 1.08 [95% CI, 0.99–1.18]) and, more specifically, CVD-related mortality ($HR_{\text{T3 versus T1}}$, 3.29 [95% CI, 2.01–5.37]; $P_{\text{trend}}$<0.001; $HR_{\text{1-SD increase}}$, 1.40 [95% CI, 1.18–1.66]). These associations were not observed among adults with MHO, and no cancer mortality risk was observed for either metabolically unhealthy individuals with obesity/overweight or with MHO. The SUN study, which began in 1999 (N=18 566), and the PREDIMED study, which began in (N=6790) in 2003, in Spain similarly analyzed the DII score in relation to mortality. Significant associations were found in differences between the highest and lowest quartiles of the DII score and mortality in both SUN (HR, 1.85 [95% CI, 1.15–2.98]; $P_{\text{trend}}$=0.004) and PREDIMED (HR, 1.42 [95% CI, 1.00–2.02]; $P_{\text{trend}}$=0.009).[32] In a meta-analysis of 14 studies, there was a positive association between increasing DII and CVD. There was a 36% increased risk of CVD incidence and mortality, with some evidence of heterogeneity (RR, 1.36 [95% CI, 1.19–1.57]; heterogeneity index, 69%; $P$<0.001).[33]
- NHANES 1999 to 2010 data from 20 256 US adults (mean, 47.5 years of age) were analyzed to evaluate the relationship between dietary uricemia score and dietary atherogenic score (which were derived in regression models on 37 micronutrients and macronutrients predicting levels of serum uric acid and apolipoprotein B, respectively) and all-cause and cause-specific mortality. Individuals in the highest dietary uricemia score quartile were at greater risk for all-cause (HR, 1.17 [95% CI, 1.07–2.30]), cancer (HR, 1.06 [95% CI, 1.01–1.14]), and CVD (HR, 1.36 [95% CI, 1.21–1.59]) mortality. Similar patterns were noted in the dietary

atherogenic score, with those in the highest quartiles (versus those in the lowest) experiencing an increased RR for all-cause (25%), cancer (11%), and CVD (40%) mortality.[34]

- A number of studies examined the relationship between sugar intake and all- and cause-specific mortality. A 6-year cohort study of 13 440 US adults (mean, 63.6 years of age) found that higher consumption (each additional 12-oz serving/d) of sugary beverages (HR, 1.11 [95% CI, 1.03–1.19]) and 100% fruit juices (HR, 1.24 [95% CI, 1.09–1.42]) was associated with higher all-cause (but not CHD-specific) mortality.[35] In 2 Swedish studies (MDCS, N=24 272; and NSHDS, N=24 475), higher sugar consumption (>20% energy intake) was linked to higher mortality risk (HR, 1.30 [95% CI, 1.12–1.51]), and low sugar consumption (<5% energy intake) was also associated with higher mortality risk (HR, 1.23 [95% CI, 1.11–1.35]) in the MDCS study.[36]
- A systematic review of 18 cohort studies (N=251 497) examined the relationship of glycemic index and glycemic load with risk of all-cause mortality and CVD and found no associations between glycemic index or glycemic load and CVD or all-cause mortality. However, a positive association was found with all-cause mortality among females with the highest (versus lowest) glycemic index (RR, 1.17 [95% CI, 1.02–1.35]).[37] Using data from 137 851 participants between 35 and 70 years of age living in high-, middle-, and low-income countries across 5 continents with a median follow-up of 9.5 years, the international PURE study reported that a high glycemic index was associated with an increased risk of a major cardiovascular event or death among participants with (HR, 1.51 [95% CI, 1.25–1.82]) and without (HR, 1.21 [95% CI, 1.11–1.34]) preexisting CVD at baseline.[38]
- In an assessment of the relationship between dairy intake and mortality, data from 3 large prospective cohort studies with 217 755 US adults showed a dose-response relationship in which 2 daily servings of dairy were associated with the lowest CVD mortality and higher intake was linked to higher mortality, especially cancer mortality. Compared with other subtypes of dairy (eg, skim/low-fat milk, cheese, yogurt, ice cream/sherbet), whole milk (and additional 0.5 serving/d) was associated with higher risks of cancer mortality (HR, 1.11 [95% CI, 1.06–1.17]), CVD mortality (HR, 1.09 [95% CI, 1.03–1.15]), and total mortality (HR, 1.11 [95% CI, 1.09–1.14]). A similar large cohort study of 45 009 Italian participants found no dose-response relationship between dairy (eg, milk, cheese, yogurt, butter) consumption and mortality, and no differences were present between full-fat and reduced-fat milk. However, there was a significant reduction of 25% in risk of all-cause mortality among those consuming 160 to 200 g/d (HR, 0.75 [95% CI, 0.61–0.91]) milk versus nonconsumers. Another European study examined the relationship between dietary protein and protein sources and mortality among 2641 Finnish males. Higher meat intake (HR, 1.23 [95% CI, 1.04–1.47]) and higher ratio of animal to plant protein (HR, 1.23 [95% CI, 1.02–1.49]) were associated with higher mortality. This relationship was more pronounced among those with a history of CVD, cancer, and type 2 diabetes.[39–41] In addition, several meta-analyses of prospective cohort studies have consistently reported that higher plant protein intake is inversely associated with total and CVD mortality, lending support for dietary recommendations to replace foods high in animal protein with plant protein sources.[42–44]
- The association between nut and peanut butter consumption and mortality has also been assessed. In a large prospective cohort study of 566 398 US adults (50–71 years of age at baseline) with a median follow-up of 15.5 years, nut consumption was inversely related to mortality (HR, 0.78 [95% CI, 0.76–0.81]; $P \leq 0.001$) and was associated with reductions in cancer, CVD, and infectious, respiratory, and liver and renal disease mortality (but not AD- or diabetes-related mortality). No significant relationships were found between peanut butter and cause-specific or all-cause mortality (HR, 1.00 [95% CI, 0.98–1.04]; $P=0.001$).[45]
- Moderate egg consumption and all-cause and cause-specific[46] mortality were investigated in a large cohort of 40 621 adults (29–69 years of age) in the EPIC-Spain prospective cohort study across 18 years. Mean egg consumption was 22 g/d (SD, 15.8 g/d) in females and 30.9 g/d (SD, 23.1 g/d) in males, and no association was found between the highest and lowest quartiles of egg consumption and all-cause mortality (HR, 1.01 [95% CI, 0.91–1.11]; $P=0.96$) or cancer and CVD mortality. However, egg consumption appears to be inversely associated with deaths resulting from other causes (HR, 0.76 [95% CI, 0.63–0.93]; $P=0.003$), specifically nervous system–related deaths (HR, 0.59 [95% CI, 0.35–1.00]; $P=0.036$).[46]
- The association between dietary choline and overall- and cause-specific mortality was examined in a large, nationally representative study of 20 325 US adults (mean, 47.4 years of age). Higher choline consumption was found to be associated with worse lipid profiles, poorer glycemic control, and lower CRP levels (all comparisons, $P<0.001$). Those with the highest compared with lowest consumption had increased risk of total (RR, 1.23 [95% CI, 1.09–1.38]), stroke (RR, 1.30 [95% CI, 1.02–1.66]), and CVD (RR, 1.33 [95% CI, 1.19–1.48]) mortality (all

comparisons $P<0.001$).[47] A subsequent meta-analysis confirmed these results and found choline to be linked to higher mortality risk (RR, 1.12 [95% CI, 1.08–1.17]; $I^2$=2.9) and CVD mortality risk (RR, 1.28 [95% CI, 1.17–1.39]; $I^2$=9.6).[47]

## CVH Impact of Diet

### *Dietary Patterns*

- The observational findings for benefits of the Mediterranean diet have been confirmed in a large primary prevention trial in Spain among patients with CVD risk factors.[48] The PREDIMED trial demonstrated an ≈30% relative reduction in the risk of stroke, MI, and death attributable to cardiovascular causes in those patients randomized to unrestricted-calorie Mediterranean-style diets supplemented with extravirgin olive oil or mixed nuts,[48] without changes in body weight.[49] In a subgroup analysis of 3541 patients without diabetes in the PREDIMED trial, HRs for incident diabetes were 0.60 (95% CI, 0.43–0.85) for the Mediterranean diet with olive oil group and 0.82 (95% CI, 0.61–1.10) for the Mediterranean diet with nuts group compared with the control group.
- In a randomized crossover trial of 118 omnivores with overweight at low to moderate CVD risk, a reduced-calorie lacto-ovo-vegetarian diet was compared with a reduced-calorie Mediterranean diet by providing face-to-face, individual counseling sessions. Both diets were equally successful in reducing body weight and fat mass. LDL-C, uric acid, and vitamin $B_{12}$ were lower during the vegetarian diet, whereas triglycerides were lower during the Mediterranean diet, without substantial differences between oxidative stress markers and inflammatory cytokines.[50]
- In a systematic review and meta-analysis of 29 observational studies, the RR for the highest versus lowest category of the Mediterranean diet was 0.81 (95% CI, 0.74–0.88) for CVD, 0.70 (95% CI, 0.62–0.80) for CHD/AMI, 0.73 (95% CI, 0.59–0.91) for unspecified stroke (ischemic/hemorrhagic), 0.82 (95% CI, 0.73–0.92) for ischemic stroke, and 1.01 (95% CI, 0.74–1.37) for hemorrhagic stroke.[51]
- In a meta-analysis of 20 prospective cohort studies, the RR for each 4-point increment of the Mediterranean diet score was 0.84 (95% CI, 0.81–0.88) for unspecified stroke, 0.86 (95% CI, 0.81–0.91) for ischemic stroke, and 0.83 (95% CI, 0.74–0.93) for hemorrhagic stroke.[52]
- In another systematic review, a meta-analysis of 3 RCTs showed a beneficial effect of the Mediterranean diet on total CVD incidence (RR, 0.62 [95% CI, 0.50–0.78]) and total MI incidence (RR, 0.65 [95% CI, 0.49–0.88]).[53]
- Another meta-analysis of 38 prospective cohort studies showed that the RR for the highest versus the lowest categories of Mediterranean diet adherence was 0.79 (95% CI, 0.77–0.82) for total CVD mortality, 0.73 (95% CI, 0.62–0.86) for CHD incidence, 0.83 (95% CI, 0.75–0.92) for CHD mortality, 0.80 (95% CI, 0.71–0.90) for stroke incidence, 0.87 (95% CI, 0.80–0.96) for stroke mortality, and 0.73 (95% CI, 0.61–0.88) for MI incidence.[53]
- Compared with a usual Western diet, a DASH-type dietary pattern with low sodium reduced SBP by 5.3, 7.5, 9.7, and 20.8 mm Hg in adults with baseline SBP <130, 130 to 139, 140 to 149, and ≥150 mm Hg, respectively.[54] Further support for BP effects of a healthy pattern with reduced sodium was seen in a dose-response meta-analysis of experimental studies including 85 clinical trials in participants with hypertension, without hypertension, or a combination. Analyses showed a linear relationship between sodium intake and reduction in SBP and DBP across the entire range of dietary sodium exposure (0.4–7.6 g/d).[55]
- In an umbrella review of systematic reviews, a meta-analysis of 33 controlled trials showed that the DASH diet was associated with decreased SBP (mean difference, −5.2 mm Hg [95% CI, −7.0 to −3.4]), DBP (−2.60 mm Hg [95% CI, −3.50 to −1.70]), TC (−0.20 mmol/L [95% CI, −0.31 to −0.10]), LDL-C (−0.10 mmol/L [95% CI, −0.20 to −0.01]), HbA1c (−0.53% [95% CI, −0.62 to −0.43]), fasting blood insulin (−0.15 µU/mL [95% CI, −0.22 to −0.08]), and body weight (−1.42 kg [95% CI, −2.03 to −0.82]).[56] A meta-analysis of 15 prospective cohort studies showed that the DASH diet was associated with decreased incident CVD (RR, 0.80 [95% CI, 0.76–0.85]), CHD (0.79 [95% CI, 0.71–0.88]), stroke (0.81 [95% CI, 0.72–0.92]), and diabetes (0.82 [95% CI, 0.74–0.92]).[56] In another systematic review and meta-analysis of 7 prospective cohort studies, the RR for each 4-point increment of DASH diet score was 0.95 (95% CI, 0.94–0.97) for CAD.[57]
- Compared with a higher-carbohydrate DASH diet, a DASH-type diet with higher protein lowered BP by 1.4 mm Hg, LDL-C by 3.3 mg/dL, triglycerides by 16 mg/dL, and HDL-C by 1.3 mg/dL. Compared with a higher-carbohydrate DASH diet, a DASH-type diet with higher unsaturated fat lowered BP by 1.3 mm Hg, increased HDL-C by 1.1 mg/dL, and lowered triglycerides by 10 mg/dL.[58] The DASH-type diet higher in unsaturated fat also improved glucose-insulin homeostasis compared with the higher-carbohydrate DASH diet.
- A secondary analysis of the AHS-2 among NH White participants showed that vegetarian dietary patterns (vegan, lacto-ovo vegetarian, and pescatarian) at

baseline were associated with lower prevalence of hypertension at 1 to 3 years of follow-up compared with the nonvegetarian patterns: The PR was 0.46 (95% CI, 0.25–0.83) for vegans, 0.57 (95% CI, 0.45–0.73) for lacto-ovo-vegetarians, and 0.62 (95% CI, 0.42–0.91) for pescatarian. This association remained after adjustment for BMI among the lacto-ovo-vegetarians.[59]

- In a systematic review and meta-analysis of 9 prospective cohort studies, higher adherence to a plant-based dietary pattern was significantly associated with lower risk of type 2 diabetes (RR, 0.77 [95% CI, 0.71–0.84]).[60]
- In an RCT of 48 835 postmenopausal females, a low-fat dietary pattern (lower fat and higher carbohydrates, vegetables, and fruit) intervention led to significant reductions in breast cancer followed by death (HR, 0.84 [95% CI, 0.74–0.96]) and in diabetes requiring insulin (HR, 0.87 [95% CI, 0.77–0.98]) over a median follow-up of 19.6 years compared with usual diet.[61]
- In a prospective cohort study of 105 159 adults followed up for a median of 5.2 years, for a 10% increment in the percentage of ultraprocessed foods in the diet, the HR was 1.12 (95% CI, 1.05–1.20) for overall CVD, 1.13 (95% CI, 1.02–1.24) for CHD, and 1.11 (95% CI, 1.01–1.21) for cerebrovascular disease.[62]
- An umbrella review of 16 meta-analyses of 116 primary prospective cohort studies with 4.8 million participants reported moderate-quality evidence for the inverse association of healthy dietary patterns with the risk of type 2 diabetes (RR, 0.81 [95% CI, 0.76–0.86]) and for a positive association between unhealthy dietary patterns and the risk of type 2 diabetes (RR, 1.44 [95% CI, 1.33–1.56]) and MetS (RR, 1.29 [95% CI, 1.09–1.52]).[63]
- A meta-analysis of 7 RCTs with 425 participants for an average duration of 8.6 weeks found that compared with breakfast consumption, breakfast skipping led to modest weight loss (WMD, −0.54 kg [95% CI, −1.05 to −0.03]) but a modest increase in LDL-C (WMD, 9.24 mg/dL [95% CI, 2.18–16.30]).[64] Another meta-analysis of 23 RCTs with 1397 participants reported that fasting and energy-restricting diets resulted in significant reductions in SBP (WMD, −1.88 mm Hg [95% CI, −2.50 to −1.25]) and DBP (WMD, −1.32 mm Hg [95% CI, −1.81 to −0.84]), and the SBP-lowering effects were stronger with fasting (WMD, −3.26 mm Hg) than energy restriction (WMD, −1.09 mm Hg).[65]

### Fats and Carbohydrates

- In meta-analyses of RCTs comparing higher and lower fiber intake, higher fiber intake lowered body weight (−0.37 kg [95% CI, −0.63 to −0.11]), TC (−0.15 mmol/L [95% CI, −0.22 to −0.07]), and SBP (−1.27 mm Hg [95% CI, −2.50 to −0.04]) and tended to lower HbA1c (−0.54% [95% CI, −1.28% to 0.20%]).[66] In similar meta-analyses of RCTs for whole grains and glycemic index, higher whole grain intake significantly reduced only body weight (−0.62 kg [95% CI, −1.19 to −0.05]), whereas no consistent health effects were found for glycemic index. In meta-analyses of observational studies, higher total dietary fiber intake was associated with a lower risk of incident CHD (RR, 0.76 [95% CI, 0.69–0.83]), CHD mortality (RR, 0.69 [95% CI, 0.60–0.81]), and incident stroke (RR, 0.78 [95% CI, 0.69–0.88]).[66] Higher whole grain intake was associated with a lower risk of incident CHD (RR, 0.80 [95% CI, 0.70–0.91]), CHD mortality (RR, 0.66 [95% CI, 0.56–0.77]), and stroke death (RR, 0.74 [95% CI, 0.58–0.94]). In a meta-analysis of 40 prospective cohort studies in the United States, Asia, and Europe, total dietary fiber (HR, 0.92 [95% CI, 0.88–0.96)] and cereal fiber (HR, 0.83 [95% CI, 0.77–0.90]) were shown to be associated with decreased risk of developing type 2 diabetes among adults with overweight or obesity in US-based studies. The same meta-analysis also reported increased risks of type 2 diabetes with higher glycemic index or glycemic load in US and Asian studies.[67]
- In a randomized trial of 609 participants without diabetes with a BMI of 28 to 40 kg/m$^2$ that compared the effects of healthy low-fat and healthy low-carbohydrate weight loss diets, weight loss at 12 months did not differ between groups.[26] A meta-analysis of 12 randomized studies confirmed the benefit of consuming low-carbohydrate healthy diets for multiple CVD risk factors, including reductions in body weight, triglycerides, LDL-C, SBP, and DBP, although the effects are modest in general and the sustainability is uncertain.[68]
- A study of NHANES 1999 to 2010 data from 24 144 participants comparing those in the fourth and first quartiles of consumption of dietary fats by type found an inverse association between total fat (HR, 0.90 [95% CI, 0.82–0.99]) and PUFAs (0.81 [95% CI, 0.78–0.84]) but an increased association between SFAs (1.08 [95% CI, 1.04–1.11]) and all-cause mortality. In the same study, a meta-analysis of 29 prospective cohorts (N=1 164 029) was also conducted and corroborated the findings for the inverse association between total fat and PUFAs and all-cause mortality. In addition, the meta-analysis showed an inverse association between monounsaturated fatty acid intake (HR, 0.94 [95% CI, 0.89–0.99]) and all-cause mortality and between monounsaturated fatty acid (0.80 [95% CI, 0.67–0.96]) and PUFA (0.84 [95% CI, 0.80–0.90]) intake and stroke mortality. A positive association between

SFA (HR, 1.10 [95% CI, 1.01–1.21]) intake and CHD mortality was observed.[69] However, another meta-analysis reported a protective association between dietary SFA intake and risk for stroke (RR, 0.87 [95% CI, 0.78–0.96]), and there was a linear relation in that every 10–g/d increase in SFA intake was associated with a 6% lower RR of stroke (RR, 0.94 [95% CI, 0.89–0.98]).[70] A recent review underscores the controversy surrounding SFA intake as a risk or protective factor for CVD and total mortality and recommends against arbitrary population-wide upper limits on SFA intake without regard to the types of SFA, the food sources, the overall micronutrient distributions, and the health outcomes of interest.[71]

- Gut microbiota is associated with the risk of obesity, type 2 diabetes, and many other cardiometabolic diseases. In a 6-month randomized controlled feeding trial of 217 healthy young adults with BMI <28 kg/m$^2$, the high-fat diet (fat, 40% energy) had overall unfavorable effects on gut microbiota: increased *Alistipes* ($P$=0.04) and *Bacteroides* ($P$<0.001) and decreased *Faecalibacterium* ($P$=0.04). The low-fat diet (fat, 20% energy) appeared to have beneficial effects on gut microbiota: increased α-diversity assessed by the Shannon index ($P$=0.03) and increased abundance of *Blautia* ($P$=0.007) and *Faecalibacterium* ($P$=0.04).[72]
- In the WHI RCT (N=48 835), a reduction of total fat consumption from 37.8% energy (baseline) to 24.3% energy (at 1 year) and 28.8% energy (at 6 years) had no effect on the incidence of CHD (RR, 0.98 [95% CI, 0.88–1.09]), stroke (RR, 1.02 [95% CI, 0.90–1.15]), or total CVD (RR, 0.98 [95% CI, 0.92–1.05]) over a mean follow-up of 8.1 years.[73] In a matched case-control study of 2428 postmenopausal females nested in the WHI Observational Study, higher plasma phospholipid long-chain SFAs (OR, 1.18 [95% CI, 1.09–1.28]) and lower PUFA n-3 (OR, 0.93 [95% CI, 0.88–0.99]) were associated with increased CHD risk. Replacing 1 mol% PUFA n-6 or *trans* fatty acid with an equivalent amount of PUFA n-3 was associated with 10% lower CHD risk (OR, 0.90 [95% CI, 0.84–0.96]).[74]
- In a study using NHANES 2007 to 2014 data (N=18 434 participants), ORs for newly diagnosed hypertension comparing the highest and lowest tertiles were 0.60 (95% CI, 0.50–0.73) for dietary n-3 fatty acids, 0.52 (95% CI, 0.43–0.62) for dietary n-6 fatty acids, and 0.95 (95% CI, 0.79–1.14) for n-6:n-3 ratio.[75]
- In a prospective study of 3042 CVD-free adults followed up for a mean of 8.4 years, exclusive olive oil use was inversely associated with the risk of developing CVD (RR, 0.07 [95% CI, 0.01–0.66]) compared with no olive oil consumption.[76]

### *Foods and Beverages*

- In a systematic review and dose-response meta-analysis of 123 prospective studies, the risk of CHD, stroke, and HF was inversely associated with consumption of whole grain ($RR_{CHD}$, 0.95 [95% CI, 0.92–0.98]; $RR_{HF}$, 0.96 [95% CI, 0.95–0.97]), vegetables and fruits ($RR_{CHD}$, 0.97 [95% CI, 0.96–0.99] and 0.94 [95% CI, 0.90–0.97]; $RR_{stroke}$, 0.92 [95% CI, 0.86-0.98] and 0.90 [95% CI, 0.84–0.97]), nuts ($RR_{CHD}$, 0.67 [95% CI, 0.43–1.05]), and fish ($RR_{CHD}$, 0.88 [95% CI, 0.79–0.99]; $RR_{stroke}$, 0.86 [95% CI, 0.75–0.99]; $RR_{HF}$, 0.80 [95% CI, 0.67–0.95]).[77] In contrast, the risk of these conditions was positively associated with consumption of egg ($RR_{HF}$, 1.16 [95% CI, 1.03–1.31]), red meat ($RR_{CHD}$, 1.15 [95% CI, 1.08–1.23]; $RR_{stroke}$, 1.12 [95% CI, 1.06–1.17]; $RR_{HF}$, 1.08 [95% CI, 1.02–1.14]), processed meat ($RR_{CHD}$, 1.27 [95% CI, 1.09–1.49]; $RR_{stroke}$, 1.17 [95% CI, 1.02–1.34]; $RR_{HF}$, 1.12 [95% CI, 1.05–1.19]), and SSBs ($RR_{CHD}$, 1.17 [95% CI, 1.11–1.23]; $RR_{stroke}$, 1.07 [95% CI, 1.02–1.12]; $RR_{HF}$, 1.08 [95% CI, 1.05–1.12]).
- In a dose-response meta-analysis of prospective cohort studies in adults, each 250–mL/d increase in SSB and ASB intake was associated with an increased risk in obesity (RR, 1.12 [95% CI, 1.05–1.19] for SSB; 1.21 [95% CI, 1.09–1.35] for ASB), type 2 diabetes (1.19 [95% CI, 1.13–1.25] for SSB; 1.15 [95% CI, 1.05–1.26] for ASB), hypertension (1.10 [95% CI, 1.06–1.14] for SSB; 1.08 [95% CI, 1.06–1.10] for ASB), and total mortality (1.04 [95% CI, 1.01–1.07] for SSB; 1.06, [95% CI, 1.02–1.10] for ASB).[78] A network meta-analysis of isocaloric substitution interventions in 38 RCTs involving 1383 participants suggested beneficial effects of replacing sucrose and fructose with starch for LDL-C and replacing fructose with glucose for insulin resistance and uric acid; however, the evidence was judged to be of low to moderate certainty and warrants replication.[79]
- In a prospective study of 512 891 adults in China (only 18% consumed fresh fruit daily), individuals who ate fresh fruit daily had 40% lower risk of CVD death (RR, 0.60 [95% CI, 0.54–0.67]), 34% lower risk of incident CHD (RR, 0.66 [95% CI, 0.58–0.75]), 25% lower risk of ischemic stroke (RR, 0.75 [95% CI, 0.72–0.79]), and 36% lower risk of hemorrhagic stroke (RR, 0.64 [95% CI, 0.56–0.74]).[80] Furthermore, when regular consumers of fruit (4 d/wk) were compared with nonconsumers (never/rare), there were lower CVD mortality (RR, 0.66 [95% CI, 0.61–0.71]), lower all-cause mortality (RR,0.73 [95% CI, 0.70–0.76]), lower cancer mortality (RR, 0.83 [95% CI, 0.78–0.89]), and lower mortality from chronic obstructive pulmonary disease (RR, 0.58 [95% CI, 0.47–0.71]).[81]

- In a meta-analysis of 22 RCTs, whole grain oats improved TC (SMD, 0.54, [95% CI, −0.95 to −0.12]) and LDL-C (SMD, 0.57 [95% CI, −0.84 to −0.31]), whole grain rice improved triglycerides (SMD, 0.22 [95% CI, −0.44 to −0.01]), and whole grains of all types improved HbA1c (SMD, −0.33 [95% CI, −0.61 to −0.04]) and CRP (SMD, −0.22 [95% CI, −0.44 to −0.00]).[82] In another meta-analysis of 8 cohort or case-control studies, whole grain or cereal fiber intake was inversely associated with type 2 diabetes (RR, 0.68 [95% CI, 0.64–0.73]).[83]
- In a meta-analysis of 14 prospective cohort studies, every 20–g/d higher intake of fish was associated with 4% reduced risk of CVD mortality (RR, 0.96 [95% CI, 0.94–0.98]).[84] The association was stronger in Asian cohorts than Western cohorts. Another meta-analysis reported similar results on the beneficial association of higher fish intake with CHD incidence (RR, 0.91 [95% CI, 0.84–0.97]) and mortality (0.85 [95% CI, 0.77–0.94]).[85] In the REGARDS study, individuals who consumed ≥2 servings of fried fish per week had a greater risk of CVD over 5.1 years of follow-up than those who consumed <1 serving per month (HR, 1.63 [95% CI, 1.11–2.40]).[86]
- An analysis of data from 6 prospective cohort studies in the United States in which baseline data were collected from 1985 to 2002 showed that higher intake of processed meat (aHR, 1.07 [95% CI, 1.04–1.11]), unprocessed red meat (aHR, 1.03 [95% CI, 1.01–1.06]), and poultry (aHR, 1.04 [95% CI, 1.01–1.06]), but not fish, was significantly associated with an increased risk of incident CVD.[87] Higher intake of processed meat (aHR, 1.03 [95% CI, 1.02–1.05]) and unprocessed red meat (aHR, 1.03 [95% CI, 1.01–1.05]), but not poultry or fish, was significantly associated with an increased risk of all-cause mortality. In an RCT (N=113 healthy adults), LDL-C and apolipoprotein B were significantly higher with red and white meat than with nonmeat consumption for 4 weeks, regardless of SFA content. Regardless of protein source, high SFA content (≈14% total energy) significantly increased LDL-C, apolipoprotein B, and large LDL particles compared with low SFA content (≈7% total energy).[88]
- In a study of 169 310 female nurses and 41 526 male health professionals, consumption of 1 serving of nuts ≥5 times per week was associated with lower risk of CVD (HR, 0.86 [95% CI, 0.79–0.93]) and CHD (HR, 0.80 [95% CI, 0.72–0.89]) compared with never or almost never consuming nuts. Results were largely consistent for peanuts, tree nuts, and walnuts.[89] In a network meta-analysis of RCTs of walnuts, pistachios, hazelnuts, cashews, and almonds on typical lipid profiles, the pistachio-enriched diets compared with other nut-enriched diets lowered triglycerides, LDL-C, and TC.[90] In another meta-analysis of 5 prospective observational studies, consumption of legumes (beans) was associated with a lower incidence of CHD (RR per 4 weekly 100-g servings, 0.86 [95% CI, 0.78–0.94]).[91]
- An umbrella review of 41 meta-analyses with 45 unique health outcomes concluded that milk consumption was more beneficial than harmful; for example, in dose-response analyses, an increment of 200 mL (≈1 cup) milk intake per day was associated with a lower risk of common cardiometabolic diseases such as CVD, stroke, hypertension, type 2 diabetes, MetS, and obesity.[92] A meta-analysis of 10 cohort studies also showed that fermented dairy foods intake was associated with reduced CVD risk (OR, 0.83 [95% CI, 0.76–0.91]), in particular cheese (OR, 0.87 [95% CI, 0.80–0.94]) and yogurt (OR, 0.78 [95% CI, 0.67–0.89]).[93]
- In a crossover RCT (N=25 individuals with normocholesterolemia and 27 with moderate hypercholesterolemia), 8-week consumption of moderate amounts of a soluble green/roasted (35:65) coffee blend significantly reduced TC, LDL-C, very-low-density lipoprotein cholesterol, triglycerides, SBP, DBP, heart rate, and body weight among participants with moderate hypercholesterolemia. The beneficial influence on SBP, DBP, heart rate, and body weight was also observed in healthy participants.[94]
- In a cross-sectional study of 12 285 adults, for males, consumption of >30 g/d alcohol was significantly associated with a higher risk of MetS (OR, 1.73 [95% CI, 1.25–2.39]), HBP (OR, 2.76 [95% CI, 1.64–4.65]), elevated blood glucose (OR, 1.70 [95% CI, 1.24–2.32]), and abdominal obesity (OR, 1.77 [95% CI, 1.07–2.92]) compared with nondrinking.[95] In males, drinkers at all levels had a lower risk of coronary disease than nondrinkers, whereas alcohol consumption was not associated with the risk of hypertension or stroke.[96] In females, consumption of 10.1 to 15.0 g/d alcohol was associated only with a higher risk of elevated blood glucose (OR, 1.65 [95% CI, 1.14–2.38]) compared with nondrinking.[95] Compared with nondrinkers, consumption of 0.1 to 10.0 g/d alcohol was associated with a lower risk of coronary disease and stroke, and consumption of 0.1 to 15.0 g/d was associated with a lower risk of hypertension in females.[96]

### *Sodium, Potassium, Phosphorus, and Magnesium*

- In a meta-regression analysis of 133 RCTs, a 100–mmol/d (2300–mg/d) reduction in sodium was associated with a 7.7–mm Hg (95% CI, −10.4 to −5.0) lower SBP and a 3.0–mm Hg (95% CI, −4.6 to −1.4) lower DBP among people with >131/78

mm Hg SBP/DBP. The association was weak in people with ≤131/78 mm Hg SBP/DBP: A 100–mmol/d reduction in sodium was associated with a 1.46–mm Hg (95% CI, −2.7 to −0.20) lower SBP and a 0.07–mm Hg (95% CI, −1.5 to 1.4) lower DBP.[97] The effects of sodium reduction on BP appear to be stronger in individuals who are older, hypertensive, and Black.[98,99]

- In a systematic review and nonlinear dose-response meta-analysis of 14 prospective cohort studies and 1 case-control study, a 1–g/d increment in sodium intake was associated with a 6% increase in stroke risk (RR, 1.06 [95% CI, 1.02–1.10]), and a 1-unit increment in dietary sodium–to–potassium ratio (millimoles per millimole) was associated with a 22% increase in stroke risk (RR, 1.22 [95% CI, 1.04–1.41]).[100]
- Nearly all observational studies demonstrate an association between higher estimated sodium intakes (eg, >4000 mg/d) and a higher risk of CVD events, in particular stroke.[101–105] Some studies have also observed higher CVD risk at estimated low intakes (eg, <3000 g/d), which suggests a potential J-shaped relationship with risk. An AHA science advisory suggested that variation in methodology might account for inconsistencies in the relationship between sodium and CVD in observational studies. Increased risk at low sodium intake in some observational studies could be related to reverse causation (illness causing low intake) or imprecise estimation of sodium intake through a single dietary recall or a single urine excretion.[105] Furthermore, an analysis of 20 years of data from the TOHP revealed a consistent benefit of reduced sodium and sodium:potassium intake and documented increased risk of mortality for high-sodium intake and a direct relationship with total mortality, even at low levels of sodium intake.[106]
- In a meta-analysis of 133 RCTs with 12 197 participants, interventions with reduced sodium versus usual sodium resulted in a mean reduction of 130 mmol (95% CI, 115–145) in 24-hour urinary sodium, 4.26 mm Hg (95% CI, 3.62–4.89) in SBP, and 2.07 mm Hg (95% CI, 1.67–2.48) in DBP.[107] The results also showed a dose-response relationship between each 50-mmol reduction in 24-hour sodium excretion and a 1.10–mm Hg (95% CI, 0.66–1.54) reduction in SBP and a 0.33–mm Hg (95% CI, 0.04–0.63 mm Hg) reduction in DBP. BP-lowering effects of sodium reductions were stronger in older people, populations who are not White, and those with higher baseline SBP levels.
- In a secondary analysis of the PREMIER trial, changes in phosphorus intake were not significantly associated with changes in BP. Phosphorus type (plant, animal, or added) significantly modified this association, with only added phosphorus associated with increases in SBP (mean coefficient, 1.24 mm Hg/100 mg [95% CI, 0.36–2.12]) and DBP (0.83 mm Hg/100 mg [95% CI, 0.22–1.44]). An increase in urinary phosphorus excretion was significantly associated with an increase in DBP (0.14 mm Hg/100 mg [95% CI, 0.01–0.28]).[108]
- In a systematic review and meta-analysis of 18 prospective cohort studies, the highest magnesium intake category was associated with an 11% decrease in total stroke risk (RR, 0.89 [95% CI, 0.83–0.94]) and a 12% decrease in ischemic stroke risk (RR, 0.88 [95% CI, 0.81–0.95]) compared with the lowest magnesium intake category. After further adjustment for calcium intake, the inverse association remained for total stroke (RR, 0.89 [95% CI, 0.80–0.99]).[109]

### *Dietary Supplements*

- In an RCT of 15 480 adults with diabetes and no history of ASCVD, 1 g n-3 fatty acids had no effect on first serious vascular event (RR, 0.97 [95% CI, 0.87–1.08]) or a composite outcome of first serious vascular event or revascularization (RR, 1.00 [95% CI, 0.91–1.09]) or mortality (RR, 0.95 [95% CI, 0.86–1.05]) compared with placebo (1 g olive oil).[110]
- A 2017 AHA science advisory summarized available evidence and suggested fish oil supplementation only for secondary prevention of CHD and SCD (Class IIa recommendation) and for secondary prevention of outcomes in patients with HF (Class IIa recommendation).[111]
- A meta-analysis of 38 RCTs of omega-3 fatty acids, stratified by EPA monotherapy and EPA+DHA therapy found that omega-3 FAs reduced cardiovascular mortality and improved cardiovascular outcomes.[112] EPA monotherapy was associated with more cardiovascular risk reduction than with EPA+DHA. This analysis included 149 051 participants, and omega-3 fatty acids was associated with reducing cardiovascular mortality (RR, 0.93 [95% CI, 0.88–0.98]; *P*=0.01), nonfatal MI (RR, 0.87 [95% CI, 0.81–0.93]; *P*=0.0001), CHD events (RR, 0.91 [95% CI, 0.87–0.96]; *P*=0.0002), MACEs (RR, 0.95 [95% CI, 0.92–0.98]; *P*=0.002), and revascularization (RR, 0.91 [95% CI, 0.87–0.95]; *P*=0.0001). There were also higher RR reductions with EPA monotherapy (0.82 [95% CI, 0.68–0.99]) than with EPA+DHA (0.94 [95% CI, 0.89–0.99]) for cardiovascular mortality, nonfatal MI (EPA, 0.72 [95% CI, 0.62–0.84]; EPA+DHA, 0.92 [95% CI, 0.85–1.00]), CHD events (EPA, 0.73 [95% CI, 0.62–0.85]; EPA+DHA, 0.94 [95% CI, 0.89–0.99]), and MACEs and revascularization. Incident AF was increased with omega-3 fatty acids (RR, 1.26 [95%

CI, 1.08–1.48]). EPA monotherapy was associated with a higher risk of total bleeding (RR, 1.49 [95% CI, 1.20–1.84]) and with AF (RR, 1.35 [95% CI, 1.10–1.66]).

- An observational study of 197 761 US veterans assessed omega-3 fatty acid supplement use and fish intake years on ischemic stroke over 3.2 years (2.2–4.3 years) and incident nonfatal CAD over 3.6 years (2.4–4.7 years). It was found that omega-3 fatty acid supplement use was independently associated with a decreased risk of ischemic stroke (HR, 0.88 [95% CI, 0.81–0.95]) but not with nonfatal CAD. Fish intake was not independently associated with either outcome.[113]
- Results from a meta-analysis of 62 RCTs with 3772 participants showed that flaxseed supplementation improved TC (WMD, −5.389 mg/dL [95% CI, −9.483 to −1.295]), triglyceride (−9.422 mg/dL [95% CI, −15.514 to −3.330]), and LDL-C (−4.206 mg/dL [95% CI, −7.260 to −1.151]) concentrations.[114]
- In an RCT of 25 871 adults (males ≥50 years of age and females ≥55 years of age), the effects of daily supplementation of 2000 IU vitamin D and 1 g marine n-3 fatty acids on the prevention of cancer and CVD were examined.[115] Vitamin D had no effect on major cardiovascular events (HR, 0.97 [95% CI, 0.85–1.12]), cancer (HR, 0.96 [95% CI, 0.88–1.06]), or any secondary outcomes. Marine n-3 fatty acid supplementation had no effect on major cardiovascular events (HR, 0.92 [95% CI, 0.80–1.06]), invasive cancer (HR, 1.03 [95% CI, 0.93–1.13]), or any secondary outcomes.
- A secondary RCT data analysis study conducted across 3 years with 161 patients with advanced HF assessed the effects of daily vitamin D supplementation of 4000 IU on lipid parameters (TC, HDL-C, LDL-C, TC/HDL-C ratio, LDL-C/HDL-C ratio, and triglycerides) and vascular calcification parameters (fetuin-A and nonphosphorylated undercarboxylated matrix Gla protein). Long-term vitamin D supplementation did not improve lipid profiles and did not affect vascular calcification markers in these patients. In addition, no sex-specific vitamin D effects were found.[116] A similar study, a post hoc analysis of the EVITA trial, assessing daily vitamin $D_3$ supplementation of 4000 IU also found no improvement in cardiac function among patients with advanced HF. However, subgroup analyses among those ≥50 years of age indicated improvements of 2.73% in LVEF (95% CI, 0.14%–5.31%) at the 12-month follow-up and 2.60% (95% CI, −2.47% to 7.67%) improvement at the 36-month follow-up.[117]
- A Cochrane review of 1 RCT with 1355 females (with previous preeclampsia) from various hospital sites in Argentina, South Africa, and Zimbabwe who began calcium supplementation before conception (500 mg daily until 20 weeks' gestation) found that calcium made little to no difference in developing serious health problems during pregnancy, including preeclampsia[118] (RR, 0.80 [95% CI, 0.61–1.06]; *P*=0.121; low-quality evidence), severe maternal morbidity and mortality (RR, 0.93 [95% CI, 0.68–1.26]; low-quality evidence), pregnancy loss or stillbirth at any age (RR, 0.83 [95% CI, 0.61–1.14]; low-quality evidence), or a cesarean section (RR, 1.11 [95% CI, 0.96–1.28]; low-quality evidence). Calcium was found to slightly reduce the risk of a composite outcome of preeclampsia or pregnancy loss or stillbirth at any age (RR, 0.82 [95% CI, 0.66–1.00]; low-quality evidence). Results should be interpreted with caution, particularly because ≈25% of the sample was lost to follow-up.[119]
- The VITAL-HF, an ancillary study of the VITAL RCT, examined whether vitamin $D_3$ (2000 IU/d) or marine omega-3 fatty acids (n-3; 1 g/d, including EPA 460 mg+DHA 380 mg) were associated with first HF-related hospitalization or recurrent hospitalization for HF among 25 871 adults with HF between 2011 and 2017. No significant relationships were found between either vitamin D or n-3 fatty acid supplementation and first HF hospitalization. However, marine n-3 supplementation (326 events) significantly reduced recurrent HF hospitalization compared with placebo (379 events; HR, 0.86 [95% CI, 0.74–0.998]; *P*=0.048).[120]
- A secondary analysis of the WHI examining the efficacy of calcium and vitamin D supplementation on AF prevention found that calcium and vitamin D had no reduction in incidence of AF compared with placebo (HR, 1.02 [95% CI, 0.92–1.13]). Although a relationship between baseline CVD risk factors and vitamin D deficiency was present, no significant association was found between baseline 25-hydroxyvitamin D serum levels and incident AF (HR, 0.92 [95% CI, 0.66–1.28] in the lowest versus highest subgroup). Similarly, using data from the WHI RCT, another study examined whether calcium and vitamin D supplementation (1000 mg elemental calcium carbonate and 400 IU vitamin $D_3$/d) moderated the effects of premenopausal hormone therapy on CVD events among 27 347 females. Females reporting prior hysterectomy (n=16 608) were randomized to the conjugated equine estrogen (0.625 mg/d)+medroxyprogesterone (2.5 mg/d) trial, and those without prior hysterectomy (n=10 739) were randomized to the conjugated equine estrogen trial (0.625 mg/d). In the conjugated equine estrogen trial, receiving calcium and vitamin D was associated with lowered stroke risk (HR, 0.49 [95% CI, 0.25–0.97]). In both trials, in females with a low intake of vitamin D, a significant

synergist effect of calcium and vitamin D and hormone therapy on LDL-C was observed ($P$=0.03).[121]
- A meta-analysis of 14 RCTs with 1088 participants 4 to 19 years of age concluded that the evidence does not support vitamin D supplementation for improving cardiometabolic health in children and adolescents.[122] Another review article similarly reported that vitamin D supplementation had no beneficial effects on SBP and DBP in children and adolescents.[123]
- Meta-analyses of RCTs examining the effects of multivitamins, vitamin D, calcium, vitamin C, B-complex, antioxidants, and vitamin $B_3$ (niacin) have demonstrated no cardiovascular benefits.[124]
- An umbrella review of 10 systematic reviews and meta-analyses examined the relationship between vitamin C supplementation and CVD biomarkers (ie, cardiovascular arterial stiffness, BP, lipid profile, endothelial function, and glycemic control) and found weak evidence for salutary effects from vitamin C supplementation on CVD biomarkers. However, subgroup analyses revealed that specific groups of participants (ie, those who were older or with higher BMI, elevated CVD risk, and lower intake of vitamin C) may benefit from vitamin C supplementation.[125]
- A 2-sample mendelian randomization study including 7781 individuals of European descent examined the relationship between vitamin E and risk of CAD and found higher vitamin E to be associated with a higher risk of CAD and MI. Specifically, each 1–mg/L increase in vitamin E was significantly associated with CAD (OR, 1.05 [95% CI, 1.03–1.06]) and MI (OR, 1.04 [95% CI, 1.03–1.05]); elevated TC (SD, 0.043 [95% CI, 0.038–0.04]), LDL-C (SD, 0.021 [95% CI, 0.016–0.027]), and triglycerides (SD, 0.026 [95% CI, 0.021–0.031]); and lower levels of HDL-C (SD, –0.019 [95% CI, –0.024 to –0.014]).[126]
- Meta-analyses of folic acid RCTs suggested reductions in stroke risk (RR, 0.80 [95% CI, 0.69–0.93]) and CVD (RR, 0.83 [95% CI, 0.73–0.93]), although the benefit was driven mainly by the China Stroke Primary Prevention Trial, a large RCT of 20 702 adults with hypertension and no history of stroke or MI.[127]

## Cost

The US Department of Agriculture reported that the food-at-home prices will increase by 8.6% (prediction interval, 5.6%–11.8%) in 2023. Egg prices are forecast to grow the fastest (37.8%; prediction interval, 18.3%–62.3%), whereas fresh fruit prices are predicted to experience little change (0%–1%; prediction interval, –5.6% to 6.5%).[128] Using data from Euromonitor International, the US Department of Agriculture calculated the share of consumer expenditures attributed to food in multiple countries in 2018. The proportion of consumer expenditures spent on food ranged from 6.4% in the United States to 9.1% in Canada, 23.4% in Mexico, and 59.0% in Nigeria.[129]

### *Cost of a Healthy Diet*

- A meta-analysis of price comparisons of healthy and unhealthy diet patterns found that the healthiest diet patterns cost, on average, ≈$1.50 more per person per day to consume.[130]
- A systematic review of studies published between 2000 and 2019 found moderate- to good-quality evidence supporting the use of pricing incentives to increase consumption or purchases of fruits and vegetables.[131] Providing incentives electronically on >1 occasion for 24 weeks or longer and allowing redemption in stores are associated with successful programs.
- In a 1-year (2013–2014) RCT of 20 after-school programs in South Carolina (10 intervention, 10 control), site leaders in the intervention group received assistance in establishing snack budgets and menus and identifying low-cost outlets to purchase snacks that met healthy eating standards. The intervention was successful in increasing the number of days that fruits and vegetables were served (3.9 d/wk versus 0.7 d/wk) and decreasing the number of days that SSBs (0.1 d/wk versus 1.8 d/wk) and sugary foods (0.3 d/wk versus 2.7 d/wk) were served.[132] Cost in the intervention group was minimized by identifying low-cost grocery outlets or large bulk warehouse stores; cost increased by $0.02 per snack in the intervention group compared with a $0.01 per snack decrease in the control group.

### *Healthy Diet and Health Care Cost Savings*

- A study evaluated the health care costs associated with following the healthy US-style eating pattern (measured by the HEI) and the healthy Mediterranean-style eating pattern (measured by the Mediterranean diet score) and found that a 20% increase in compliance with the HEI was estimated to result in annual cost savings in the United States of $31.5 billion (range, $23.9–$38.9 billion). Half of the cost savings were attributed to the reduction in costs associated with CVD, whereas the other half were attributed to cancer and type 2 diabetes cost reductions. Similarly, a 20% increase in conformance with the Mediterranean diet score resulted in annual cost savings of $16.7 billion (range, $6.7–$25.4 billion). The biggest contributors to these costs savings were HD ($5.4 billion), type 2 diabetes ($4.6 billion), AD ($2.6 billion), stroke ($1.0 billion), and, to a lesser degree, site-specific cancer (<$1 billion).[133]

- Based on combined data from NHANES 2013 to 2016 and a community-based randomized trial of cash and subsidized CSA intervention, a microsimulation model was developed to assess the cost-effectiveness of improving dietary quality (as measured by the HEI) on CVD and type 2 diabetes in US adults with low income. Implementation of the model in the short term (10-year time horizon) and long term (life-course time horizon) demonstrated that both a cash transfer ($300) and subsidized CSA ($300/y subsidy) lowered total discounted DALYs accumulated over the life course attributable to CVD and diabetes complications from 24 797 per 10 000 people (95% CI, 24 584–25 001) at baseline to 23 463 per 10 000 (95% CI, 23 241–23 666) under the cash intervention and 22 304 per 10 000 (95% CI, 22 084–22 510) under the CSA intervention. Both interventions demonstrated incremental cost-effectiveness ratios of <$100 000 per prevented DALY, with the cash transfer being more effective in the short term and the CSA being equally cost-effective in the long term, highlighting cost savings to society of −$191 100 per DALY averted (95% CI, −191 767 to −188 919) for the cash intervention and −$93 182 per DALY averted (95% CI, −93 707 to −92 503) for the CSA intervention.[134]

### *Cost-Effectiveness of Sodium Reduction and SSB Tax*

- A global cost-effectiveness analysis modeled the cost-effectiveness of a so-called soft regulation national policy to reduce sodium intake in countries around the world using the UK experience (government-supported industry agreements, government monitoring of industry compliance, public health campaign).[135] Model estimates were based on sodium intake, BP, and CVD data from 183 countries. Country-specific cost data were used to estimate the cost-effectiveness ratio, defined as purchasing power parity–adjusted international dollars (equivalent to country-specific purchasing power of US $1) per DALY saved over 10 years. Globally, the estimated average cost-effectiveness ratio was $204 (international dollars) per DALY (95% CI, 149–322) saved. The estimated cost-effectiveness ratio was highly favorable in high-, middle-, and low-income countries. A US study examined the cost-effectiveness of implementing voluntary sodium target reformulation among people ever working in the food system and those in the processed food industry and found benefits in both. Achieving FDA reformulations across 10 years could lead to 20-year health gains in those who had ever worked in the food system of 180 000 QALYs (95% UI, 150 000–209 000) and health care–related savings of $5.2 billion (95% UI, $3.5–$8.3 billion) with an incremental cost-effectiveness ratio of $62 000 (95% UI, 1000–171 000) per each QALY gained. Those working in the processed food industry could see similar improvements of 32 000 gained QALYs (95% UI, 27 000–37 000), health cost savings of $1 billion (95% UI, $0.7–$1.6 billion), and an incremental cost-effectiveness ratio of $486 000 (95% UI, $148 000–$1 094 000) for each QALY gained. The long-term reformulation would cost the industry $16.6 billion (95% UI, 12–31 billion). This highlights that potential health benefits and cost savings are greater than the costs associated with sodium reformulation.[136]
- A policy review of worldwide consumption of SSBs found that SSB consumption has increased significantly, which is problematic given the mounting evidence illustrating the association between high SSB daily intake and heightened risk of obesity and CVD. This review also presents evidence in support of an SSB tax because of its effectiveness in lowering SSB consumption in several countries to date.[137] In the United States, a validated microsimulation model (CVD PREDICT) was used to assess cost-effectiveness, CVD reductions, and QALYs gained as a result of imposing a penny-per-ounce tax on SSBs. Cost savings were identified for the US government ($106.56 billion) and private sector ($15.60 billion). A 100% price pass-through led to reductions of 4494 (2.06%) lifetime MI events (95% UI, 2640–6599) and 1540 (1.42%) total IHD deaths (95% UI, 995–2118) compared with no tax and to a gain of 0.020 lifetime QALYs. The lifetime cost to the beverage industry is $0.92 billion (or $49.72 billion if electing to absorb half the proposed SSB tax).[138] Similar evidence was found in the Philippines, where a 13%/L SSB tax was associated with fewer deaths resulting from diabetes (−5913), IHD (−10 339), and stroke (−7950) across 20 years and averting 13 890 cases of catastrophic expenditure. In addition, health care savings of $627 million and annual revenue increases of $813 million were projected over 20 years.[139]

## Global Trends in Key Dietary Factors

Analysis of SSB sales data suggests that the regions in the world with the highest SSB consumption are North America, Latin America, Australasia, and Western Europe.[140] A number of countries and US cities have implemented SSB taxes. In Mexico, a 1–peso/L excise tax was implemented in January 2014. In a study using store purchase data from 6645 Mexican households, posttax volume of beverages purchased decreased by 5.5% in 2014 and by 9.7% in 2015 compared with the predicted volume of beverages purchased based on pretax trends.

Although all socioeconomic groups experienced declines in SSB purchases, the lowest socioeconomic group had the greatest decline in SSB purchases (9.0% in 2014 and 14.3% in 2015).[141] Data from 3 waves (2004–2018) of the Health Workers Cohort Study Mexico were used to examine the change in probability of belonging to 1 of 4 categories of soft drink consumption (non, low, medium, high) after the tax was implemented.[142] After the tax, the prevalence of medium or high consumers decreased from 50% to 43%, and the prevalence of nonconsumers increased from 10% to 14%. The probability of being a nonconsumer of soft drinks increased by 4.7% (95% CI, 0.3%–9.1%) and that of being a low consumer increased by 8.3% (95% CI, 0.6%–16.0%) compared with the pretax period. The probability of being in the medium and high levels of soft drink consumption decreased by 6.8% (95% CI, 0.5%–13.2%) and 6.1% (95% CI, 0.4%–11.9%), respectively. In Berkeley, CA, a 1–cent/oz SSB excise tax was implemented in January 2015.[143] According to store-level data, posttax year 1 SSB sales declined by 9.6% compared with SSB sales predicted from pretax trends. In comparison, SSB sales increased by 6.9% in non-Berkeley stores in adjacent cities. Three years after the tax was implemented, these declines were sustained across demographically diverse Berkeley neighborhoods compared with sales in the neighboring locales of San Francisco and Oakland.[144]

In 2010, the mean sodium intake among adults worldwide was 3950 mg/d.[145] Across world regions, mean sodium intakes were highest in Central Asia (5510 mg/d) and lowest in eastern sub-Saharan Africa (2180 mg/d). Across countries, the lowest observed mean national intakes were ≈1500 mg/d. Between 1990 and 2010, global mean sodium intake appeared to remain relatively stable, although data on trends in many world regions were suboptimal.

In a systematic review of population-level sodium initiatives, a reduction in mean sodium intake occurred in 5 of 10 initiatives.[146] Successful population-level sodium initiatives tended to use multiple strategies and included structural activities such as food product reformulation. For example, the United Kingdom initiated a nationwide salt reduction program in 2003 to 2004 that included consumer awareness campaigns, progressively lower salt targets for various food categories, clear nutritional labeling, and working with industry to reformulate foods. Mean sodium intake in the United Kingdom decreased by 15% from 2003 to 2011,[147] along with concurrent decreases in BP (3.0/1.4 mm Hg) in patients not taking antihypertensive medication, stroke mortality (42%), and CHD mortality (40%; $P<0.001$ for all comparisons). These findings remained statistically significant after adjustment for changes in demographics, BMI, and other dietary factors.

## Global Burden

## (See Chart 5-3)

- Based on 204 countries and territories in 2021, the age-standardized mortality rate attributable to dietary risks was highest in central Asia and lowest in high-income Asia Pacific (Chart 5-3). In 2021, 7.34 million deaths were attributable to dietary risks (95% UI, 2.69-10.92), which represents a 54.50% increase from 1990 (95% UI, 41.82-66.29).
- A report from the GBD Study 2019 estimated the impact of 15 dietary risk factors on mortality and DALYs worldwide using a comparative risk assessment approach.[148] In 2019, an estimated 7.9 million deaths (95% UI, 6.5–9.8 million; 14% of all deaths) and 188 million DALYs (95% UI, 156–225 million; 7% of all DALYs) were attributable to dietary risks. The leading dietary risk factors were high sodium intake (1.9 million [95% UI, 0.5–4.2 million] deaths), low whole grain intake (1.8 million [95% UI, 0.9–2.3 million] deaths), and low legume intake (1.1 million [95% UI, 0.3–1.8 million] deaths). Countries with low-middle SDI and middle SDI scores had the highest age-standardized rates of diet-related deaths (119 [95% UI, 96–147] and 116 [95% UI, 92–147] deaths per 100 000 population), whereas countries with high SDI scores had the lowest age-standardized rates of diet-related deaths (56 [95% UI, 47–69] deaths per 100 000 population). Age-standardized diet-related death rates decreased between 1990 and 2019 from 154 (95% UI, 128–186) to 101 (95% UI, 82–124) deaths per 100 000 population, although the proportion of deaths attributable to dietary risks was largely stable.

**Table 5-1. Population-Level Measurement of Diet in the Essential 8 for CVH**

| Domain | CVH metric | Method of measurement | Quantification of CVH metric: adults (≥20 y) | Quantification of CVH metric: children* (2–19 y) |
|---|---|---|---|---|
| Health behaviors | Diet | Measurement: Self-reported daily intake of a DASH-style eating pattern<br>Example tools for measurement: DASH diet score[149,150] (populations); MEPA[151] (individuals) | Quantiles of DASH-style diet adherence or HEI-2015 (population)<br>Scoring (population):<br>Points — Quantile<br>100 — ≥95th percentile (top/ideal diet)<br>80 — 75th–94th percentile<br>50 — 50th–74th percentile<br>25 — 25th–49th percentile<br>0 — 1st–24th percentile (bottom/least ideal quartile)<br>Scoring (individual):<br>Points — MEPA score (points)<br>100 — 15–16<br>80 — 12–14<br>50 — 8–11<br>25 — 4–7<br>0 — 0–3 | Quantiles of DASH-style diet adherence or HEI-2015 (population) or MEPA (individuals)*; 2–19 y of age (see Supplemental Material for younger ages)<br>Scoring (population):<br>Points — Quantile<br>100 — ≥95th percentile (top/ideal diet)<br>80 — 75th–94th percentile<br>50 — 50th–74th percentile<br>25 — 25th–49th percentile<br>0 — 1st–24th percentile (bottom/least ideal quartile)<br>Scoring (individual):<br>Points — MEPA score (points)<br>100 — 9–10<br>80 — 7–8<br>50 — 5–6<br>25 — 3–4<br>0 — 0–2 |

CVH indicates cardiovascular health; DASH, Dietary Approaches to Stop Hypertension; HEI, Healthy Eating Index; and MEPA, Mediterranean Eating Pattern for Americans.

*Cannot meet these metrics until solid foods are being consumed.

Notes on implementation:

Diet: See Supplemental Material Appendix 1. For adults and children, a score of 100 points for the CVH diet metric should be assigned for the top (95th percentile) or a score of 15 to 16 on the MEPA (for individuals) or for those in the ≥95th percentile on the DASH score or HEI-2015 (for populations). The 75th to 94th percentile should be assigned 80 points, given that there is likely improvement that can be made even among those in this top quartile. For individuals, the MEPA points are stratified for the 100-point scoring system approximately by quantiles. In children, a modified MEPA is suggested on the basis of age-appropriate foods. The writing group recognizes that the quantiles may need to be adjusted or recalibrated at intervals with population shifts in eating patterns. In children, the scoring applies only once solid foods are being consumed. For now, the reference population for quantiles of HEI or DASH score should be the National Health and Nutrition Examination Survey sample from 2015 to 2018. The writing group acknowledges that this may need to change or be updated over time. Clinicians should use judgment in assigning points for culturally contextual healthy diets. For additional notes on scoring in children, see Supplemental Material Appendix 2.

Source: Adapted with permission from Lloyd-Jones et al[1] Supplemental Material. Copyright © 2022, American Heart Association, Inc.

**Table 5-2. Scoring Criteria for the DASH-Style Diet Score**

| Component | Foods (NHANES 24-h recall) | Scoring criteria | Note |
|---|---|---|---|
| Fruits | All fruits and fruit juices | Quintile 1: 1 point<br>Quintile 2: 2 points<br>Quintile 3: 3 points<br>Quintile 4: 4 points<br>Quintile 5: 5 points | Higher score represents more ideal intake<br>Quintile 1 is lowest consumption, and quintile 5 is highest consumption |
| Vegetables | All vegetables except potatoes and legumes | | |
| Nuts and legumes | Nuts and peanut butter, dried beans, peas, tofu | | |
| Whole grains | Brown rice, dark breads, cooked cereal, whole grain cereal, other grains, popcorn, wheat germ, bran | | |
| Low-fat dairy | Skim milk, yogurt, cottage cheese | | |
| Sodium | Sum of sodium content of all foods reported as consumed | Quintile 1: 5 points<br>Quintile 2: 4 points<br>Quintile 3: 3 points<br>Quintile 4: 2 points<br>Quintile 5: 1 point | Reverse scoring in that higher quintiles represent less ideal intake<br>Quintile 1 is lowest consumption, and quintile 5 is highest consumption |
| Red and processed meats | Beef, pork, lamb, deli meats, organ meats, hot dogs, bacon | | |
| Sweetened beverages | Carbonated and noncarbonated sweetened beverages | | |

The DASH diet score is assessed and points scored using the methods of Fung et al.[152] Quintiles of point score should be assigned using the most recent or most relevant NHANES data, appropriate to the question being addressed.

DASH indicates Dietary Approaches to Stop Hypertension; and NHANES, National Health and Nutrition Examination Survey.

Source: Reproduced with permission from Fung et al.[152] Copyright © 2008, American Medical Association. All rights reserved.

**Table 5-3. Scoring Criteria for the Mediterranean Eating Pattern for Americans[151]**

| Screener item | Question | Scoring criteria | Score |
|---|---|---|---|
| Olive oil | How much olive oil do you consume per day (including that used in frying, meals eaten away from home, salads)? | ≥2 servings of olive oil per day | 1: If scoring condition met<br>0: If scoring condition not met<br>(range, 0–16) |
| Green leafy vegetables | How many servings of green leafy vegetables do you consume per day? | ≥7 servings of green leafy vegetables per week | |
| Other vegetables | How many servings of other vegetables do you consume per day? | ≥2 servings of other vegetables per day | |
| Berries | How many servings of berries do you consume per week? | ≥2 servings of berries per week | |
| Other fruit | How many servings of other fruit do you consume per week? | ≥1 servings of other fruit per day | |
| Meat | How many servings of red meat, hamburger, bacon, or sausage do you consume per week? | ≤3 servings of red meat, hamburger, bacon, or sausage per week | |
| Fish | How many servings of fish or shellfish/seafood do you consume per week? | ≥1 serving of fish per week | |
| Chicken | How many servings of chicken do you consume per week? | ≤5 servings of chicken per week | |
| Cheese | How many servings of full-fat or regular cheese or cream cheese do you consume per week? | ≤4 servings of full-fat or regular cheese or cream cheese per week | |
| Butter/cream | How many servings of butter or cream do you consume per week? | ≤5 servings of butter or cream per week | |
| Beans | How many servings of beans do you consume per week? | ≥3 servings of beans per week | |
| Whole grains | How many servings of whole grains do you consume per day? | ≥3 servings of whole grains per day | |
| Sweets and pastries | How many servings of commercial sweets, candy bars, pastries, cookies, or cakes do you consume per week? | ≤4 servings of commercial sweets, candy bars, pastries, cookies, or cakes per week | |
| Nuts | How many servings of nuts do you consume per week? | ≥4 servings of nuts per week | |
| Fast food | How many times per week do you consume meals from fast-food restaurants? | ≤1 meal at a fast-food restaurant per week | |
| Alcohol | How much alcohol do you drink per week? | >0 or ≤2 servings of alcohol per day for men and >0 or ≤1 servings of alcohol per day for women | |

Source: Reprinted with permission from Lloyd-Jones et al[1] Supplemental Material. Copyright © 2022, American Heart Association, Inc.

**Table 5-4. Population Mean Consumption* of Food Groups and Nutrients of Interest by Sex and Race and Ethnicity Among US Adults ≥20 Years of Age, NHANES 2017 to 2018**

| | NH White males | | NH Black males | | Mexican American males | | NH White females | | NH Black females | | Mexican American females | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Average consumption | % Meeting guidelines | Average consumption | % Meeting guidelines | Average consumption | % Meeting guidelines | Average consumption | % Meeting guidelines | Average consumption | % Meeting guidelines | Average consumption | % Meeting guidelines |
| Foods | | | | | | | | | | | | |
| Whole grains, servings/d | 0.9±0.8 | 7.1 | 0.7±1.1 | 3.1 | 0.6±0.9 | 2.5 | 0.8±0.6 | 3.4 | 0.7±1.1 | 3.6 | 0.7±0.9 | 2.5 |
| Whole fruit, servings/d | 1.3±1.2 | 8.8 | 1.1±2.4 | 5.9 | 1.7±2.2 | 7.1 | 1.3±1.0 | 7.6 | 1.1±1.9 | 6.2 | 1.7±1.9 | 13.2 |
| Total fruit, servings/d | 1.7±1.4 | 13.5 | 1.7±2.9 | 11.9 | 2.2±2.4 | 12.1 | 1.5±1.2 | 10.0 | 1.8±2.5 | 13.7 | 2.2±2.3 | 19.3 |
| Nonstarchy vegetables, servings/d | 2.0±1.1 | 5.8 | 1.5±1.8 | 2.1 | 2.1±1.7 | 5.6 | 2.3±1.2 | 9.3 | 1.9±2.3 | 8.4 | 2.3±1.8 | 9.5 |
| Starchy vegetables,† servings/d | 0.9±0.7 | NA | 0.9±1.2 | NA | 0.7±0.9 | NA | 0.9±0.7 | NA | 0.9±1.2 | NA | 0.7±0.9 | NA |

(*Continued*)

**Table 5-4. Continued**

| | NH White males | | NH Black males | | Mexican American males | | NH White females | | NH Black females | | Mexican American females | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Average consumption | % Meeting guidelines | Average consumption | % Meeting guidelines | Average consumption | % Meeting guidelines | Average consumption | % Meeting guidelines | Average consumption | % Meeting guidelines | Average consumption | % Meeting guidelines |
| Legumes, servings/wk | 1.2±1.8 | 21.4 | 1.2±3.9 | 18.2 | 3.4±6.1 | 40.6 | 1.2±1.6 | 21.9 | 0.99±3.3 | 17.0 | 2.8±5.1 | 42.1 |
| Fish and shellfish, servings/wk | 1.0±1.8 | 15.0 | 1.5±4.2 | 21.6 | 1.5±3.8 | 19.3 | 1.1±1.5 | 21.2 | 1.9±3.8 | 33.7 | 1.2±3.2 | 18.0 |
| Nuts and seeds, servings/wk | 5.8±6.7 | 36.0 | 4.0±11.1 | 21.9 | 3.6±8.2 | 22.5 | 6.1±6.0 | 37.9 | 3.5±9.8 | 21.0 | 3.4±6.5 | 33.2 |
| Unprocessed red meats, servings/wk | 3.6±2.5 | NA | 2.9±4.1 | NA | 4.2±4.3 | NA | 2.6±1.9 | NA | 1.7±3.0 | NA | 2.6±3.3 | NA |
| Processed meat, servings/wk | 2.4±1.8 | 58.8 | 2.0±3.2 | 66.6 | 2.1±2.8 | 68.0 | 1.7±1.4 | 68.6 | 1.8±3.1 | 68.3 | 1.0±1.9 | 87.1 |
| SSBs, servings/wk | 7.3±7.3 | 55.6 | 9.8±12.4 | 38.6 | 9.9±10.7 | 37.9 | 6.4±6.7 | 66.7 | 8.6±13.6 | 44.1 | 6.5±12.8 | 57.3 |
| Sweets and bakery desserts, servings/wk | 4.2±4.0 | 51.9 | 3.3±6.4 | 65.2 | 4.5±6.8 | 58.6 | 3.8±3.2 | 53.7 | 4.0±8.0 | 58.9 | 4.4±6.1 | 53.1 |
| Refined grain, servings/d | 5.1±1.5 | 7.9 | 5.1±2.8 | 7.1 | 6.6±2.9 | 1.3 | 5.1±1.6 | 10.4 | 5.1±2.7 | 9.2 | 6.5±3.0 | 7.2 |
| Nutrients | | | | | | | | | | | | |
| Total calories, kcal/d | 2415±541 | NA | 2284 ±1220 | NA | 2450±967 | NA | 1797±398 | NA | 1810±839 | NA | 1772±671 | NA |
| EPA/DHA, mg/d | 0.079 ±0.107 | 6.5 | 0.09 ±0.213 | 9.0 | 0.082 ±0.140 | 10.0 | 0.083 ±0.114 | 7.6 | 0.124 ±0.334 | 12.6 | 0.093 ±0.209 | 7.3 |
| α-Linoleic acid, g/d | 1.75±0.64 | 47.8 | 1.71±0.97 | 48.7 | 1.66±0.72 | 41.7 | 1.84±0.62 | 84.0 | 2.0±1.0 | 90.1 | 1.79±0.77 | 86.5 |
| n-6 PUFAs, % energy | 8.0±2.99 | NA | 9.88±10.2 | NA | 7.74±5.75 | NA | 11.5±5.04 | NA | 13.1±11.1 | NA | 10.7±5.77 | NA |
| Saturated fat, % energy | 12.4±2.2 | 24.3 | 11.3±4.0 | 32.0 | 11.1±3.3 | 34.6 | 12.3±2.1 | 21.9 | 11.3±4.2 | 38.6 | 11.1±3.3 | 39.7 |
| Ratio of (PUFAs+MUFAs)/ SFAs | 1.8±0.5 | 11.2 | 2.3±2.6 | 29.4 | 1.9±1.2 | 12.9 | 2.2±0.6 | 26.9 | 2.6±1.7 | 40.6 | 2.4±1.2 | 37.5 |
| Dietary cholesterol, mg/d | 299±137 | 61.7 | 320±275 | 55.6 | 315±195 | 55.1 | 304±130 | 62.9 | 313±216 | 54.9 | 350±244 | 52.1 |
| Carbohydrate, % energy | 44.4±6.1 | NA | 46.0±12.8 | NA | 46.7±9.2 | NA | 46.3±6.2 | NA | 47.4±11.5 | NA | 49.0±9.9 | NA |
| Dietary fiber, g/d | 15.1±4.4 | 4.1 | 13.7±8.3 | 3.8 | 18.5±8.9 | 14.6 | 16.7±4.3 | 6.1 | 15.2±8.3 | 5.1 | 19.7±8.4 | 16.0 |
| Sodium, g/d | 3.4±1.3 | 6.5 | 3.4±3.98 | 11.3 | 3.4±0.94 | 6.9 | 3.4±0.65 | 7.8 | 3.5±0.91 | 5.7 | 3.5±0.95 | 7.2 |
| Added sugar, % energy | 11.8±25.0 | 37.9 | 17.8±43.2 | 23.5 | 13.0±21.3 | 38.3 | 17.8±9.6 | 19.7 | 20.4±33.6 | 16.6 | 18.0±32.7 | 28.4 |

Values for average consumption are mean±SD. Data are from NHANES 2017 to 2018, derived from two 24-hour dietary recalls per person, with population SD adjusted for within-person versus between-person variation. All values are energy adjusted by individual regressions or percent energy, and for comparability, means and proportions are reported for a 2000–kcal/d diet. To obtain actual mean consumption levels, the group means for each food or nutrient can be multiplied by the group-specific total calories (kilocalories per day) divided by 2000 kcal/d. The calculations for foods use the US Department of Agriculture Food Patterns Equivalent Database on composition of various mixed dishes, which incorporates partial amounts of various foods (eg, vegetables, nuts, processed meats) in mixed dishes; in addition, the characterization of whole grains is now derived from the US Department of Agriculture database instead of the ratio of total carbohydrate to fiber.

DHA indicates docosahexaenoic acid; EPA, eicosapentaenoic acid; MUFA, monounsaturated fatty acid; NA, not available; NH, non-Hispanic; NHANES, National Health and Nutrition Examination Survey; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid; and SSB, sugar-sweetened beverage.

*All intakes and guidelines adjusted to a 2000–kcal/d diet. Servings are defined as follows: whole grains, 1-oz equivalents; fruits and vegetables, 1/2-cup equivalents; legumes, 1/2 cup; fish/shellfish, 3.5 oz or 100 g; nuts and seeds, 1 oz; unprocessed red or processed meat, 3.5 oz or 100 g; SSBs, 8 fl oz; and sweets and bakery desserts, 50 g. Guidelines are defined as follows: whole grains, 3 or more 1-oz equivalent (eg, 21 g whole wheat bread, 82 g cooked brown rice, 31 g Cheerios) servings/d; fruits, ≥2 cups/d; nonstarchy vegetables, ≥2.5 cups/d; legumes, ≥1.5 cups/wk; fish or shellfish, 2 or more 100-g (3.5-oz) servings/wk; nuts and seeds, 4 or more 1-oz servings/wk; processed meats (bacon, hot dogs, sausage, processed deli meats), 2 or fewer 100-g (3.5-oz) servings/wk (one-fourth of discretionary calories); SSBs (defined as ≥50 cal/8 oz, excluding 100% fruit juices), ≤36 oz/wk (approximately one-fourth of discretionary calories); sweets and bakery desserts, 2.5 or fewer 50-g servings/wk (approximately one-fourth of discretionary calories); EPA/DHA, ≥0.250 g/d[153]; α-linoleic acid, ≥1.6/1.1 g/d (males/females); saturated fat, <10% energy; dietary cholesterol, <300 mg/d; dietary fiber, ≥28 g/d; sodium, <2.3 g/d; ratio of (PUFAs+MUFAs)/SFAs, ≥2.5; and added sugars, ≤6.5% total energy intake. No dietary targets are listed for starchy vegetables and unprocessed red meats because of their positive association with long-term weight gain and their positive or uncertain relation with diabetes and cardiovascular disease.

†Including white potatoes (chips, fries, mashed, baked, roasted, mixed dishes), corn, plantains, green peas. Sweet potatoes, pumpkin, and squash are considered red-orange vegetables by the US Department of Agriculture and are included in nonstarchy vegetables.

Source: Unpublished analyses courtesy of Dr Junxiu Liu, Icahn School of Medicine at Mount Sinai, using NHANES.[154]

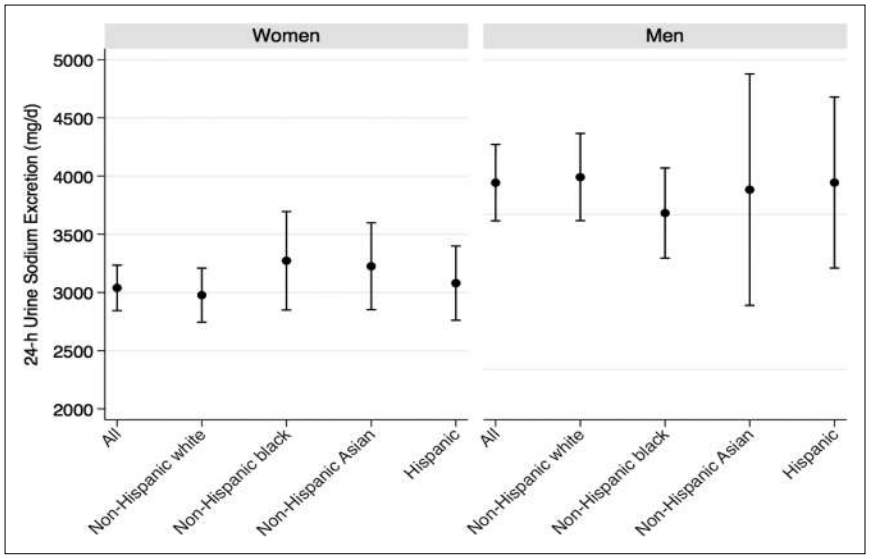



**Chart 5-1. Estimated mean sodium intake, by 24-hour urinary excretion, United States, 2013 to 2014.**
Estimates based on nationally representative sample of 827 nonpregnant, noninstitutionalized US adults 20 to 69 years of age who completed a 24-hour urine collection in NHANES 2013 to 2014. NHANES indicates National Health and Nutrition Examination Survey.
Source: Data derived from Cogswell et al[155] using NHANES.[154]

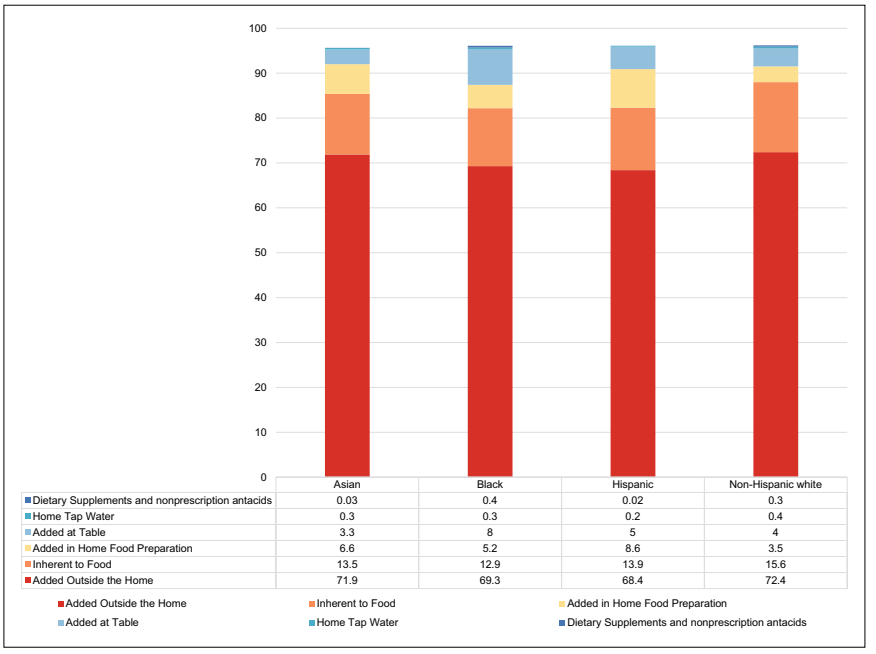



**Chart 5-2. Sources of sodium intake in adults in 3 geographic regions in the United States, 2013 to 2014.**
Sources of sodium intake were determined by four 24-hour dietary recalls with special procedures in which duplicate samples of salt added to food at the table and in home food preparation were collected in 450 adults recruited in 3 geographic regions (Birmingham, AL; Palo Alto, CA; and Minneapolis–St. Paul, MN) with equal numbers of males and females from 4 racial and ethnic groups (Asian, Black, Hispanic, and non-Hispanic White individuals).
Source: Data derived from Harnack et al.[4]

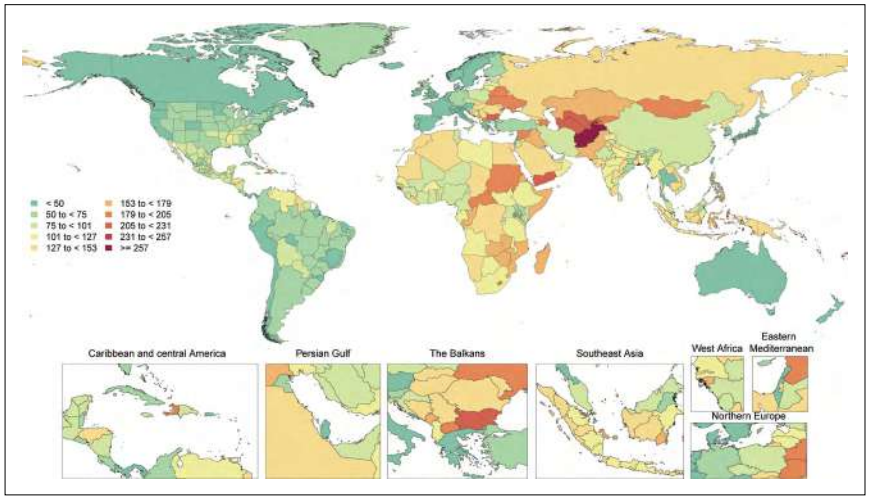



**Chart 5-3. Age-standardized global mortality rates attributable to dietary risks per 100 000, both sexes, 2021.**
During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.
GBD indicates Global Burden of Disease.
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[156]

## REFERENCES


1. Lloyd-Jones DM, Allen NB, Anderson CAM, Black T, Brewer LC, Foraker RE, Grandner MA, Lavretsky H, Perak AM, Sharma G, et al; on behalf of the American Heart Association. Life's Essential 8: updating and enhancing the American Heart Association's construct of cardiovascular health: a presidential advisory from the American Heart Association. *Circulation*. 2022;146:e18–e43. doi: 10.1161/CIR.0000000000001078
2. Anderson CAM, Thorndike AN, Lichtenstein AH, Van Horn L, Kris-Etherton PM, Foraker R, Spees C. Innovation to create a healthy and sustainable food system: a science advisory from the American Heart Association. *Circulation*. 2019;139:e1025–e1032. doi: 10.1161/CIR.0000000000000686
3. Lloyd-Jones DM, Ning H, Labarthe D, Brewer L, Sharma G, Rosamond W, Foraker RE, Black T, Grandner MA, Allen NB, et al. Status of cardiovascular health in US adults and children using the American Heart Association's new "Life's Essential 8" metrics: prevalence estimates from the National Health and Nutrition Examination Survey (NHANES), 2013-2018. *Circulation*. 2022;146:822–835. doi: 10.1161/circulationaha.122.060911
4. Harnack LJ, Cogswell ME, Shikany JM, Gardner CD, Gillespie C, Loria CM, Zhou X, Yuan K, Steffen LM. Sources of sodium in US adults from 3 geographic regions. *Circulation*. 2017;135:1775–1783. doi: 10.1161/CIRCULATIONAHA.116.024446
5. Woodruff RC, Zhao L, Ahuja JKC, Gillespie C, Goldman J, Harris DM, Jackson SL, Moshfegh A, Rhodes D, Sebastian RS, et al. Top food category contributors to sodium and potassium intake–United States, 2015-2016. *MMWR Morb Mortal Wkly Rep*. 2020;69:1064–1069. doi: 10.15585/mmwr.mm6932a3
6. Clarke LS, Overwyk K, Bates M, Park S, Gillespie C, Cogswell ME. Temporal trends in dietary sodium intake among adults aged >/=19 years–United States, 2003-2016. *MMWR Morb Mortal Wkly Rep*. 2021;70:1478–1482. doi: 10.15585/mmwr.mm7042a4
7. Liu J, Rehm CD, Onopa J, Mozaffarian D. Trends in diet quality among youth in the United States, 1999-2016. *JAMA*. 2020;323:1161–1174. doi: 10.1001/jama.2020.0878
8. US Department of Agriculture and US Department of Health and Human Services. Dietary Guidelines for Americans, 2020-2025. 9th ed. 2015. Accessed April 14, 2023. https://dietaryguidelines.gov/
9. Shan Z, Rehm CD, Rogers G, Ruan M, Wang DD, Hu FB, Mozaffarian D, Zhang FF, Bhupathiraju SN. Trends in dietary carbohydrate, protein, and fat intake and diet quality among US adults, 1999-2016. *JAMA*. 2019;322:1178–1187. doi: 10.1001/jama.2019.13771
10. Liu J, Micha R, Li Y, Mozaffarian D. Trends in food sources and diet quality among US children and adults, 2003-2018. *JAMA Netw Open*. 2021;4:e215262. doi: 10.1001/jamanetworkopen.2021.5262
11. Anderson CE, Martinez CE, Ritchie LD, Paolicelli C, Reat A, Borger C, Whaley SE. Longer Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) participation duration is associated with higher diet quality at age 5 years. *J Nutr*. 2022;152:1974–1982. doi: 10.1093/jn/nxac134
12. Schwingshackl L, Boeing H, Stelmach-Mardas M, Gottschald M, Dietrich S, Hoffmann G, Chaimani A. Dietary supplements and risk of cause-specific death, cardiovascular disease, and cancer: a systematic review and meta-analysis of primary prevention trials. *Adv Nutr*. 2017;8:27–39. doi: 10.3945/an.116.013516
13. Cowan AE, Tooze JA, Gahche JJ, Eicher-Miller HA, Guenther PM, Dwyer JT, Potischman N, Bhadra A, Carroll RJ, Bailey RL. Trends in overall and micronutrient-containing dietary supplement use in US adults and children, NHANES 2007-2018. *J Nutr*. 2023;152:2789–2801. doi: 10.1093/jn/nxac168
14. Arcaya MC, Tucker-Seeley RD, Kim R, Schnake-Mahl A, So M, Subramanian SV. Research on neighborhood effects on health in the United States: a systematic review of study characteristics. *Soc Sci Med*. 2016;168:16–29. doi: 10.1016/j.socscimed.2016.08.047
15. Rachele JN, Kavanagh A, Brown WJ, Healy AM, Schmid CJ, Turrell G. Neighborhood socioeconomic disadvantage and body mass index among residentially stable mid-older aged adults: findings from the HABITAT multilevel longitudinal study. *Prev Med*. 2017;105:271–274. doi: 10.1016/j.ypmed.2017.09.017
16. Garfinkel-Castro A, Kim K, Hamidi S, Ewing R. Obesity and the built environment at different urban scales: examining the literature. *Nutr Rev*. 2017;75:51–61. doi: 10.1093/nutrit/nuw037
17. Buszkiewicz JH, Bobb JF, Hurvitz PM, Arterburn D, Moudon AV, Cook A, Mooney SJ, Cruz M, Gupta S, Lozano P, et al. Does the built environment have independent obesogenic power? Urban form and trajectories of weight gain. *Int J Obes (Lond)*. 2021;45:1914–1924. doi: 10.1038/s41366-021-00836-z
18. Vinyard M, Zimmer M, Herrick KA, Story M, Juan W, Reedy J. Healthy Eating Index--2015 scores vary by types of food outlets in the United States. *Nutrients*. 2021;13:2717. doi: 10.3390/nu13082717
19. May-Wilson S, Matoba N, Wade KH, Hottenga JJ, Concas MP, Mangino M, Grzeszkowiak EJ, Menni C, Gasparini P, Timpson NJ, et al. Large-scale GWAS of food liking reveals genetic determinants and genetic correlations with distinct neurophysiological traits. *Nat Commun*. 2022;13:2743. doi: 10.1038/s41467-022-30187-w
20. Ferguson JF, Allayee H, Gerszten RE, Ideraabdullah F, Kris-Etherton PM, Ordovas JM, Rimm EB, Wang TJ, Bennett BJ; on behalf of the American Heart Association Council on Functional Genomics and Translational Biology, Council on Epidemiology and Prevention, and Stroke Council. Nutrigenomics, the microbiome, and gene-environment interactions: new directions in cardiovascular disease research, prevention, and treatment: a scientific statement from the American Heart Association. *Circ Cardiovasc Genet*. 2016;9:291–313. doi: 10.1161/HCG.0000000000000030
21. Zeevi D, Korem T, Zmora N, Israeli D, Rothschild D, Weinberger A, Ben-Yacov O, Lador D, Avnit-Sagi T, Lotan-Pompan M, et al. Personalized nutrition by prediction of glycemic responses. *Cell*. 2015;163:1079–1094. doi: 10.1016/j.cell.2015.11.001
22. Merino J, Dashti HS, Sarnowski C, Lane JM, Todorov PV, Udler MS, Song Y, Wang H, Kim J, Tucker C, et al. Genetic analysis of dietary intake identifies new loci and functional links with metabolic traits. *Nat Hum Behav*. 2022;6:155–163. doi: 10.1038/s41562-021-01182-w
23. Sergeant S, Hugenschmidt CE, Rudock ME, Ziegler JT, Ivester P, Ainsworth HC, Vaidya D, Case LD, Langefeld CD, Freedman BI, et al. Differences in arachidonic acid levels and fatty acid desaturase (FADS) gene variants in African Americans and European Americans with diabetes or the metabolic syndrome. *Br J Nutr*. 2012;107:547–555. doi: 10.1017/S0007114511003230
24. Tobi EW, Slieker RC, Luijk R, Dekkers KF, Stein AD, Xu KM, Slagboom PE, van Zwet EW, Lumey LH, Heijmans BT; Biobank-Based Integrative Omics Studies Consortium. DNA methylation as a mediator of the association between prenatal adversity and risk factors for metabolic disease in adulthood. *Sci Adv*. 2018;4:eaao4364. doi: 10.1126/sciadv.aao4364
25. Huang JV, Cardenas A, Colicino E, Schooling CM, Rifas-Shiman SL, Agha G, Zheng Y, Hou L, Just AC, Litonjua AA, et al. DNA methylation in blood as a mediator of the association of mid-childhood body mass index with cardio-metabolic risk score in early adolescence. *Epigenetics*. 2018;13:1072–1087. doi: 10.1080/15592294.2018.1543503
26. Gardner CD, Trepanowski JF, Del Gobbo LC, Hauser ME, Rigdon J, Ioannidis JPA, Desai M, King AC. Effect of low-fat vs low-carbohydrate diet on 12-month weight loss in overweight adults and the association with genotype pattern or insulin secretion: the DIETFITS randomized clinical trial. *JAMA*. 2018;319:667–679. doi: 10.1001/jama.2018.0245
27. Ding M, Ellervik C, Huang T, Jensen MK, Curhan GC, Pasquale LR, Kang JH, Wiggs JL, Hunter DJ, Willett WC, et al. Diet quality and genetic association with body mass index: results from 3 observational studies. *Am J Clin Nutr*. 2018;108:1291–1300. doi: 10.1093/ajcn/nqy203
28. Westerman K, Liu Q, Liu S, Parnell LD, Sebastiani P, Jacques P, DeMeo DL, Ordovas JM. A gene-diet interaction-based score predicts response to dietary fat in the Women's Health Initiative. *Am J Clin Nutr*. 2020;111:893–902. doi: 10.1093/ajcn/nqaa037
29. Shan Z, Guo Y, Hu FB, Liu L, Qi Q. Association of low-carbohydrate and low-fat diets with mortality among US adults. *JAMA Intern Med*. 2020;180:513–523. doi: 10.1001/jamainternmed.2019.6980
30. Wang DD, Li Y, Bhupathiraju SN, Rosner BA, Sun Q, Giovannucci EL, Rimm EB, Manson JE, Willett WC, Stampfer MJ, et al. Fruit and vegetable intake and mortality: results from 2 prospective cohort studies of US men and women and a meta-analysis of 26 cohort studies. *Circulation*. 2021;143:1642–1654. doi: 10.1161/CIRCULATIONAHA.120.048996
31. Park Y-MM, Choi MK, Lee S-S, Shivappa N, Han K, Steck SE, Hébert JR, Merchant AT, Sandler DP. Dietary inflammatory potential and risk of mortality in metabolically healthy and unhealthy phenotypes among overweight and obese adults. *Clin Nutr*. 2019;38:682–688. doi: 10.1016/j.clnu.2018.04.002
32. Garcia-Arellano A, Martínez-González MA, Ramallal R, Salas-Salvadó J, Hébert JR, Corella D, Shivappa N, Forga L, Schröder H, Muñoz-Bravo C, et al; SUN and PREDIMED Study Investigators. Dietary inflammatory index and all-cause mortality in large cohorts: the SUN and PREDIMED studies. *Clin Nutr*. 2019;38:1221–1231. doi: 10.1016/j.clnu.2018.05.003

33. Shivappa N, Godos J, Hebert JR, Wirth MD, Piuri G, Speciani AF, Grosso G. Dietary Inflammatory Index and cardiovascular risk and mortality: a meta-analysis. *Nutrients*. 2018;10:200. doi: 10.3390/nu10020200
34. Mazidi M, Katsiki N, Mikhailidis DP, Bartłomiejczyk MA, Banach M. Association of empirical dietary atherogenic indices with all-cause and cause-specific mortality in a multi-ethnic adult population of the United States. *Nutrients*. 2019;11:2323–2323. doi: 10.3390/nu11102323
35. Collin LJ, Judd S, Safford M, Vaccarino V, Welsh JA. Association of sugary beverage consumption with mortality risk in US adults: a secondary analysis of data from the REGARDS study. *JAMA Netw Open*. 2019;2:e193121. doi: 10.1001/jamanetworkopen.2019.3121
36. Ramne S, Alves Dias J, González-Padilla E, Olsson K, Lindahl B, Engström G, Ericson U, Johansson I, Sonestedt E. Association between added sugar intake and mortality is nonlinear and dependent on sugar source in 2 Swedish population–based prospective cohorts. *Am J Clin Nutr*. 2019;109:411–423. doi: 10.1093/ajcn/nqy268
37. Shahdadian F, Saneei P, Milajerdi A, Esmaillzadeh A. Dietary glycemic index, glycemic load, and risk of mortality from all causes and cardiovascular diseases: a systematic review and dose-response meta-analysis of prospective cohort studies. *Am J Clin Nutr*. 2019;110:921–937. doi: 10.1093/ajcn/nqz061
38. Jenkins DJA, Dehghan M, Mente A, Bangdiwala SI, Rangarajan S, Srichaikul K, Mohan V, Avezum A, Diaz R, Rosengren A, et al; PURE Study Investigators. Glycemic index, glycemic load, and cardiovascular disease and mortality. *N Engl J Med*. 2021;384:1312–1322. doi: 10.1056/NEJMoa2007123
39. Virtanen HEK, Voutilainen S, Koskinen TT, Mursu J, Kokko P, Ylilauri MPT, Tuomainen T-P, Salonen JT, Virtanen JK. Dietary proteins and protein sources and risk of death: the Kuopio Ischaemic Heart Disease Risk Factor Study. *Am J Clin Nutr*. 2019;109:1462–1471. doi: 10.1093/ajcn/nqz025
40. Pala V, Sieri S, Chiodini P, Masala G, Palli D, Mattiello A, Panico S, Tumino R, Frasca G, Fasanelli F, et al. Associations of dairy product consumption with mortality in the European Prospective Investigation Into Cancer and Nutrition (EPIC)–Italy cohort. *Am J Clin Nutr*. 2019;110:1220–1230. doi: 10.1093/ajcn/nqz183
41. Ding M, Li J, Qi L, Ellervik C, Zhang X, Manson JE, Stampfer M, Chavarro JE, Rexrode KM, Kraft P, et al. Associations of dairy intake with risk of mortality in women and men: three prospective cohort studies. *BMJ*. 2019;367:l6204. doi: 10.1136/bmj.l6204
42. Chen Z, Glisic M, Song M, Aliahmad HA, Zhang X, Moumdjian AC, Gonzalez-Jaramillo V, van der Schaft N, Bramer WM, Ikram MA, et al. Dietary protein intake and all-cause and cause-specific mortality: results from the Rotterdam Study and a meta-analysis of prospective cohort studies. *Eur J Epidemiol*. 2020;35:411–429. doi: 10.1007/s10654-020-00607-6
43. Naghshi S, Sadeghi O, Willett WC, Esmaillzadeh A. Dietary intake of total, animal, and plant proteins and risk of all cause, cardiovascular, and cancer mortality: systematic review and dose-response meta-analysis of prospective cohort studies. *BMJ*. 2020;370:m2412. doi: 10.1136/bmj.m2412
44. Qi XX, Shen P. Associations of dietary protein intake with all-cause, cardiovascular disease, and cancer mortality: a systematic review and meta-analysis of cohort studies. *Nutr Metab Cardiovasc Dis*. 2020;30:1094–1105. doi: 10.1016/j.numecd.2020.03.008
45. Amba V, Murphy G, Etemadi A, Wang S, Abnet CC, Hashemian M. Nut and peanut butter consumption and mortality in the National Institutes of Health-AARP Diet and Health Study. *Nutrients*. 2019;11:1508–1508. doi: 10.3390/nu11071508
46. Zamora-Ros R, Cayssials V, Cleries R, Redondo ML, Sánchez M-J, Rodríguez-Barranco M, Sánchez-Cruz J-J, Mokoroa O, Gil L, Amiano P, et al. Moderate egg consumption and all-cause and specific-cause mortality in the Spanish European Prospective Into Cancer and Nutrition (EPIC-Spain) study. *Eur J Nutr*. 2019;58:2003–2010. doi: 10.1007/s00394-018-1754-6
47. Mazidi M, Katsiki N, Mikhailidis DP, Banach M. Dietary choline is positively related to overall and cause-specific mortality: results from individuals of the National Health and Nutrition Examination Survey and pooling prospective data. *Br J Nutr*. 2019;122:1262–1270. doi: 10.1017/S0007114519001065
48. Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Aros F, Gomez-Gracia E, Ruiz-Gutierrez V, Fiol M, Lapetra J, et al. Retraction and republication: primary prevention of cardiovascular disease with a Mediterranean Diet. N Engl J Med 2013;368:1279-90. *N Engl J Med*. 2018;378:2441–2442. doi: 10.1056/NEJMc1806491
49. Estruch R, Martinez-Gonzalez MA, Corella D, Salas-Salvado J, Fito M, Chiva-Blanch G, Fiol M, Gomez-Gracia E, Aros F, Lapetra J, et al; PREDIMED Study Investigators. Effect of a high-fat Mediterranean diet on bodyweight and waist circumference: a prespecified secondary outcomes analysis of the PREDIMED randomised controlled trial. *Lancet Diabetes Endocrinol*. 2019;7:e6–e17. doi: 10.1016/S2213-8587(19)30074-9
50. Sofi F, Dinu M, Pagliai G, Cesari F, Gori AM, Sereni A, Becatti M, Fiorillo C, Marcucci R, Casini A. Low-calorie vegetarian versus mediterranean diets for reducing body weight and improving cardiovascular risk profile: CARDIVEG Study (Cardiovascular Prevention With Vegetarian Diet). *Circulation*. 2018;137:1103–1113. doi: 10.1161/CIRCULATIONAHA.117.030088
51. Rosato V, Temple NJ, La Vecchia C, Castellan G, Tavani A, Guercio V. Mediterranean diet and cardiovascular disease: a systematic review and meta-analysis of observational studies. *Eur J Nutr*. 2019;58:173–191. doi: 10.1007/s00394-017-1582-0
52. Chen GC, Neelakantan N, Martin-Calvo N, Koh WP, Yuan JM, Bonaccio M, Iacoviello L, Martinez-Gonzalez MA, Qin LQ, van Dam RM. Adherence to the Mediterranean diet and risk of stroke and stroke subtypes. *Eur J Epidemiol*. 2019;34:337–349. doi: 10.1007/s10654-019-00504-7
53. Becerra-Tomas N, Blanco Mejia S, Viguiliouk E, Khan T, Kendall CWC, Kahleova H, Rahelic D, Sievenpiper JL, Salas-Salvado J. Mediterranean diet, cardiovascular disease and mortality in diabetes: a systematic review and meta-analysis of prospective cohort studies and randomized clinical trials. *Crit Rev Food Sci Nutr*. 2020;60:1207–1227. doi: 10.1080/10408398.2019.1565281
54. Juraschek SP, Miller ER 3rd, Weaver CM, Appel LJ. Effects of sodium reduction and the DASH diet in relation to baseline blood pressure. *J Am Coll Cardiol*. 2017;70:2841–2848. doi: 10.1016/j.jacc.2017.10.011
55. Filippini T, Malavolti M, Whelton PK, Naska A, Orsini N, Vinceti M. Blood pressure effects of sodium reduction: dose-response meta-analysis of experimental studies. *Circulation*. 2021;143:1542–1567. doi: 10.1161/CIRCULATIONAHA.120.050371
56. Chiavaroli L, Viguiliouk E, Nishi SK, Blanco Mejia S, Rahelic D, Kahleova H, Salas-Salvado J, Kendall CW, Sievenpiper JL. DASH dietary pattern and cardiometabolic outcomes: an umbrella review of systematic reviews and meta-analyses. *Nutrients*. 2019;11:338. doi: 10.3390/nu11020338
57. Yang ZQ, Yang Z, Duan ML. Dietary approach to stop hypertension diet and risk of coronary artery disease: a meta-analysis of prospective cohort studies. *Int J Food Sci Nutr*. 2019;70:668–674. doi: 10.1080/09637486.2019.1570490
58. Loo RL, Zou X, Appel LJ, Nicholson JK, Holmes E. Characterization of metabolic responses to healthy diets and association with blood pressure: application to the Optimal Macronutrient Intake Trial for Heart Health (OmniHeart), a randomized controlled study. *Am J Clin Nutr*. 2018;107:323–334. doi: 10.1093/ajcn/nqx072
59. Matsumoto S, Beeson WL, Shavlik DJ, Siapco G, Jaceldo-Siegl K, Fraser G, Knutsen SF. Association between vegetarian diets and cardiovascular risk factors in non-Hispanic white participants of the Adventist Health Study-2. *J Nutr Sci*. 2019;8:e6. doi: 10.1017/jns.2019.1
60. Qian F, Liu G, Hu FB, Bhupathiraju SN, Sun Q. Association between plant-based dietary patterns and risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA Intern Med*. 2019;179:1335–1344. doi: 10.1001/jamainternmed.2019.2195
61. Prentice RL, Aragaki AK, Howard BV, Chlebowski RT, Thomson CA, Van Horn L, Tinker LF, Manson JE, Anderson GL, Kuller LE, et al. Low-fat dietary pattern among postmenopausal women influences long-term cancer, cardiovascular disease, and diabetes outcomes. *J Nutr*. 2019;149:1565–1574. doi: 10.1093/jn/nxz107
62. Srour B, Fezeu LK, Kesse-Guyot E, Alles B, Mejean C, Andrianasolo RM, Chazelas E, Deschasaux M, Hercberg S, Galan P, et al. Ultra-processed food intake and risk of cardiovascular disease: prospective cohort study (NutriNet-Sante). *BMJ*. 2019;365:l1451. doi: 10.1136/bmj.l1451
63. Jayedi A, Soltani S, Abdolshahi A, Shab-Bidar S. Healthy and unhealthy dietary patterns and the risk of chronic disease: an umbrella review of meta-analyses of prospective cohort studies. *Br J Nutr*. 2020;124:1133–1144. doi: 10.1017/S0007114520002330
64. Bonnet JP, Cardel MI, Cellini J, Hu FB, Guasch-Ferré M. Breakfast skipping, body composition, and cardiometabolic risk: a systematic review and meta-analysis of randomized trials. *Obesity (Silver Spring)*. 2020;28:1098–1109. doi: 10.1002/oby.22791
65. Kord-Varkaneh H, Nazary-Vannani A, Mokhtari Z, Salehi-Sahlabadi A, Rahmani J, Clark CCT, Fatahi S, Zanghelini F, Hekmatdoost A, Okunade K, et al. The influence of fasting and energy restricting diets on blood pressure in humans: a systematic review and meta-analysis. *High Blood Press Cardiovasc Prev*. 2020;27:271–280. doi: 10.1007/s40292-020-00391-0
66. Reynolds A, Mann J, Cummings J, Winter N, Mete E, Te Morenga L. Carbohydrate quality and human health: a series of systematic

reviews and meta-analyses. *Lancet*. 2019;393:434–445. doi: 10.1016/S0140-6736(18)31809-9
67. Hardy DS, Garvin JT, Xu H. Carbohydrate quality, glycemic index, glycemic load and cardiometabolic risks in the US, Europe and Asia: a dose-response meta-analysis. *Nutr Metab Cardiovasc Dis*. 2020;30:853–871. doi: 10.1016/j.numecd.2019.12.050
68. Dong T, Guo M, Zhang P, Sun G, Chen B. The effects of low-carbohydrate diets on cardiovascular risk factors: a meta-analysis. *PLoS One*. 2020;15:e0225348. doi: 10.1371/journal.pone.0225348
69. Mazidi M, Mikhailidis DP, Sattar N, Toth PP, Judd S, Blaha MJ, Hernandez AV, Penson PE, Banach M; International Lipid Expert Panel (ILEP) and Lipid and Blood Pressure Meta-Analysis Collaboration (LBPMC) Group. Association of types of dietary fats and all-cause and cause-specific mortality: a prospective cohort study and meta-analysis of prospective studies with 1,164,029 participants. *Clin Nutr*. 2020;39:3677–3686. doi: 10.1016/j.clnu.2020.03.028
70. Kang ZQ, Yang Y, Xiao B. Dietary saturated fat intake and risk of stroke: systematic review and dose-response meta-analysis of prospective cohort studies. *Nutr Metab Cardiovasc Dis*. 2020;30:179–189. doi: 10.1016/j.numecd.2019.09.028
71. Astrup A, Magkos F, Bier DM, Brenna JT, de Oliveira Otto MC, Hill JO, King JC, Mente A, Ordovas JM, Volek JS, et al. Saturated fats and health: a reassessment and proposal for food-based recommendations: JACC state-of-the-art review. *J Am Coll Cardiol*. 2020;76:844–857. doi: 10.1016/j.jacc.2020.05.077
72. Wan Y, Wang F, Yuan J, Li J, Jiang D, Zhang J, Li H, Wang R, Tang J, Huang T, et al. Effects of dietary fat on gut microbiota and faecal metabolites, and their relationship with cardiometabolic risk factors: a 6-month randomised controlled-feeding trial. *Gut*. 2019;68:1417–1429. doi: 10.1136/gutjnl-2018-317609
73. Howard BV, Van Horn L, Hsia J, Manson JE, Stefanick ML, Wassertheil-Smoller S, Kuller LH, LaCroix AZ, Langer RD, Lasser NL, et al. Low-fat dietary pattern and risk of cardiovascular disease: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA*. 2006;295:655–666. doi: 10.1001/jama.295.6.655
74. Liu Q, Matthan NR, Manson JE, Howard BV, Tinker LF, Neuhouser ML, Van Horn LV, Rossouw JE, Allison MA, Martin LW, et al. Plasma phospholipid fatty acids and coronary heart disease risk: a matched case-control study within the Women's Health Initiative Observational Study. *Nutrients*. 2019;11:1672. doi: 10.3390/nu11071672
75. Chen J, Sun B, Zhang D. Association of dietary n3 and n6 fatty acids intake with hypertension: NHANES 2007–2014. *Nutrients*. 2019;11:1232. doi: 10.3390/nu11061232
76. Kouli G-M, Panagiotakos DB, Kyrou I, Magriplis E, Georgousopoulou EN, Chrysohoou C, Tsigos C, Tousoulis D, Pitsavos C. Olive oil consumption and 10-year (2002-2012) cardiovascular disease incidence: the ATTICA study. *Eur J Nutr*. 2019;58:131–138. doi: 10.1007/s00394-017-1577-x
77. Bechthold A, Boeing H, Schwedhelm C, Hoffmann G, Knuppel S, Iqbal K, De Henauw S, Michels N, Devleesschauwer B, Schlesinger S, et al. Food groups and risk of coronary heart disease, stroke and heart failure: a systematic review and dose-response meta-analysis of prospective studies. *Crit Rev Food Sci Nutr*. 2019;59:1071–1090. doi: 10.1080/10408398.2017.1392288
78. Qin P, Li Q, Zhao Y, Chen Q, Sun X, Liu Y, Li H, Wang T, Chen X, Zhou Q, et al. Sugar and artificially sweetened beverages and risk of obesity, type 2 diabetes mellitus, hypertension, and all-cause mortality: a dose-response meta-analysis of prospective cohort studies. *Eur J Epidemiol*. 2020;35:655–671. doi: 10.1007/s10654-020-00655-y
79. Schwingshackl L, Neuenschwander M, Hoffmann G, Buyken AE, Schlesinger S. Dietary sugars and cardiometabolic risk factors: a network meta-analysis on isocaloric substitution interventions. *Am J Clin Nutr*. 2020;111:187–196. doi: 10.1093/ajcn/nqz273
80. Du H, Li L, Bennett D, Guo Y, Key TJ, Bian Z, Sherliker P, Gao H, Chen Y, Yang L, et al; China Kadoorie Biobank Study. Fresh fruit consumption and major cardiovascular disease in China. *N Engl J Med*. 2016;374:1332–1343. doi: 10.1056/NEJMoa1501451
81. Du H, Li L, Bennett D, Guo Y, Turnbull I, Yang L, Bragg F, Bian Z, Chen Y, Chen J, et al; China Kadoorie Biobank Study. Fresh fruit consumption in relation to incident diabetes and diabetic vascular complications: a 7-y prospective study of 0.5 million Chinese adults. *PLoS Med*. 2017;14:e1002279. doi: 10.1371/journal.pmed.1002279
82. Marshall S, Petocz P, Duve E, Abbott K, Cassettari T, Blumfield M, Fayet-Moore F. The effect of replacing refined grains with whole grains on cardiovascular risk factors: a systematic review and meta-analysis of randomized controlled trials with GRADE clinical recommendation. *J Acad Nutr Diet*. 2020;120:1859–1883.e31. doi: 10.1016/j.jand.2020.06.021
83. Wang Y, Duan Y, Zhu L, Fang Z, He L, Ai D, Jin Y. Whole grain and cereal fiber intake and the risk of type 2 diabetes: a meta-analysis. *Int J Mol Epidemiol Genet*. 2019;10:38–46.
84. Jayedi A, Shab-Bidar S, Eimeri S, Djafarian K. Fish consumption and risk of all-cause and cardiovascular mortality: a dose-response meta-analysis of prospective observational studies. *Public Health Nutr*. 2018;21:1297–1306. doi: 10.1017/S1368980017003834
85. Zhang B, Xiong K, Cai J, Ma A. Fish consumption and coronary heart disease: a meta-analysis. *Nutrients*. 2020;12:2278. doi: 10.3390/nu12082278
86. Nahab F, Pearson K, Frankel MR, Ard J, Safford MM, Kleindorfer D, Howard VJ, Judd S. Dietary fried fish intake increases risk of CVD: the REasons for Geographic And Racial Differences in Stroke (REGARDS) study. *Public Health Nutr*. 2016;19:3327–3336. doi: 10.1017/S136898001600152X
87. Zhong VW, Van Horn L, Greenland P, Carnethon MR, Ning H, Wilkins JT, Lloyd-Jones DM, Allen NB. Associations of processed meat, unprocessed red meat, poultry, or fish intake with incident cardiovascular disease and all-cause mortality. *JAMA Intern Med*. 2020;180:503–512. doi: 10.1001/jamainternmed.2019.6969
88. Bergeron N, Chiu S, Williams PT, King SM, Krauss RM. Effects of red meat, white meat, and nonmeat protein sources on atherogenic lipoprotein measures in the context of low compared with high saturated fat intake: a randomized controlled trial. *Am J Clin Nutr*. 2019;110:24–33. doi: 10.1093/ajcn/nqz035
89. Guasch-Ferre M, Liu X, Malik VS, Sun Q, Willett WC, Manson JE, Rexrode KM, Li Y, Hu FB, Bhupathiraju SN. Nut consumption and risk of cardiovascular disease. *J Am Coll Cardiol*. 2017;70:2519–2532. doi: 10.1016/j.jacc.2017.09.035
90. Liu K, Hui S, Wang B, Kaliannan K, Guo X, Liang L. Comparative effects of different types of tree nut consumption on blood lipids: a network meta-analysis of clinical trials. *Am J Clin Nutr*. 2020;111:219–227. doi: 10.1093/ajcn/nqz280
91. Afshin A, Micha R, Khatibzadeh S, Mozaffarian D. Consumption of nuts and legumes and risk of incident ischemic heart disease, stroke, and diabetes: a systematic review and meta-analysis. *Am J Clin Nutr*. 2014;100:278–288. doi: 10.3945/ajcn.113.076901
92. Zhang X, Chen X, Xu Y, Yang J, Du L, Li K, Zhou Y. Milk consumption and multiple health outcomes: umbrella review of systematic reviews and meta-analyses in humans. *Nutr Metab (Lond)*. 2021;18:7. doi: 10.1186/s12986-020-00527-y
93. Zhang K, Chen X, Zhang L, Deng Z. Fermented dairy foods intake and risk of cardiovascular diseases: a meta-analysis of cohort studies. *Crit Rev Food Sci Nutr*. 2020;60:1189–1194. doi: 10.1080/10408398.2018.1564019
94. Martínez-López S, Sarriá B, Mateos R, Bravo-Clemente L. Moderate consumption of a soluble green/roasted coffee rich in caffeoylquinic acids reduces cardiovascular risk markers: results from a randomized, cross-over, controlled trial in healthy and hypercholesterolemic subjects. *Eur J Nutr*. 2019;58:865–878. doi: 10.1007/s00394-018-1726-x
95. Suliga E, Kozieł D, Ciesla E, Rebak D, Głuszek-Osuch M, Głuszek S. Consumption of alcoholic beverages and the prevalence of metabolic syndrome and its components. *Nutrients*. 2019;11:2764. doi: 10.3390/nu11112764
96. Suliga E, Kozieł D, Ciesla E, Rebak D, Głuszek-Osuch M, Naszydłowska E, Głuszek S. The consumption of alcoholic beverages and the prevalence of cardiovascular diseases in men and women: a cross-sectional study. *Nutrients*. 2019;11:1318. doi: 10.3390/nu11061318
97. Graudal N, Hubeck-Graudal T, Jurgens G, Taylor RS. Dose-response relation between dietary sodium and blood pressure: a meta-regression analysis of 133 randomized controlled trials. *Am J Clin Nutr*. 2019;109:1273–1278. doi: 10.1093/ajcn/nqy384
98. Mozaffarian D, Fahimi S, Singh GM, Micha R, Khatibzadeh S, Engell RE, Lim S, Danaei G, Ezzati M, Powles J; Global Burden of Diseases Nutrition and Chronic Diseases Expert Group. Global sodium consumption and death from cardiovascular causes. *N Engl J Med*. 2014;371:624–634. doi: 10.1056/NEJMoa1304127
99. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, Obarzanek E, Conlin PR, Miller ER, 3rd, et al; DASH-Sodium Collaborative Research Group. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet: DASH-Sodium Collaborative Research Group. *N Engl J Med*. 2001;344:3–10. doi: 10.1056/NEJM200101043440101
100. Jayedi A, Ghomashi F, Zargar MS, Shab-Bidar S. Dietary sodium, sodium-to-potassium ratio, and risk of stroke: a systematic review and

nonlinear dose-response meta-analysis. *Clin Nutr*. 2019;38:1092–1100. doi: 10.1016/j.clnu.2018.05.017
101. Kalogeropoulos AP, Georgiopoulou VV, Murphy RA, Newman AB, Bauer DC, Harris TB, Yang Z, Applegate WB, Kritchevsky SB. Dietary sodium content, mortality, and risk for cardiovascular events in older adults: the Health, Aging, and Body Composition (Health ABC) Study. *JAMA Intern Med*. 2015;175:410–419. doi: 10.1001/jamainternmed.2014.6278
102. Mente A, O'Donnell M, Rangarajan S, Dagenais G, Lear S, McQueen M, Diaz R, Avezum A, Lopez-Jaramillo P, Lanas F, et al; PURE, EPIDREAM and ONTARGET/TRANSCEND Investigators. Associations of urinary sodium excretion with cardiovascular events in individuals with and without hypertension: a pooled analysis of data from four studies. *Lancet*. 2016;388:465–475. doi: 10.1016/S0140-6736(16)30467-6
103. O'Donnell M, Mente A, Rangarajan S, McQueen MJ, Wang X, Liu L, Yan H, Lee SF, Mony P, Devanath A, et al; PURE Investigators. Urinary sodium and potassium excretion, mortality, and cardiovascular events. *N Engl J Med*. 2014;371:612–623. doi: 10.1056/NEJMoa1311889
104. Whelton PK, Appel LJ, Sacco RL, Anderson CA, Antman EM, Campbell N, Dunbar SB, Frohlich ED, Hall JE, Jessup M, et al. Sodium, blood pressure, and cardiovascular disease: further evidence supporting the American Heart Association sodium reduction recommendations. *Circulation*. 2012;126:2880–2889. doi: 10.1161/CIR.0b013e318279acbf
105. Cobb LK, Anderson CA, Elliott P, Hu FB, Liu K, Neaton JD, Whelton PK, Woodward M, Appel LJ; on behalf of the American Heart Association Council on Lifestyle and Metabolic Health. Methodological issues in cohort studies that relate sodium intake to cardiovascular disease outcomes: a science advisory from the American Heart Association. *Circulation*. 2014;129:1173–1186. doi: 10.1161/CIR.0000000000000015
106. Cook NR, Appel LJ, Whelton PK. Sodium intake and all-cause mortality over 20 years in the Trials of Hypertension Prevention. *J Am Coll Cardiol*. 2016;68:1609–1617. doi: 10.1016/j.jacc.2016.07.745
107. Huang L, Trieu K, Yoshimura S, Neal B, Woodward M, Campbell NRC, Li Q, Lackland DT, Leung AA, Anderson CAM, et al. Effect of dose and duration of reduction in dietary sodium on blood pressure levels: systematic review and meta-analysis of randomised trials. *BMJ*. 2020;368:m315. doi: 10.1136/bmj.m315
108. McClure ST, Rebholz CM, Mitchell DC, Selvin E, Appel LJ. The association of dietary phosphorus with blood pressure: results from a secondary analysis of the PREMIER trial. *J Hum Hypertens*. 2019;34:132–142. doi: 10.1038/s41371-019-0231-x
109. Zhao B, Hu L, Dong Y, Xu J, Wei Y, Yu D, Xu J, Zhang W. The effect of magnesium intake on stroke incidence: a systematic review and meta-analysis with trial sequential analysis. *Front Neurol*. 2019;10:852. doi: 10.3389/fneur.2019.00852
110. Bowman L, Mafham M, Wallendszus K, Stevens W, Buck G, Barton J, Murphy K, Aung T, Haynes R, Cox J, et al; ASCEND Study Collaborative Group. Effects of n-3 fatty acid supplements in diabetes mellitus. *N Engl J Med*. 2018;379:1540–1550. doi: 10.1056/NEJMoa1804989
111. Siscovick DS, Barringer TA, Fretts AM, Wu JH, Lichtenstein AH, Costello RB, Kris-Etherton PM, Jacobson TA, Engler MB, Alger HM, et al; on behalf of the American Heart Association Nutrition Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Epidemiology and Prevention; Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; and Council on Clinical Cardiology. Omega-3 polyunsaturated fatty acid (fish oil) supplementation and the prevention of clinical cardiovascular disease: a science advisory from the American Heart Association. *Circulation*. 2017;135:e867–e884. doi: 10.1161/CIR.0000000000000482
112. Khan SU, Lone AN, Khan MS, Virani SS, Blumenthal RS, Nasir K, Miller M, Michos ED, Ballantyne CM, Boden WE, et al. Effect of omega-3 fatty acids on cardiovascular outcomes: a systematic review and meta-analysis. *EClinicalMedicine*. 2021;38:100997. doi: 10.1016/j.eclinm.2021.100997
113. Ward RE, Cho K, Nguyen XM, Vassy JL, Ho YL, Quaden RM, Gagnon DR, Wilson PWF, Gaziano JM, Djousse L. Omega-3 supplement use, fish intake, and risk of non-fatal coronary artery disease and ischemic stroke in the Million Veteran Program. *Clin Nutr*. 2019;39:574–579.
114. Hadi A, Askarpour M, Salamat S, Ghaedi E, Symonds ME, Miraghajani M. Effect of flaxseed supplementation on lipid profile: an updated systematic review and dose-response meta-analysis of sixty-two randomized controlled trials. *Pharmacol Res*. 2020;152:104622. doi: 10.1016/j.phrs.2019.104622
115. Manson JE, Cook NR, Lee IM, Christen W, Bassuk SS, Mora S, Gibson H, Gordon D, Copeland T, D'Agostino D, et al; VITAL Research Group. Vitamin D supplements and prevention of cancer and cardiovascular disease. *N Engl J Med*. 2019;380:33–44. doi: 10.1056/NEJMoa1809944
116. Zittermann A, Ernst JB, Prokop S, Fuchs U, Dreier J, Kuhn J, Knabbe C, Borgermann J, Berthold HK, Pilz S, et al. Daily supplementation with 4000 IU vitamin D3 for three years does not modify cardiovascular risk markers in patients with advanced heart failure: the Effect of Vitamin D on Mortality in Heart Failure trial. *Ann Nutr Metab*. 2019;74:62–68. doi: 10.1159/000495662
117. Zittermann A, Ernst JB, Prokop S, Fuchs U, Gruszka A, Dreier J, Kuhn J, Knabbe C, Berthold HK, Gouni-Berthold I, et al. Vitamin D supplementation of 4000IU daily and cardiac function in patients with advanced heart failure: the EVITA trial. *Int J Cardiol*. 2019;280:117–123. doi: 10.1016/j.ijcard.2019.01.027
118. Hofmeyr GJ, Betrán AP, Singata-Madliki M, Cormick G, Munjanja SP, Fawcus S, Mose S, Hall D, Ciganda A, Seuc AH, et al; Calcium and Pre-Eclampsia Study Group. Prepregnancy and early pregnancy calcium supplementation among women at high risk of pre-eclampsia: a multicentre, double-blind, randomised, placebo-controlled trial. *Lancet*. 2019;393:330–339. doi: 10.1016/S0140-6736(18)31818-X
119. Hofmeyr GJ, Manyame S, Medley N, Williams MJ. Calcium supplementation commencing before or early in pregnancy, for preventing hypertensive disorders of pregnancy. *Cochrane Database Syst Rev*. 2019;9:CD011192. doi: 10.1002/14651858.CD011192.pub3
120. Djousse L, Cook NR, Kim E, Bodar V, Walter J, Bubes V, Luttmann-Gibson H, Mora S, Joseph J, Lee IM, et al. Supplementation with vitamin D and/or omega-3 fatty acids and incidence of heart failure hospitalization: VITAL-Heart Failure. *Circulation*. 2019;141:784–786. doi: 10.1161/CIRCULATIONAHA.119.044645
121. Jiang X, Nudy M, Aragaki AK, Robbins JA, Manson JE, Stefanick ML, O'Sullivan DM, Shikany JM, LeBlanc ES, Kelsey AM, et al. Women's Health Initiative clinical trials: potential interactive effect of calcium and vitamin D supplementation with hormonal therapy on cardiovascular disease. *Menopause*. 2019;26:841–849. doi: 10.1097/gme.0000000000001360
122. Hauger H, Laursen RP, Ritz C, Mølgaard C, Lind MV, Damsgaard CT. Effects of vitamin D supplementation on cardiometabolic outcomes in children and adolescents: a systematic review and meta-analysis of randomized controlled trials. *Eur J Nutr*. 2020;59:873–884. doi: 10.1007/s00394-019-02150-x
123. Abboud M. Vitamin D supplementation and blood pressure in children and adolescents: a systematic review and meta-analysis. *Nutrients*. 2020;12:1163. doi: 10.3390/nu12041163
124. Jenkins DJA, Spence JD, Giovannucci EL, Kim YI, Josse R, Vieth R, Blanco Mejia S, Viguiliouk E, Nishi S, Sahye-Pudaruth S, et al. Supplemental vitamins and minerals for CVD prevention and treatment. *J Am Coll Cardiol*. 2018;71:2570–2584. doi: 10.1016/j.jacc.2018.04.020
125. Ashor AW, Brown R, Keenan PD, Willis ND, Siervo M, Mathers JC. Limited evidence for a beneficial effect of vitamin C supplementation on biomarkers of cardiovascular diseases: an umbrella review of systematic reviews and meta-analyses. *Nutr Res*. 2019;61:1–12. doi: 10.1016/j.nutres.2018.08.005
126. Wang T, Xu L. Circulating vitamin E levels and risk of coronary artery disease and myocardial infarction: a mendelian randomization study. *Nutrients*. 2019;11:2153. doi: 10.3390/nu11092153
127. Huo Y, Li J, Qin X, Huang Y, Wang X, Gottesman RF, Tang G, Wang B, Chen D, He M, et al; CSPPT Investigators. Efficacy of folic acid therapy in primary prevention of stroke among adults with hypertension in China: the CSPPT randomized clinical trial. *JAMA*. 2015;313:1325–1335. doi: 10.1001/jama.2015.2274
128. US Department of Agriculture and Economic Research Service. Summary findings: food price outlook. 2023. Accessed April 14, 2023. https://ers.usda.gov/data-products/food-price-outlook/summary-findings/
129. USDA Economic Research Service. Data on expenditures on food and alcoholic beverages in selected countries. Accessed April 14, 2023. https://ers.usda.gov/topics/international-markets-us-trade/international-consumer-and-food-industry-trends/#data
130. Rao M, Afshin A, Singh G, Mozaffarian D. Do healthier foods and diet patterns cost more than less healthy options? A systematic review and meta-analysis. *BMJ Open*. 2013;3:e004277. doi: 10.1136/bmjopen-2013-004277
131. Healthy Food America. *Healthy Food Pricing Incentives: A Systematic Review of Current Evidence*. June 2019. Accessed October 15, 2023. https://www.healthyfoodamerica.org/healthy_food_pricing_incentives_a_systematic_review_of_current_evidence
132. Beets MW, Weaver RG, Turner-McGrievy G, Huberty J, Ward DS, Freedman D, Hutto B, Moore JB, Beighle A. Making healthy eating policy practice: a group randomized controlled trial on changes in snack quality, costs, and consumption in after-school programs. *Am J Health Promot*. 2016;30:521–531. doi: 10.4278/ajhp.141001-QUAN-486

133. Scrafford CG, Bi X, Multani JK, Murphy MM, Schmier JK, Barraj LM. Health economic evaluation modeling shows potential health care cost savings with increased conformance with healthy dietary patterns among adults in the United States. *J Acad Nutr Diet*. 2019;119:599–616. doi: 10.1016/j.jand.2018.10.002
134. Basu S, O'Neill J, Sayer E, Petrie M, Bellin R, Berkowitz SA. Population health impact and cost-effectiveness of community-supported agriculture among low-income US adults: a microsimulation analysis. *Am J Public Health*. 2020;110:119–126. doi: 10.2105/AJPH.2019.305364
135. Webb M, Fahimi S, Singh GM, Khatibzadeh S, Micha R, Powles J, Mozaffarian D. Cost effectiveness of a government supported policy strategy to decrease sodium intake: global analysis across 183 nations. *BMJ*. 2017;356:i6699. doi: 10.1136/bmj.i6699
136. Collins B, Kypridemos C, Pearson-Stuttard J, Huang YUE, Bandosz P, Wilde P, Kersh R, Capewell S, Mozaffarian D, Whitsel LP, et al. FDA sodium reduction targets and the food industry: are there incentives to reformulate? Microsimulation cost-effectiveness analysis. *Milbank Q*. 2019;97:858–880. doi: 10.1111/1468-0009.12402
137. Park H, Yu S. Policy review: Implication of tax on sugar-sweetened beverages for reducing obesity and improving heart health. *Health Policy Technol*. 2019;8:92–95. doi: 10.1016/j.hlpt.2018.12.002
138. Wilde P, Huang Y, Sy S, Abrahams-Gessel S, Jardim TV, Paarlberg R, Mozaffarian D, Micha R, Gaziano T. Cost-effectiveness of a US national sugar-sweetened beverage tax with a multistakeholder approach: who pays and who benefits. *Am J Public Health*. 2019;109:276–284. doi: 10.2105/AJPH.2018.304803
139. Saxena A, Koon AD, Lagrada-Rombaua L, Angeles-Agdeppa I, Johns B, Capanzana M. Modelling the impact of a tax on sweetened beverages in the Philippines: an extended cost-effectiveness analysis. *Bull World Health Organ*. 2019;97:97–107. doi: 10.2471/BLT.18.219980
140. Popkin BM, Hawkes C. Sweetening of the global diet, particularly beverages: patterns, trends, and policy responses. *Lancet Diabetes Endocrinol*. 2016;4:174–186. doi: 10.1016/S2213-8587(15)00419-2
141. Colchero MA, Rivera-Dommarco J, Popkin BM, Ng SW. In Mexico, evidence of sustained consumer response two years after implementing a sugar-sweetened beverage tax. *Health Aff (Millwood)*. 2017;36:564–571. doi: 10.1377/hlthaff.2016.1231
142. Sanchez-Romero LM, Canto-Osorio F, Gonzalez-Morales R, Colchero MA, Ng SW, Ramirez-Palacios P, Salmeron J, Barrientos-Gutierrez T. Association between tax on sugar sweetened beverages and soft drink consumption in adults in Mexico: open cohort longitudinal analysis of Health Workers Cohort Study. *BMJ*. 2020;369:m1311. doi: 10.1136/bmj.m1311
143. Silver LD, Ng SW, Ryan-Ibarra S, Taillie LS, Induni M, Miles DR, Poti JM, Popkin BM. Changes in prices, sales, consumer spending, and beverage consumption one year after a tax on sugar-sweetened beverages in Berkeley, California, US: a before-and-after study. *PLoS Med*. 2017;14:e1002283. doi: 10.1371/journal.pmed.1002283
144. Lee MM, Falbe J, Schillinger D, Basu S, McCulloch CE, Madsen KA. Sugar-sweetened beverage consumption 3 years after the Berkeley, California, sugar-sweetened beverage tax. *Am J Public Health*. 2019;109:637–639. doi: 10.2105/AJPH.2019.304971
145. Powles J, Fahimi S, Micha R, Khatibzadeh S, Shi P, Ezzati M, Engell RE, Lim SS, Danaei G, Mozaffarian D; Global Burden of Diseases Nutrition and Chronic Diseases Expert Group (NutriCoDE). Global, regional and national sodium intakes in 1990 and 2010: a systematic analysis of 24 h urinary sodium excretion and dietary surveys worldwide. *BMJ Open*. 2013;3:e003733. doi: 10.1136/bmjopen-2013-003733
146. Barberio AM, Sumar N, Trieu K, Lorenzetti DL, Tarasuk V, Webster J, Campbell NRC, McLaren L. Population-level interventions in government jurisdictions for dietary sodium reduction: a Cochrane Review. *Int J Epidemiol*. 2017;46:1551–1405. doi: 10.1093/ije/dyw361
147. He FJ, Brinsden HC, MacGregor GA. Salt reduction in the United Kingdom: a successful experiment in public health. *J Hum Hypertens*. 2014;28:345–352. doi: 10.1038/jhh.2013.105
148. GBD Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. 2020;396:1223–1249. doi: 10.1016/S0140-6736(20)30752-2
149. Mellen PB, Gao SK, Vitolins MZ, Goff DC Jr. Deteriorating dietary habits among adults with hypertension: DASH dietary accordance, NHANES 1988-1994 and 1999-2004. *Arch Intern Med*. 2008;168:308–314. doi: 10.1001/archinternmed.2007.119
150. Gao S. *Diet and Exercise: Behavioral Management of Hypertension and Diabetes* [dissertation]. Seattle: University of Washington; 2006.
151. Cerwinske LA, Rasmussen HE, Lipson S, Volgman AS, Tangney CC. Evaluation of a dietary screener: the Mediterranean Eating Pattern for Americans tool. *J Hum Nutr Diet*. 2017;30:596–603. doi: 10.1111/jhn.12451
152. Fung TT, Chiuve SE, McCullough ML, Rexrode KM, Logroscino G, Hu FB. Adherence to a DASH-style diet and risk of coronary heart disease and stroke in women. *Arch Intern Med*. 2008;168:713–720. doi: 10.1001/archinte.168.7.713
153. Micha R, Wallace SK, Mozaffarian D. Red and processed meat consumption and risk of incident coronary heart disease, stroke, and diabetes mellitus: a systematic review and meta-analysis. *Circulation*. 2010;121:2271–2283. doi: 10.1161/CIRCULATIONAHA.109.924977
154. Centers for Disease Control and Prevention and National Center for Health Statistics. National Health and Nutrition Examination Survey (NHANES) public use data files. Accessed April 1, 2023. https://cdc.gov/nchs/nhanes/
155. Cogswell ME, Loria CM, Terry AL, Zhao L, Wang CY, Chen TC, Wright JD, Pfeiffer CM, Merritt R, Moy CS, et al. Estimated 24-hour urinary sodium and potassium excretion in US adults. *JAMA*. 2018;319:1209–1220. doi: 10.1001/jama.2018.1156
156. Global Burden of Disease Study and Institute for Health Metrics and Evaluation. University of Washington. Accessed August 2, 2023. http://ghdx.healthdata.org/

# 6. OVERWEIGHT AND OBESITY

*See Tables 6-1 through 6-5 and Charts 6-1 through 6-4*

Click here to return to the Table of Contents

Click here to return to the Abbreviations

## Classification of Overweight/Obese

- BMI is calculated as weight in kilograms divided by height in meters squared. Obesity in adults is defined as BMI ≥30.0 kg/m$^2$, and severe obesity is usually defined as BMI ≥40 kg/m$^2$.[1] Overweight in adults is defined as BMI ≥25.0 but <30 kg/m$^2$.[2,3]
- Obesity in adults can be further subdivided into class 1 (BMI 30–<35 kg/m$^2$) and class 2 (BMI 35–<40 kg/m$^2$); severe obesity is classified as class 3 (BMI ≥40 kg/m$^2$).[2,3]
- For children and adolescents, obesity is defined as BMI ≥95th percentile and severe obesity as BMI ≥120% of the 95th percentile.[4] Overweight in children is defined as BMI ≥85th but <95th percentile.
- Abdominal obesity is also defined as a WC ≥102 cm (40 in) in males and ≥88 cm (35 in) in females.[5]
- Lower BMI thresholds have been recommended for Asian adults, with overweight defined as ≥23 to <27.5 kg/m$^2$ and obesity as ≥27.5 kg/m$^2$, with a WC >90 cm (males) or >80 cm (females) associated with increased cardiovascular risk in these populations.[6] Accordingly, the American Diabetes Association lowered the BMI cut point for diabetes screening in Asian adults to ≥23 kg/m$^2$.[7]
- It should be noted that the risk for CVDs and diabetes conferred by an elevated BMI is not uniform across racial and ethnic groups and may overestimate risk among Black adults and underestimate risk in Asian people.[8] Even among different Asian populations, the BMI cut point for observed risk varies from 22 to 26 kg/m$^2$, and for high risk, the BMI varies from 26 to 31 kg/m$^2$.[8,9]

The 2024 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2024. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

## Prevalence and Secular Trends

### *Youth*

#### *Prevalence in Children/Adolescents*

*(See Table 6-1)*

- According to NHANES data from 2017 until March 2020 (before the COVID-19 pandemic), among US children and adolescents 2 to 19 years of age, the prevalence of obesity was 19.7% overall, 20.9% for males, and 18.5% for females.[10] Obesity prevalence increased with age, being 12.7% for those 2 to 5 years of age, 20.7% for those 6 to 11 years of age, and 22.2% for those 12 to 19 years of age (Table 6-1).[10]
- There were significant racial and ethnic disparities in obesity.[10] The highest prevalence of obesity was seen among Hispanic male and NH Black female youth. According to NHANES data from 2017 to March 2020, the prevalence of obesity among children and adolescents 2 to 19 years of age was 17.6% and 15.4% for NH White, 18.8% and 30.8% for NH Black, 13.1% and 5.2% for NH Asian, and 29.3% and 23.0% for Hispanic males and females, respectively (Table 6-1).
- Among youth, percent body fat was not consistent by BMI categories. In NHANES data from 2011 to 2018 in youth 8 to 19 years of age, percent body fat was highest among Hispanic females (35.7%) and males (28.2%).[11] There was no significant difference in percent body fat between NH Black, White, or Asian females (32.7%, 33.2%, and 32.7%, respectively). Percent body fat was lower among NH Black males at 23.9% compared with NH White or Asian males at 26.0% and 26.6%, respectively. Among female youth with obesity, NH Asian females had lower percent body fat (40.5%) than NH White females (42.8%; $P$=0.0072).
- There are regional/geographic differences in prevalence of obesity in youth across the United States. According to NHANES data from 1999 to 2014 among adolescents 12 to 19 years of age, across 9 regions, the prevalence of obesity was lowest in the Mountain and New England areas (both <15%) and highest in the central United States (21%–24%), followed by the South and Mid-Atlantic regions (19%–20%) and the Pacific and West North Central regions (17%–18%).[12] Another analyses of pooled data from 25 cohorts of children and adolescents (N=14 313) found BMI $z$ scores to be higher in the Midwest and lower in the South and West compared with the Northeast after adjustment for sociodemographic characteristics.[13]

### Youth Secular Trends

*(See Chart 6-1)*

- Comparing data across NHANES survey years shows that the prevalence of overweight, obesity, and severe obesity among all children and adolescents 2 to 19 years of age increased from 10.2%, 5.2%, and 1.0% in 1971 to 1974 to 16.1%, 19.3%, and 6.1%, respectively, in 2017 to 2018 (Chart 6-1). For males, the prevalence increased from 10.3%, 5.3%, and 1.0% in 1971 to 1974 to 14.7%, 20.5%, and 6.9% in 2017 to 2018. For females, the prevalence increased from 10.1%, 5.1%, and 1.0% in 1971 to 1974 to 17.6%, 18.0%, and 5.2% in 2017 to 2018.[4]

## Adults

### Prevalence in Adults

*(See Tables 6-2 and 6-3 and Charts 6-2 and 6-3)*

- According to NHANES data from 2017 through March 2020 (before the pandemic), the age-adjusted prevalence of overweight or obesity among adults ≥20 years of age in the United States was 71.2%.[10] The prevalence of obesity was 41.9% and was similar for males (41.8%) and females (41.8%) (Table 6-2).
- This prevalence of obesity by age categories for adults ≥20 years of age from this same time frame (2017–March 2020) was 39.8% in younger adults 20 to 39 years of age, 44.3% in middle-aged adults 40 to 59 years of age, and 41.5% in adults ≥60 years of age (Table 6-2).[1]
- There were significant disparities by racial and ethnic groups with the highest prevalence of obesity among NH Black females. Among adults ≥20 years of age, according to data from NHANES 2017 through March 2020 (before the pandemic), the prevalence of obesity for males and females was 43.1% and 39.6% for NH White, 40.4% and 57.9% for NH Black, 17.6% and 14.5% for NH Asian, and 45.2% and 45.7% for Hispanic adults, respectively (Table 6-2).[10]
- In data from NHANES 2017 through March 2020 (before the pandemic), the age-adjusted prevalence of severe obesity among adults ≥20 years of age in the United States was 9.2% with greater prevalence in females (11.7%) than males (6.6%; Table 6-3).[10] Significant disparities were noted by racial and ethnic groups with the greatest prevalence of severe obesity among Black females (19.1%).
- Using that same time frame (2017–March 2020) yields age-adjusted prevalence of severe obesity stratified by age groups of 9.7% for individuals 20 to 39 years of age, 10.7% for those 40 to 59 years of age, and 6.1% for individuals ≥60 years of age (Table 6-3).[10]
- An analysis using US state-level prevalence of obesity estimates that if current trends continue, in 2030, the prevalence of adult obesity will reach nearly 1 in 2 adults (48.9%), with nearly 1 in 4 adults (24.2%) projected to have severe obesity (BMI ≥35 kg/m$^2$).[14]
- According to BRFSS data among adults ≥18 years of age in the United States in 2020, the age-adjusted prevalence by BMI categories was 31.9% for obesity (BMI ≥30 kg/m$^2$), 35.2% for overweight (BMI, 25–29.9 kg/m$^2$), 31.0% for normal weight (BMI, 18.5–24.9 kg/m$^2$), and 1.8% for underweight (BMI <18.5 kg/m$^2$).[15]
- There is significant geographic variation in the prevalence of obesity across the United States (Chart 6-2). According to BRFSS 2021 data, the total US prevalence was 33.9% with the highest prevalence of obesity in the South (36.3%), followed by the Midwest (35.4%), the Northeast (29.9%), and the West (28.7%).[16] By state, the highest prevalence of obesity was in West Virginia (40.7%) and the lowest in Colorado (25.0%; unpublished NHLBI tabulation using BRFSS[15]).
- In a meta-analysis, 70% of adults with obesity were not obese in childhood or adolescence.[17] Thus, additional strategies are needed to prevent obesity in adulthood.

### Secular Trends in Adults

- Comparing NHANES data from 1999 to 2000 with data from 2017 to 2018 shows that the prevalence of obesity increased from 27.5% (95% CI, 24.3%–30.8%) to 43% (95% CI, 37.6%–48.6%) among US males with severe obesity increasing from 3.1% to 6.9%. All racial and ethnic groups experienced an increase in obesity and severe obesity during this time frame except for Black males, for whom the obesity prevalence did not increase after 2005 to 2006 (Chart 6-3). The increase in obesity biennially was greater among Mexican American males (3%) than NH White males (1.4%; $P<0.001$).[18]
- Among females, the prevalence of obesity increased from 33.4% (95% CI, 29.8%–37.1%) in 1999 to 2000 to 41.9% (95% CI, 37.8%–46.1%) in 2017 to 2018; severe obesity increased from 6.2% to 11.5%. This same pattern of increase was seen among NH White and NH Black females, whereas Mexican American females experienced a rise in obesity, but severe obesity increased only after 2009 to 2010.[18]
- An analysis using BRFSS data of US adults found that the prevalence of obesity increased 3%, along with a 0.6% increase in BMI, in the COVID-19 pandemic period of March 2020 to March 2021 compared with the prepandemic January 2019 to March 2020 period.[19]

## Social Determinants of Health and Health Equity

### *Urbanization*

- There are differences in obesity prevalence by urbanization status. In US data from NHANES 2013 to 2016, the age-adjusted prevalence of obesity for females living in nonmetropolitan statistical areas was greater at 47.2% than for females living in small (<250 000) or medium (250 000–999 999) metropolitan statistical areas at 42.5% or for females living in large metropolitan statistical areas (≥1 million population) at 38.1%.[20] For males, the age-adjusted prevalence of obesity was higher for small or medium metropolitan statistical areas at 42.4% compared with large metropolitan statistical areas at 31.8%, but the prevalence of obesity was similar to that of nonmetropolitan statistical areas at 38.9%. The prevalence of severe obesity, however, was higher in males living in nonmetropolitan statistical areas at 9.9% compared with males in large metropolitan statistical areas at 4.1%; for females, it was 13.5% versus 8.1%.
- Among children and adolescents, a meta-analysis found that obesity rates were 26% higher among children living in rural areas compared with children living in urban areas (OR, 1.26 [95% CI, 1.21–1.32]).[21] An analysis of preschoolers also found that indexed BMI was higher among children living in rural areas than children living in urban areas (β=0.13 [95% CI, 0.09–0.42]), suggesting that the rural-urban disparity may begin as early as 3 to 4 years of age.[22]

### *Income and Education*

### *(See Tables 6-1 through 6-3)*

- There were significant differences in the prevalence of obesity in the United States by SES with the lowest prevalence of obesity in the highest education and income groups according to NHANES data for adults ≥20 years of age from 2017 through March 2020 (before the pandemic).[10] For education, the prevalence of obesity was 40.1% for those with less than a high school diploma, 46.4% for individuals with a high school diploma or some college, and 34.2% for individuals with a college degree or above. For family income relative to FPL, the prevalence of obesity was 43.9% for those with income ≤130% FPL, 46.5% for those with income >130% to 350% FPL, and 39% for individuals with income >350% FPL (Table 6-2).
- Similar patterns of disparity by education and income were seen for the prevalence of severe obesity (Table 6-3).
- There was also significant disparity by SES among youth and adolescents. According to data from NHANES 2017 through March 2020, the prevalence of obesity among children and adolescents 2 to 19 years of age was greatest among those with a family income level relative to ≤130% FPL at 25.8% versus 21.2% for family income >130% to 350% FPL and 11.5% for family income >350% FPL (Table 6-1).[10]

### *Composite Social Determinants*

- According to data from the NHIS from 2013 to 2017, there was a graded association with increasing burden of social determinants of health being associated with a higher prevalence of obesity. For example, in adjusted models, for the fourth quartile of unfavorable social determinants of health compared with the first quartile, there was a 15%, 50%, and 70% higher prevalence of overweight, obesity class 1 or 2, and obesity class 3, respectively.[23]

## Family History and Genetics

- Although environmental factors certainly are a leading contributor to obesity and its growing rates, there are considerable genetic components in the tendency toward overweight and obesity status,[24] with heritability estimates ranging from 40% to 70%.[25]
- Monogenic or mendelian causes of obesity include variants with strong effects in genes that control appetite and energy balance (eg, *LEP*, *MC4R*, *POMC*). Obesity that occurs in the context of genetic syndromes (eg, Prader-Willi syndrome) also can reflect monogenic or mendelian causes.[26] Monogenic obesity inherited in a mendelian pattern is generally rare and associated with other organ-specific abnormalities.
- Polygenic obesity has a heritability pattern similar to that of complex diseases.[27] Many GWASs, ≈60 to date, have identified >1100 independent loci associated with polygenic obesity.[27] These GWASs have estimated that common genetic variants may account for >20% of the variation in BMI.[28]
- In GWAS analyses targeting African ancestry, only <30% of loci associated with BMI and waist-to-hip ratio in European ancestry were also associated in African ancestry.[29]
- One GWAS conducted specifically in children identified 3 new loci with susceptibility for childhood BMI, with a GRS (combining these 3 with 12 other previously identified loci) explaining 2% of variations in childhood BMI.[30]
- One of the first loci to be identified was the *FTO* gene (first intron of fat mass and obesity),[31] which is relatively common among individuals of European ancestry with a minor allele frequency of 40% to 45%.[27,32] *FTO* has a relatively large effect on BMI of 0.35 kg/m$^2$ per allele, or ≈1 kg in weight for a person who is 1.7 m tall. The association of *FTO*

SNPs with BMI was similar in populations of African or Asian ancestry but less prevalent in these populations compared with European ancestry.[27,32] This locus has been replicated in diverse populations and across different age groups.[32–36] The mechanisms underlying the association between variation at *FTO* and obesity remain incompletely elucidated but could be related to mitochondrial thermogenesis or food intake.[31]

- Large-scale exome sequencing projects have complemented GWASs, given their ability to capture rare coding variants. For example, in N=645 626 predominantly European ancestral populations, novel associations were identified for genes that encode G protein–coupled receptors, the largest human genome drug target class.[37] A rare predicted loss-of-function variant in *GPR75* also was identified. Carriers of this variant had, on average, 12-lb-lower body weight.
- A GRS comprising 2.1 million common variants was tested in a cohort of >300 000 individuals from birth to middle age and showed that among middle-aged adults, there was a 13-kg gradient in weight and a 25-fold gradient in risk of severe obesity across increasing deciles of polygenic scores.[38] Similarly, a weight gradient was seen after birth to early childhood of up to 12-kg difference by 18 years of age. However, obesity-related genetic risks are not deterministic; in the same analysis, 17% of people of normal weight were in the top decile of polygenic risk.[38]
- In another analysis, GRS explained 5.2% of BMI variance, and gene-by-environment interaction explained an additional 1.9%.[39]
- However, there is considerable uncertainty in obesity GRSs. A study of N=291 273 unrelated White British UK Biobank participants reported that only 0.4% of participants assigned to the 90% BMI GRS threshold had corresponding 95% credible intervals fully contained in the top decile.[40]
- Polygenic risk associated with higher BMI is associated with increased risk for CAD, HF, and mortality.[38] A mendelian randomization study has shown that a high-BMI GRS is associated with shorter life span in the UK Biobank (HR per 1-SD BMI GRS for increase in mortality, 1.07 [95% CI, 1.05–1.09]).[41]
- Mendelian randomization analysis also was used to evaluate the health consequences of obesity across a spectrum of human diseases. In data from the UK Biobank, a high GRS for obesity was associated with a 70% increased risk for diabetes (OR, 1.70 [95% CI, 1.62–1.79]), a 35% increased risk for hypertension (OR, 1.35 [95% CI, 1.31–1.38]), a 27% increased risk for CAD (OR, 1.27 [95% CI, 1.19–1.36]), a 23% increased risk for ischemic stroke (OR, 1.23 [95% CI, 1.02–1.48]), a 33% increased risk for HF (OR, 1.33 [95% CI, 1.14–1.54]), and a 40% increased risk for VTE (OR, 1.40 [95% CI, 1.30–1.49]).[42]
- Genetic variants may also influence responsiveness to weight loss interventions.[43] A GWAS (N=1166) conducted in a low-calorie diet intervention trial identified 2 loci, *NKX6.3/MIR486* and *RBSG4,* that were associated with degree of weight loss. Both loci were replicated in a second low-calorie diet intervention study (N=789).[43]
- Genetic variants also may affect weight loss or weight gain in the context of a behavioral intervention. For example, the *MTIF3* lead variant rs1885988, a previously identified BMI locus, was consistently associated with greater weight loss after lifestyle behavioral interventions in 2 RCTs, with each copy of the minor G allele being associated with a mean of 1.14-kg (95% CI, −1.75 to −0.53) weight loss in the lifestyle arm compared with a mean of 0.33-kg weight gain (95% CI, −0.30 to 0.95) in the comparison arm.[44]
- Environmental exposures may interact with common variants to affect obesity traits. In a study of >500 000 predominantly European ancestral populations, 4 significant loci were identified that modified the effect of current smoking on obesity traits: *INPP4B*, *CHRNB4*, *VEGFA*, and *RSPO3*.[45] *INPP4B* was previously identified in obesity[46] and smoking[47] GWASs, whereas *VEGFA* lead variants were identified in a gene-by-smoking study of rheumatoid arthritis.[48]
- Epigenetic modifications such as DNA methylation have both genetic and environmental contributors and may contribute to risk of and adverse consequences of obesity. An epigenome-wide association study in 479 people demonstrated that increased methylation at the *HIF3A* locus in circulating white blood cells and in adipose tissue was associated with increased BMI.[49]

## Obesity Prevention

- A prior meta-analysis suggested that school-based interventions aimed at promoting healthy weights were generally, albeit modestly, effective in reducing excessive weight gain in children (average BMI reduction, −0.14 kg/m$^2$ [95% CI, −0.21 to −0.06] for single-component interventions).[50]
- Another meta-analysis of technology-based interventions in youth (telemedicine or digital technology mHealth tools) found only small effects on pediatric obesity, with a standardized difference in weight outcomes of only −0.13 and 79% of included studies not demonstrating a significant difference between treatment and comparator groups.[51]
- A systematic review and meta-analysis of RCTs demonstrated that lifestyle interventions did prevent

cumulative weight gain among nonobese adults (−1.15 kg [95% CI, −1.50 to −0.80]); however, further study is needed to determine the feasibility for implementation and cost-effectiveness for these programs.[52]
- Studies have shown that even in the same BMI category, different metabolic phenotypes exist such as individuals with obesity with normal cardiometabolic characteristics designated as MHO and normal-weight individuals with abnormal cardiometabolic characteristics designated as having normal-weight obesity, and those different phenotypes are associated with CVD risk differently.[53–55] So, within the same BMI level, interventional focus should prioritize those with unfavorable metabolic risk profiles.

## Obesity Treatment

### *Diet and Surgery*

- A meta-analysis of 54 RCTs with >30 000 participants with obesity found that diets for the intention of weight reduction, usually low in total fat and saturated fat with or without exercise advice, were associated with a reduction in all-cause mortality (RR, 0.82 [95% CI, 0.71–0.95]) but no statistically significant reduction in CVD mortality or CVD events.[56]
- A systematic review of 122 RCTs and 2 observational studies indicated that behavior-based weight loss interventions conferred modest but significantly greater weight loss at 12 to 18 months (−2.39 kg [95% CI, −2.86 to −1.93]) and less weight regain (−1.59 kg [95% CI, −2.38 to −0.79]) than control groups.[57]
- A subanalysis from the Look AHEAD trial demonstrated that participants (with baseline BMI ≥25 kg/m$^2$) in the intensive lifestyle intervention group who lost at least 10% of their body weight had a 20% lower risk for a cardiovascular event over a 10-year follow-up (HR, 0.80 [95% CI, 0.65–0.99]) compared with those who gained or lost ≤2% body weight.[58]
- Modern bariatric surgery procedures have strong evidence for efficacy and safety for individuals and should be considered in patients with BMI ≥40 kg/m$^2$ or ≥35 kg/m$^2$ if serious obesity-related comorbidities are present.[59] A more recent statement from the American Society of Metabolic and Bariatric Surgery updated its indications such that bariatric surgery is recommended for individuals with BMI ≥35 kg/m$^2$ regardless of the presence or severity of comorbidities and should be considered for individuals with BMI 30 to 35 kg/m$^2$ who have metabolic disease.[60] In addition, adjusting BMI thresholds among Asian individuals is recommended such that individuals with BMI ≥27.5 kg/m$^2$ be considered for bariatric surgery.
- One meta-analysis including studies with >10-year follow-up showed that gastric bypass conferred 57% excess weight loss, laparoscopic adjustable gastric band conferred 46%, and sleeve gastrectomy conferred 58%, but reoperations were common across all 3 procedures.[61]
- In 1 large meta-analysis of prospective controlled trials and matched control studies, bariatric surgery was associated with a lower rate of mortality (HR, 0.51 [95% CI, 0.48–0.54]) and longer life expectancy (median, 6.1 years) than usual care for obesity management. There were greater survival benefits among individuals with diabetes (HR for mortality, 0.41 [95% CI, 0.37–0.45]) than those without diabetes (HR, 0.71 [95% CI, 0.59–0.84]).[62]
- A meta-analysis of 39 observational studies with follow-up ranging from 2 to 24 years found that bariatric surgery was associated with reduced risk for all-cause mortality (HR, 0.55 [95% CI, 0.49–0.62]) and CVD mortality (HR, 0.59 [95% CI, 0.47–0.73]) compared with nonsurgical control subjects.[63] In addition, bariatric surgery was associated with reduced risk of HF (HR, 0.50 [95% CI, 0.38–0.66]), MI (HR, 0.58 [95% CI, 0.43–0.76]), and stroke (HR, 0.64 [95% CI, 0.53–0.77]), with a nonsignificant favorable trend for reduction in AF (HR, 0.82, [95% CI, 0.64–1.06]).

### *Pharmacotherapy*

- Metformin has weight-reduction effects. In a meta-analysis of 21 trials, metformin compared with control conferred a modest reduction in BMI overall with a WMD of −0.98 kg/m$^2$ (95% CI, −1.2 to −0.72), which was greater among individuals with simple obesity (WMD, −1.31 [95% CI, −2.07 to −0.54]) compared with those with obesity with type 2 diabetes (WMD, −1.00 [95% CI, −1.30 to −0.70]), although both groups were statistically significant.[64]
- The older FDA-approved antiobesity medications orlistat, naltrexone-bupropion, phentermine-topiramate, and liraglutide have been shown to confer a placebo-corrected weight reduction of ≈5% to 10%.[65]
- SGLT-2 inhibitor medications can confer modest weight loss.[66] In a recent meta-analysis of 116 RCTs, including patients with and without type 2 diabetes, SGLT-2 inhibitors conferred a mean weight reduction of −1.79 kg (95% CI, −1.93 to −1.66) compared with placebo. This effect was seen for all SGLT-2 inhibitor drugs and across diabetes status.[67]
- Among patients with type 2 diabetes, meta-analyses of trials have shown that all GLP1-RAs conferred weight loss, albeit with some differences among type and dose of GLP1-RAs.[68,69] In a 2017 meta-analysis, the greatest weight loss was with liraglutide (−1.96 kg [95% CI, −2.67 to −1.25]), followed

by twice-daily exenatide (−1.67 kg [95% CI, −2.29 to −1.05]), dulaglutide (−1.57 kg [95% CI, −2.48 to −0.66]), once-weekly exenatide (−1.49 kg [95% CI, −2.58 to −0.40]), and lixisenatide (−0.78 kg [95% CI, −1.48 to −0.09]).[68]

- More recently, GLP1-RAs have emerged as effective pharmacological options for weight loss with cardiovascular safety among patients with overweight/obesity with or without type 2 diabetes.[70–72] In the STEP 3 trial, semaglutide 2.4 mg/wk reduced weight from baseline by 10% more than placebo at 68 weeks in adults with overweight/obesity as an adjunct to a low-calorie diet and intensive behavioral therapy.[72] In the STEP 1 trial, among patients with overweight/obesity, semaglutide 2.4 mg/wk conferred 12.4% greater weight reduction, which is a treatment difference of −12.7 kg (28 lb) compared with placebo.[70] In both trials, there were more gastrointestinal side effects leading to discontinuation in the GLP1-RA–treated group.
- In another meta-analysis, greater weight loss compared with placebo was conferred by semaglutide 2.4 mg/wk and <2.4 mg/wk SC and liraglutide >1.8 mg/d SC than was seen with other types of GLP1-RAs.[73]
- Dual agonists of glucose-dependent insulinotropic peptide and glucagon-like peptide 1 are also emerging pharmacotherapies for weight loss. Tirzepatide, a dual glucose-dependent insulinotropic peptide/glucagon-like peptide 1 agonist, was studied in the SURMOUNT-1 trial of 2539 adult patients without type 2 diabetes who were obese (BMI ≥30 kg/m$^2$) or overweight (BMI ≥27 kg/m$^2$) with a history of weight-related comorbidities and showed that this drug achieved significant weight loss in a dose-dependent manner.[74] The highest dose of tirzepatide (15 mg) conferred 22.5% weight reduction with mean weight loss of 23.6 kg (52.0 lb) at 72 weeks compared with placebo.
- Semaglutide and liraglutide are approved by the FDA for long-term weight management in adults with overweight or obesity who had at least 1 weight-related condition such as type 2 diabetes, hypertension, or dyslipidemia, in conjunction with a reduced-calorie diet and increased PA.[75] Tirzepatide is currently under consideration for fast-track approval by the FDA for a weight management indication.
- It should be noted that GLP1-RAs are a treatment for weight management, not a cure. Weight regain is common after cessation of therapy.[76] In the STEP 1 trial, 1 year after the discontinuation of the subcutaneous semaglutide 2.4 mg/wk, participants regained two-thirds of their prior weight loss.
- GLP1-RA have also been evaluated for treatment of obesity-related conditions such as NAFLD. Among patients with type 2 diabetes and NAFLD, a meta-analysis showed that GLP1-RAs significantly reduced BMI (WMD, −1.57 kg/m$^2$ [95% CI, −2.72 to −0.39]), as well as WC and body weight.[77] Furthermore, in a meta-analysis, GLP1-RA treatment was associated with a significant reduction in percentage of liver fat content as assessed by magnetic resonance-based imaging (pooled WMD, −3.92% [95% CI, −6.27% to −1.56%]).[78]
- GLP1-RAs have also been evaluated for treatment in youth with obesity. In a meta-analysis of 9 studies including 574 children and adolescents with obesity, GLP1-RAs conferred modest reductions in BMI (WMD, −1.24 kg/m$^2$ [95% CI, −1.71 to 0.77]) and reductions in body weight (WMD, −1.50 kg [95% CI, −2.50 to −0.50]), showing efficacy and safety in youth with obesity.[79]
- It is notable that among patients with type 2 diabetes and obesity, GLP1-RAs also significantly reduce major adverse cardiovascular events (RR, 0.88 [95% CI, 0.81–0.96]).[80]
- Dedicated cardiovascular outcome trials for GLP1-RAs in individuals with overweight or obesity but without diabetes are ongoing. However, a recent meta-analysis of 9 RCTs of patients with overweight and obesity but without diabetes demonstrated that cardiovascular events were fewer in individuals treated with GLP1-RA compared with placebo (8.7% versus 11.2%; RR, 0.81 [95% CI, 0.70–0.92]).[81]

## Mortality

- In the SPRINT trial, there was a J-shaped relationship between BMI and mortality; however, this relationship was no longer statistically significant after adjustment for traditional CVD risk factors.[82]
- In contrast, a large meta-analysis of 230 cohort studies including >30 million individuals found a statistically significant J-shaped relationship of BMI with mortality, with both underweight and increasing BMI being associated with an increased risk of death.[83] The RR for mortality for a 5-unit increment in BMI was 1.04 (95% CI, 1.04–1.07) for all participants and 1.27 (95% CI, 1.21–1.33) for healthy nonsmokers. The lowest mortality rates were seen at a BMI of 23 to 24 kg/m$^2$ among never-smokers and at 20 to 22 kg/m$^2$ in cohort studies with longer durations of follow-up.[83]
- Another meta-analysis of 35 studies and 923 295 participants also found a J-shaped relationship of body fat with mortality, with the lowest mortality risk seen for body fat percent of 25% and fat mass of 20 kg. For every 10% increase in body fat percent, there was an 11% increase risk in all cause-mortality (HR, 1.11 [95% CI, 1.02-1.20]).[84]

- Being overweight or obese was associated with a 21% (RR, 1.21 [95% CI, 1.08–1.35]) and 52% (RR, 1.52 [95% CI, 1.31–1.77]) increased risk of SCD compared with being normal weight in a meta-analysis of >10 studies.[85]
- An analysis from the Organization for Economic Co-Operation and Development that examined the impact of obesity on morbidity, mortality, and health expenditure in 52 countries estimated that over the next 30 years (2020–2050) 3 million premature deaths globally will be attributed to overweight/obesity with a reduction in life expectancy by 2.7 years.[86]

## Complications of Obesity

### *Cardiovascular Disease*

- Obesity is associated with increased risk of adverse cardiovascular outcomes. A recent umbrella review examined 12 systematic reviews including 53 meta-analyses, >500 cohort studies, and 12 mendelian randomization studies.[87] This study found that for every 5–kg/m$^2$ increase in measured BMI, the RR was 1.07 (95% CI, 1.02–1.12) for stroke, 1.15 (95% CI, 1.12–1.20) for CHD, 1.23 (95% CI, 1.17–1.30) for AF, 1.41 (95% CI, 1.32–1.50) for HF, and 1.49 (95% CI, 1.40–1.60) for hypertension.[87] Mendelian randomization analyses suggest that obesity is causally related to CVD: for each 5–kg/m$^2$ increase in genetically determined BMI, the RR was 1.19 (95% CI, 1.03–1.37) for CHD, 1.23 (95% CI, 1.13–1.33) for PAD, 1.64 (95% CI, 1.47–1.82) for hypertension, and 1.92 (95% CI, 1.12–3.30) for HF, but no association with stroke was seen.
- In an analysis pooling data from 10 large US prospective cohorts, lifetime risks for incident CVD were higher in middle-aged adults with overweight and obesity compared with individuals with normal weight.[88] The HR for incident CVD in males was 1.21 (95% CI, 1.14–1.28) for overweight, 1.67 (95% CI, 1.55–1.79) for obesity, and 3.14 (95% CI, 2.48–3.07) for morbid obesity. The HR for incident CVD in females was 1.32 (95% CI, 1.24–1.40) for overweight. 1.85 (95% CI, 1.72–1.99) for obesity, and 2.53 (95% CI, 2.20–2.91) for morbid obesity. Although the overweight group had a longevity similar to that of the normal BMI group, an increased risk of developing CVD at an earlier age translates to a greater proportion of years lived with CVD morbidity.[88]

### *Coronary Heart Disease*

- Mendelian randomization studies suggest a causal role of obesity and CAD (OR, 1.49 [95% CI, 1.39–1.60]) per 1 SD of genetically predicted BMI, although this is accounted for in part by intermediate factors such as hypertension, lipids, and diabetes.[89] After accounting for these potential cardiovascular risk mediators, the OR for CAD per 1-SD increase in genetically predicted BMI was attenuated to 1.14 (95% CI, 1.04–1.26).
- In a meta-analysis pooling data from 1.8 million participants, each 5–kg/m$^2$ higher BMI was associated with a 27% increased risk for CHD (HR, 1.27 [95% CI, 1.23–1.31]) after adjustment for confounders.[90] Approximately half of the excess risk of CHD associated with overweight/obesity status was mediated by BP, cholesterol, and glucose.
- Among patients with CAD, fluctuations in body weight were associated with an increased risk of cardiovascular events and mortality that was independent of traditional CVD risk factors.[91] Among >9500 participants in the Treating to New Target trial, for the highest quintile of weight fluctuation compared with the lowest, there was a 64% greater risk of coronary events, 85% greater risk of cardiovascular events, 117% greater risk of MI, 136% greater risk of stroke, and 124% greater risk of death.[91]

### *Stroke*

- A meta-analysis including 4.4 million participants indicated a J-shaped relationship of BMI with stroke, with the nadir observed at a BMI of 23 to 24 kg/m$^2$.[92] The pooled RR for stroke was 1.10 (95% CI, 1.06–1.13) for each 5-unit increment in BMI.
- In another meta-analysis, the HR of incident stroke for each 5–kg/m$^2$ higher BMI was 1.18 (95% CI, 1.14–1.22) after adjustment for confounders.[90] Approximately three-quarters of the excess risk of CHD associated with overweight/obesity status was mediated by BP, cholesterol, and glucose.

### *Heart Failure*

- In a meta-analysis, a J-shaped relationship was noted between BMI and HF risk. Compared with normal weight, the OR for incident HF was 1.22 (95% CI, 0.95–1.58) for underweight, 1.11 (95% CI, 0.97–1.27) for overweight, 1.62 (95% CI, 1.32–1.99) for obesity, and 1.73 (95% CI, 1.30–2.21) for severe obesity.[93] In that same analysis, intentional weight loss with bariatric surgery was associated with improvement in measures of cardiac structure and function among patients with obesity with a reduction in left atrial size ($P$=0.02) and improvement in LV diastology ($P$<0.0001).[93]
- Data from the ARIC cohort showed that the association of severe obesity (BMI ≥35 kg/m$^2$) with incident HF was greater than for the other subtypes of CVD, including CHD and stroke (HR, 3.74 [95% CI, 3.24–4.31] for HF versus 2.00 [95% CI, 1.67–2.40] and 1.75 [95% CI, 1.40–2.20] for CHD and stroke, respectively) over a 23-year follow-up.[94]

- The stronger association of higher BMI with incident HF compared with other CVD subtypes was also noted in a pooled analysis across 10 cohorts. For males, compared with normal weight, the lifetime risk of HF was an HR of 1.22 (95% CI, 1.07–1.40) for overweight, 1.95 (95% CI, 1.68–2.27) for obesity, and 5.26 (95% CI, 3.65–7.57) for severe obesity. For females, the HR for HF was 1.37 (95% CI, 1.21–1.55) for overweight, 2.28 (95% CI, 2.00–2.60) for obesity, and 4.32 (95% CI, 3.39–5.19) for severe obesity.[88]
- Cumulative weight (ie, BMI-years) over a lifetime has a stronger association with incident HF. In an analysis from MESA, BMIs at 20 and 40 years of age were more strongly associated with increased risk of incident HF than BMI measured in mid to late adulthood (45–84 years of age). Even after accounting for present weight at later adulthood, higher BMI per 5 kg/m$^2$ (determined by self-reported weight) at 20 years of age was independently associated with an HR of incident HF of 1.27 (95% CI, 1.07–1.50), and at 40 years of age, the HR was 1.36 (95% CI, 1.18–1.57).[95]
- Regionality of fat distribution influences HF risk.[96] Visceral adipose tissue, but not subcutaneous adipose tissue, was associated with incident HFpEF in the MESA cohort. For each 1-SD increment in visceral adipose tissue, the HR was 2.24 (95% CI, 1.44–3.49), and for subcutaneous adipose tissue, the HR was 1.30 (95% CI, 0.79–2.12).[97]
- NAFLD, which is also strongly linked to obesity, is associated with incident HF with a 60% higher odds of incident HF according to a recent meta-analysis (OR, 1.60 [95% CI, 1.24–2.05]).[98]
- Despite the increased risk of incident HF associated with obesity, many studies have demonstrated an "obesity paradox" wherein the short-term outcomes of patients with HF and overweight or obesity are more favorable compared with outcomes of individuals with HF with normal BMI (<25 kg/m2). In one meta-analysis of patients with chronic HF, the risk of cardiovascular mortality (RR, 1.20 [95% CI, 1.01–1.43]) and hospitalization (RR, 1.19 [95% CI, 1.09–1.30)] was highest for patients with low BMI (<20 kg/m$^2$) and lowest for patients with overweight (BMI, 25–29.9 kg/m$^2$; RR, 0.79 [95% CI, 0.70–0.90] for cardiovascular mortality and RR, 0.92 [95% CI, 0.86–0.97] for hospitalizations), with a similar favorable (but not significant) trend also for better outcomes in patients with obesity, compared with patients with HF and normal weight (BMI, 20–24.9 kg/m$^2$).[99]

### *Atrial Fibrillation*

- Obesity is a strong risk factor for AF; it is associated with incident AF and persistent AF.[100] A mendelian randomization study supported a causal relationship between BMI and AF risk.[101] A BMI gene score per 1-unit increase conferred an HR of 1.15 (95% CI, 1.04–1.26) in an age- and sex-adjusted analysis, which was similar to the meta-analysis of observed BMI with an HR of 1.05 (95% CI, 1.04–1.06) for 1–kg/m$^2$ higher BMI.[101]
- In a large meta-analysis of 25 studies including >2 million participants, each 5-kg increase in weight was associated with a 28% greater risk of AF (RR, 1.28 [95% CI, 1.20–1.38]).[102] The association between BMI and AF was not linear, although there was a generally stronger association with AF with increasing BMI levels. However, even a BMI of 22.5 to 24.0 kg/m$^2$ (HR, 1.09 [95% CI, 1.04–1.13]) compared with 20 to 22.5 kg/m$^2$ (reference) also had an increased risk with greatest risk of AF for BMI ≥40 kg/m$^2$ (HR, 3.45 [95% CI, 2.56–4.64]).
- As demonstrated in a recent meta-analysis, among patients with a history of catheter ablation for AF, those who lost weight experienced a lower risk of recurrent AF than those who did not (RR, 0.35 [95% CI, 0.18–0.67]).[103] The reduced risk of AF after ablation was seen predominantly among patients who lost ≥10% of weight (RR, 0.18 [95% CI, 0.03–0.89]) but not for patients with <10% of weight loss (RR, 1.00 [95% CI, 0.51–1.96]). There was also a lower risk of recurrent AF among patients who lost weight before the ablation procedure.[103]
- For patients with overweight/obesity and AF, current guidelines recommend a ≥10% reduction in weight, a BMI <27 kg/m$^2$, and at least a 2-MET increase in PA. Bariatric surgery could be considered in appropriate candidates.[100]

### *COVID-19*

- Obesity is a risk factor for severe COVID-19 and COVID-19–associated mortality.[104] In a meta-analysis of 186 studies including >1.3 million patients, the RR of mortality in COVID-19 associated with obesity was 1.45 (95% CI, 1.31–1.61) compared with those with a BMI <30 kg/m$^2$ with an increased risk of death of 1.12 (95% CI, 1.08–1.18) for every 5–kg/m$^2$ increase in BMI. This relationship was J shaped with the lowest risk of COVID-19–associated mortality around a BMI of 22 to 24 kg/m$^2$.[105]
- In the AHA COVID-19 registry, obese patients were more likely to be hospitalized with COVID-19 than nonobese patients and had greater multivariable-adjusted risk for the composite outcome of in-hospital death or mechanical ventilation (OR for class 1, 2, and 3 obesity: 1.28 [95% CI, 1.09–1.51], 1.57 [95% CI, 1.29–1.91], and 1.80 [95% CI, 1.47–2.20], respectively). There was a significant interaction with age, with severe obesity being associated with a greater risk of in-hospital death only for

individuals ≤50 years of age (HR, 1.36 [95% CI, 1.01–1.84]).[106] Obese patients also had greater risk of VTE (HR, 1.81 [95% CI, 1.22–2.98]).
- The STOP-COVID registry of 5133 patients admitted to critical care units with COVID-19 during March to July 2020 found that CVD risk factors rather than preexisting CVD were the major contributors to 28-day CVD events and mortality, with BMI ranking second (only after age) as the strongest predictor of risk.[107]

### *Complications in Youth*

- Overweight and obesity in youth frequently track into adulthood. In a meta-analysis including >200 000 participants, children and adolescents with obesity were ≈5 times more likely to have obesity in adulthood. Approximately 55% of children with obesity will have obesity in adolescence, and ≈80% of adolescents with obesity will still have obesity in adulthood, with ≈70% remaining obese after 30 years of age.[17]
- In an NHANES analysis, obesity in youth (3–19 years of age) was associated with increased prevalence of cardiometabolic risk factors, including greater SBP and DBP, lower HDL-C, and higher levels of triglycerides and HbA1c, particularly in males.[108]
- Childhood obesity is associated with cardiometabolic risk factors in adulthood such as BP elevation and dyslipidemia.[109] In a meta-analysis, high BMI in childhood was associated with an increased risk of diabetes (OR, 1.70 [95% CI, 1.30–2.22]) and CHD (1.20 [95% CI, 1.10–1.31]) in adulthood.[110] However, only 31% of later-life adulthood diabetes and 22% of adulthood hypertension and CHD occurred in children ≥12 years of age who were overweight or obese.
- In another meta-analysis of 22 studies including >5 million youth 2 to 19 years of age, childhood and adolescent BMI per 1-SD increment conferred a 12% increased risk of CHD in adulthood (HR, 1.12 [95% CI, 1.01–1.25]).[111] The associations did not change significantly after adjustment for SES or differ by sex.
- In another analysis using longitudinal data from 2.3 million adolescents 16 to 19 years of age who were followed up for 40 years, overweight status and obesity status were strongly associated with increased cardiovascular mortality in adulthood. The HRs for CHD mortality and CVD mortality were 4.9 (95% CI, 3.9–6.1) and 3.5 (95% CI, 2.9–4.1) for BMIs ≥95th percentile compared with the 5th to 24th age-sex BMI percentile, respectively, after adjustment for sex, age, birth year, and sociodemographic characteristics.[112] There was also a graded increase in CHD and CVD deaths for BMIs in the 50th to 74th, 75th to 84th, and 85th to 94th percentiles, which includes BMI percentiles within a normal acceptable range.[112] For example, for CHD deaths, the HRs were 1.11 (95% CI, 0.94–1.31), 1.49 (95% CI, 1.27–1.76), 2.17 (95% CI, 1.78–2.64), and 3.02 (95%, CI, 2.50–3.65), for BMIs in the 25th to 49th, 50th to 74th, 75th to 84th, and 85th to 94th percentiles, respectively, compared with the 5th to 24th percentile (reference group).
- Elevated BMI is a risk factor for incident hypertension among adolescents. The HPPCA in Suzhou, China, examined the BMI and blood pressures at least 4 times between the years 2012 to 2020 for 46 788 adolescents 12 to 17 years of age.[113] The authors found that compared with a medium BMI increase, a smaller BMI increase was associated with lower odds for developing incident adolescent hypertension (OR, 0.54 [95% CI, 0.39–0.75] and 0.66 [95% CI, 0.48–0.90] for males and females, respectively), whereas the high and highest BMI increase groups were associated with increased odds for hypertension (OR, 1.90 [95% CI, 1.44–2.51] and 2.89 [95% CI, 1.90–4.39] for males and 2.30 [95% CI, 1.72–3.09] and 4.71 [95% CI, 3.06–7.26] for females).

## Health Care Use and Cost

- Adjusted to 2019 US dollars, a study using data from MEPS, a nationally representative US sample, and controlling for confounders estimated that obesity was associated with $1861 (95% CI, $1656–$2053) in excess costs per person annually among individuals with obesity compared with individuals with normal weight.[114] Severe obesity was associated with excess annual costs of $3097 (95% CI, $2777–$3413) per person among adults. Each 1-unit increase in BMI >30 kg/m$^2$ was associated with an additional $253 (95% CI, $167–$347) cost per year per person.
- In that same MEPS analysis, obesity in children was associated with $116 (95% CI, $14–$201) in excess costs per child and $1.32 billion in medical spending with severe obesity costing $310 (95% CI, $124–$474) more per child.[114]
- In that same MEPS analysis, medical expenditures associated with higher BMI were greater among females.[114] There was a J-shaped relationship between medical expenditures and BMI with the lowest expenditures seen at a BMI of 20.5 kg/m$^2$ for adult females and 23.5 kg/m$^2$ for adult males.[114]
- In another analysis, it was established that the total direct medical cost attributed to obesity for noninstitutionalized adults in the United States was $260.0 billion in 2016, more than double that of 2001 ($124.2 billion).[115]

## Global Burden of Disease

***(See Tables 6-4 and 6-5 and Chart 6-4)***

- According to the GBD Study, the global age-standardized prevalence of obesity (BMI ≥30 kg/m$^2$) tripled between 1980 and 2019, increasing from 4.6% to 14.0%.[116] Throughout this time period, females have consistently had a higher prevalence of obesity than males.
- The World Obesity Federation's 2023 Obesity Atlas has estimated that more than half of the world's population (51%), or >4 billion individuals, will be either overweight or obese by 2035, and among the total population, 1 in 4 people, or nearly 2 billion individuals, will have obesity.[117]
- Globally, for adults ≥20 years of age, the proportion with obesity is estimated to increase from 14% (347 million) in males and 18% (466 million) in females in 2020 to 23% of males (690 million) and 27% of females (842 million) by 2035.[117]
- Globally, childhood obesity is estimated to double by 2035. For youth 5 to 19 years of age, the prevalence of obesity (+2 SD above WHO growth reference median) is estimated to reach 20% of males (208 million) and 18% of females (175 million) by 2035, up from 10% and 8% of males and females in the year 2020.[117] Obesity rates are rising more rapidly in youth than adults.
- Thirty-nine million children <5 years of age were overweight or obese in 2020 globally.[118]
- The prevalence of obesity is increasing more rapidly in lower-income countries. Of the 10 countries expected to experience the greatest increases in obesity for both adults and youth by 2035, 9 of 10 countries are of low or lower to middle income, and all are from either Africa or Asia.[117]
- There is an ≈10-fold difference in death rates resulting from obesity across the world, ranging from <5% in low-income countries such as sub-Saharan Africa to 8% to 10% in high-income countries such as Western Europe, East Asia, Asia Pacific, South Asia, and Australasia, with the highest obesity-related death rates ≥15% in middle-income countries such as Eastern Europe, Central Asia, Latin American, and North Africa. The higher death rates attributable to obesity in middle-income countries likely stem from having not only a high prevalence of obesity but also poorer health and health care infrastructure relative to high-income countries that have similarly high levels of obesity.[119]
- Globally, the GBD Study 2021 reported that elevated BMI ranked 7 (ie, in the top 10) of modifiable risk factors attributable to the burden of CVD, accounting for 95 million (95% CI, 1.12–2.91 million) deaths attributable to CVD and 3.7 million (95% CI, 1.97–5.49 million) deaths resulting from any cause.[120] That same year (2021), the DALYs from all causes attributable to high BMI were 1560 per 100 000 (95% CI, 711–2380 per 100 000).
- Data from the GBD Study indicated that obesity (≥25 kg/m$^2$)-related DALYs were rising at a rate of 0.48% annually from 2000 to 2019 (Table 6-4) and were predicted to increase by 39.8% between the years 2020 and 2030. The highest obesity-related DALYS were observed in Eastern Mediterranean and middle-SDI countries.[121] High-SDI countries had the lowest obesity-related death rate (Table 6-4).
- Based on 204 countries and territories in 2021, age-standardized mortality rates attributable to high BMI were lowest in high-income Asia Pacific and highest in southern sub-Saharan Africa, North Africa and the Middle East, and Oceania. (Chart 6-4).[122] Globally, high BMI was attributed to 3.69 (95% UI, 1.97–5.63) million deaths in 2021, a change of 160.97% (95% UI, 144.04%–176.20%) compared with 1990 (Table 6-5).
- Although the rate of increase in obesity prevalence seems to be declining in most high-income counties, the prevalence rate continues to rise in many low- and middle-income countries.[27,123] Data from the Non-Communicable Disease Risk Factor Collaboration reported that increases in BMI in rural areas accounted for >55% of the global rise in mean BMI from 1985 to 2017 and >80% of the rise in some low- and middle-income regions.[124] These data challenge the notion that urbanization is responsible for the obesity epidemic and call attention to the need for improvement in prevention strategies and CVH in rural areas.
- Overweight and obesity contribute to significant economic costs globally. A recent analysis estimated that the economic impact of overweight and obesity in 2019 across 161 countries was 2.2% of global gross domestic product.[125] Furthermore, if these trends continued at same rate, the economic impact of overweight and obesity is estimated to rise to 3.3% of global gross domestic product by 2060, with the largest increases being concentrated in lower-resource countries.
- In a similar analysis, the World Obesity Federation's 2023 Obesity Atlas estimated that the economic impact of an elevated BMI could reach as much as $4.32 trillion annually by 2035, which is ≈3% of the gross domestic product, an increase from $1.96 trillion or 2.4% of global gross domestic product in 2020.[117]

**Table 6-1. Prevalence of Children and Adolescents 2 to 19 Years of Age With Obesity, by Demographic Characteristics: United States, 2017 to March 2020**

| Characteristic | Both sexes | | Males | | Females | |
|---|---|---|---|---|---|---|
| | Sample size, n | Prevalence percentage (95% CI) | Sample size, n | Prevalence percentage (95% CI) | Sample size, n | Prevalence percentage (95% CI) |
| Total | 4749 | 19.7 (17.9–21.6) | 2410 | 20.9 (18.9–22.9) | 2339 | 18.5 (16.3–21.0) |
| Age group, y | | | | | | |
| 2–5 | 1141 | 12.7 (10.8–14.8) | 566 | 13.6 (10.8–16.8) | 575 | 11.8 (9.3–14.8) |
| 6–11 | 1765 | 20.7 (17.9–23.7) | 894 | 22.9 (19.5–26.5) | 871 | 18.5 (15.2–22.1) |
| 12–19 | 1843 | 22.2 (19.7–24.8) | 950 | 22.6 (19.7–25.7) | 893 | 21.7 (18.1–25.7) |
| Race and ethnicity | | | | | | |
| NH White | 1471 | 16.6 (13.7–19.8) | 743 | 17.6 (14.8–20.7) | 728 | 15.4 (11.2–20.5) |
| NH Black | 1270 | 24.8 (21.6–28.1) | 662 | 18.8 (15.9–22.1) | 608 | 30.8 (26.0–35.8) |
| NH Asian | 420 | 9.0 (6.5–12.2) | 208 | 13.1 (8.8–18.4) | 212 | 5.2 (2.3–9.9) |
| Hispanic | 1143 | 26.2 (22.4–30.2) | 562 | 29.3 (23.1–36.0) | 581 | 23.0 (19.6–26.6) |
| Family income relative to FPL, % | | | | | | |
| ≤130 | 1748 | 25.8 (22.8–29.1) | 864 | 26.4 (22.4–30.8) | 884 | 25.2 (22.3–28.3) |
| 130–350 | 1514 | 21.2 (18.5–24.0) | 789 | 20.7 (17.6–24.1) | 725 | 21.7 (18.3–25.3) |
| >350 | 956 | 11.5 (8.9–14.5) | 471 | 15.1 (11.1–19.8) | 485 | 8.2 (5.0–12.5) |

Obesity is defined as a body mass index of greater than or equal to the age- and sex-specific 95th percentile of the 2000 Centers for Disease Control and Prevention growth charts. Children and adolescents were included and categorized into age categories based on age at examination in months. Pregnant females were excluded from the analysis.

FPL indicates federal poverty level; and NH, non-Hispanic.

Source: Adapted from Stierman et al[10] using National Health and Nutrition Examination Survey.[126]

**Table 6-2. Prevalence of Adults ≥20 Years of Age With Obesity, by Demographic Characteristics: United States, 2017 to March 2020**

| Characteristic | Both sexes | | Males | | Females | |
|---|---|---|---|---|---|---|
| | Sample size, n | Prevalence percentage (95% CI) | Sample size, n | Prevalence percentage (95% CI) | Sample size, n | Prevalence percentage (95% CI) |
| Total (age adjusted) | 8295 | 41.9 (39.4–44.3) | 4051 | 41.8 (37.7–45.9) | 4244 | 41.8 (39.3–44.4) |
| Total age (crude) | 8295 | 41.9 (39.4–44.3) | 4051 | 41.6 (37.4–45.8) | 4244 | 42.1 (39.6–44.8) |
| Age group, y | | | | | | |
| 20–39 | 2489 | 39.8 (35.3–44.3) | 1177 | 39.9 (33.1–47.0) | 1312 | 39.6 (34.9–44.3) |
| 40–59 | 2765 | 44.3 (41.3–47.4) | 1320 | 45.9 (41.0–50.9) | 1445 | 42.8 (38.7–47.1) |
| ≥60 | 3041 | 41.5 (38.4–44.7) | 1554 | 38.4 (32.9–44.1) | 1487 | 44.2 (40.5–47.9) |
| Race and ethnicity | | | | | | |
| NH White | 2866 | 41.4 (37.9–44.9) | 1432 | 43.1 (37.4–48.9) | 1434 | 39.6 (36.2–43.0) |
| NH Black | 2213 | 49.9 (47.2–52.6) | 1058 | 40.4 (36.3–44.6) | 1155 | 57.9 (54.0–61.7) |
| NH Asian | 1014 | 16.1 (13.6–18.9) | 466 | 17.6 (13.7–22.2) | 548 | 14.5 (11.4–18.1) |
| Hispanic | 1806 | 45.6 (42.9–48.2) | 880 | 45.2 (41.7–48.8) | 926 | 45.7 (42.4–49.1) |
| Family Income relative to FPL, % | | | | | | |
| ≤130 | 2019 | 43.9 (41.7–46.1) | 892 | 38.6 (33.6–43.8) | 1127 | 47.9 (44.0–51.7) |
| 130–350 | 2815 | 46.5 (43.6–49.4) | 1400 | 43.9 (40.5–47.3) | 1415 | 48.8 (44.5–53.0) |
| >350 | 2312 | 39.0 (34.2–43.9) | 1189 | 42.4 (34.9–50.2) | 1123 | 35.1 (31.1–39.3) |
| Education | | | | | | |
| Less than high school diploma | 1538 | 40.1 (36.5–43.8) | 803 | 35.3 (30.4–40.6) | 735 | 45.3 (41.0–49.7) |
| High school diploma or some college | 4709 | 46.4 (44.0–48.9) | 2259 | 45.9 (41.9–50.0) | 2450 | 46.8 (43.9–49.8) |
| College degree or above | 2037 | 34.2 (30.1–38.5) | 984 | 36.3 (29.0–44.1) | 1053 | 32.2 (28.5–36.1) |

Obesity is defined as a body mass index ≥30 kg/m$^2$. Except when reported as crude estimates, estimates were age adjusted by the direct method to the projected US census 2000 population using the age groups 20 to 39, 40 to 59, and ≥60 years. Statistical comparisons were not performed on crude estimates. Pregnant women were excluded from the analysis.

FPL indicates federal poverty level; and NH, non-Hispanic.

Source: Adapted from Stierman et al[10] using National Health and Nutrition Examination Survey.[126]

**Table 6-3. Prevalence of Adults ≥20 Years of Age With Severe Obesity, by Demographic Characteristics, United States, 2017 to March 2020**

| Characteristic | Both sexes | | Males | | Females | |
|---|---|---|---|---|---|---|
| | Sample size, n | Prevalence percentage (95% CI) | Sample size, n | Prevalence percentage (95% CI) | Sample size, n | Prevalence percentage (95% CI) |
| Total (age adjusted) | 8295 | 9.2 (8.0–10.6) | 4051 | 6.6 (5.3–8.1) | 4244 | 11.7 (10.0–13.7) |
| Total age (crude) | 8295 | 9.0 (7.8–10.3) | 4051 | 6.4 (5.1–8.0) | 4244 | 11.4 (9.7–13.3) |
| Age group, y | | | | | | |
| 20–39 | 2489 | 9.7 (7.7–12.0) | 1177 | 7.0 (4.7–10.1) | 1312 | 12.4 (9.8–15.3) |
| 40–59 | 2765 | 10.7 (8.9–12.8) | 1320 | 8.1 (5.5–11.5) | 1445 | 13.2 (10.0–16.9) |
| ≥60 | 3041 | 6.1 (5.2–7.2) | 1554 | 3.5 (2.6–4.5) | 1487 | 8.3 (6.8–10.0) |
| Race and ethnicity | | | | | | |
| NH White | 2866 | 9.5 (7.9–11.3) | 1432 | 6.8 (5.1–8.9) | 1434 | 12.0 (9.8–14.6) |
| NH Black | 2213 | 14.0 (11.9–16.3) | 1058 | 7.9 (6.3–9.7) | 1155 | 19.1 (16.0–22.6) |
| NH Asian | 1014 | 1.8 (1.0–2.8) | 466 | 2.4 (0.9–5.1) | 548 | 1.1 (0.2–3.3) |
| Hispanic | 1806 | 7.4 (6.1–8.9) | 880 | 6.0 (4.2–8.4) | 926 | 8.8 (7.0–10.9) |
| Family income relative to FPL, % | | | | | | |
| ≤130 | 2019 | 10.9 (8.2–13.9) | 892 | 7.4 (5.3–9.9) | 1127 | 13.5 (10.0–17.7) |
| 130–350 | 2815 | 11.8 (10.1–13.6) | 1400 | 8.8 (7.1–10.8) | 1415 | 14.5 (11.8–17.4) |
| >350 | 2312 | 6.9 (5.4–8.6) | 1189 | 4.6 (2.9–6.8) | 1123 | 9.5 (7.0–12.4) |
| Education | | | | | | |
| Less than high school diploma | 1538 | 7.6 (5.8–9.6) | 803 | 3.3 (2.0–5.1) | 735 | 12.2 (9.6–15.3) |
| High school diploma or some college | 4709 | 11.3 (10.3–12.4) | 2259 | 9.0 (7.2–11.0) | 2450 | 13.5 (11.6–15.7) |
| College degree or above | 2037 | 6.1 (4.3–8.5) | 984 | 3.3 (1.9–5.4) | 1053 | 8.5 (5.7–12.2) |

Severe obesity is defined as a body mass index ≥40 kg/m$^2$. Except when reported as crude estimates, estimates were age adjusted by the direct method to the projected US census 2000 population using the age groups 20 to 39, 40 to 59, and ≥60 years. Statistical comparisons were not performed on crude estimates. Pregnant women were excluded from the analysis.

FPL indicates federal poverty level; and NH, non-Hispanic.

Source: Adapted from Stierman et al[10] using National Health and Nutrition Examination Survey.[126]

**Table 6-4. DALYs and Mortality of Individuals With Obesity From the GBD Study 2019**

| | DALYs | | | | Mortality | | | |
|---|---|---|---|---|---|---|---|---|
| | n (Year 2019) | Age-standardized DALYs per 100 000 in 2019 | Annual percentage change 2000–2019 | *P* value | n (Year 2019) | Age-standardized death rate per 100 000 in 2019 | Annual percentage change 2000–2019 | *P* value |
| Overall | 160 265 357 (105 969 034–218 870 439) | 1933 (1277–2640) | 0.48 (0.38–0.58 | <0.001 | 5 019 360 (3 223 364–7 110 736) | 62.59 (39.92–89.13) | −0.01 (−0.13 to 0.11) | 0.881 |
| Sex | | | | | | | | |
| Male | 82 840 928 (52 774 866–115 149 374) | 2070 (1312–2889) | 0.74 (0.63–0.85) | <0.001 | 2 477 387 (1 515 677–3 568 860) | 66.55 (39.76–97.21) | 0.33 (0.15–0.52) | <0.001 |
| Female | 77 424 429 (53 176 344–104 577 664) | 1790 (1229–2417) | 0.25 (0.17–0.34) | <0.001 | 2 541 973 (1 683 590–3 561 055) | 58.14 (38.53–81.39) | −0.27 (−0.38 to −0.16) | <0.001 |
| WHO region | | | | | | | | |
| Africa | 12 324 913 (8 371 480–16 578 508) | 2221 (1486–3025) | 0.87 (0.80–0.95) | <0.001 | 361 539 (237 293–499 448) | 79.20 (50.92–111.98) | 0.86 (0.78–0.94) | <0.001 |
| Eastern Mediterranean | 17 923 202 (12 584 59–23 768 056) | 3721 (2591–4954) | 1.04 (0.92–1.15) | <0.001 | 522 392 (352 647–707 166) | 130.97 (87.38–179.78) | 1.01 (0.87–1.14) | <0.001 |

(*Continued*)

**Table 6-4. Continued**

| | DALYs | | | | Mortality | | | |
|---|---|---|---|---|---|---|---|---|
| | n (Year 2019) | Age-standardized DALYs per 100 000 in 2019 | Annual percentage change 2000–2019 | *P* value | n (Year 2019) | Age-standardized death rate per 100 000 in 2019 | Annual percentage change 2000–2019 | *P* value |
| Europe | 32 474 360 (22 183 037–43 473 404) | 2206 (1519–2946) | −0.90 (−1.10 to −0.70) | <0.001 | 1 243 937 (810 492–1 717 794) | 75.41 (49.74–103.02) | −1.16 (−1.41 to−0.89) | <0.001 |
| Region of Americas | 30 395 450 (21 207 720–39 622 411) | 2457 (1725–3200) | 0.17 (0.09–0.26) | <0.001 | 940 265 (625 116–1 268 476) | 72.83 (48.62–97.90) | −0.27 (−0.44 to −0.10) | 0.002 |
| South-East Asia | 33 558 095 (20 816 783–46 899 343) | 1786 (1096–2513) | 2.63 (2.48–2.77) | <0.001 | 918 795 (550 880–1 327 038) | 53.60 (31.54–78.85) | 2.37 (1.93–2.81) | <0.001 |
| Western Pacific | 33 058 032 (16 759 032–52 761 895) | 1229 (624–1963) | 1.22 (0.98–1.46) | <0.001 | 1 015 716 (483 041–1 701 367) | 38.38 (18.10–64.89) | 0.87 (0.48–1.26) | <0.001 |
| SDI | | | | | | | | |
| High | 26 809 080 (18 213 631–36 348 663) | 1631 (1121–2198) | −0.14 (−0.19 to −0.09) | <0.001 | 901 712 (573 462–1 289 616) | 45.65 (29.76–63.76) | −1.02 (−1.20 to −0.84) | <0.001 |
| High-middle | 39 587 645 (26 141 026–54 009 607) | 1982 (1312–2706) | −0.91 (−1.09 to −0.73) | <0.001 | 1 376 628 (877 166–1 953 869) | 69.14 (44.00–98.24) | −1.21 (−1.44 to −0.99) | <0.001 |
| Middle | 55 465 889 (36 710 764–75 810 218) | 2119 (1388–2920) | 1.26 (1.18–1.35) | <0.001 | 1 647 281 (1 051 542–2 333 137) | 68.92 (43.02–99.26) | 1.05 (0.92–1.19) | <0.001 |
| Low-middle | 28 007 122 (17 469 919–39 227 162) | 1892 (1174–2682) | 2.41 (2.18–2.63) | <0.001 | 804 748 (490 930–1 158 654) | 60.34 (36.27–88.37) | 2.07 (1.79–2.36) | <0.001 |
| Low | 10 276 830 (6 088 926–14 897 027) | 1698 (990–2492) | 1.87 (1.79–1.94) | <0.001 | 285 468 (162 714–429 330) | 55.55 (31.38–85.09) | 1.68 (1.59–1.78) | <0.001 |

Data in the parentheses are 95% uncertainty intervals.

DALY indicates disability-adjusted life-year; GBD, Global Burden of Disease; SDI, sociodemographic index; and WHO World Health Organization.

Source: Reprinted from Chong et al.[121] Copyright 2023 The Authors. Published by Elsevier Ltd. This is an open access article under the terms of the Creative Commons CC BY-NC-ND License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

**Table 6-5. Deaths Caused by High BMI Worldwide, by Sex, 2021**

| | Deaths | | |
|---|---|---|---|
| | Both sexes (95% UI) | Male (95% UI) | Female (95% UI) |
| Total No. of deaths (millions), 2021 | 3.69 (1.97 to 5.63) | 1.68 (0.91 to 2.55) | 2.01 (1.08 to 3.05) |
| Percent change in total number, 1990–2021, % | 160.97 (144.04 to 176.20) | 177.92 (156.74 to 198.40) | 148.33 (129.99 to 171.26) |
| Percent change in total number, 2010 to 2021, % | 45.65 (38.36 to 52.62) | 47.07 (39.55 to 55.76) | 44.48 (37.26 to 51.94) |
| Mortality rate per 100 000, age standardized, 2021 | 43.61 (23.35 to 66.42) | 43.70 (23.72 to 66.34) | 43.03 (23.03 to 65.16) |
| Percent change in rate, age standardized, 1990–2021, % | 8.13 (1.02 to 14.82) | 14.47 (5.95 to 22.77) | 4.42 (−3.71 to 13.82) |
| Percent change in rate, age standardized, 2010 to 2021, % | 2.98 (−2.18 to 8.10) | 4.51 (−1.12 to 10.32) | 2.19 (−3.30 to 7.23) |
| PAF, all ages, 2021, % | 5.35 (2.80 to 7.89) | 4.39 (2.32 to 6.41) | 6.53 (3.42 to 9.71) |
| Percent change in PAF, all ages, 1990–2021, % | 74.88 (65.66 to 84.10) | 80.48 (70.51 to 89.43) | 72.79 (62.03 to 84.89) |
| Percent change in PAF, all ages, 2010–2021, % | 11.81 (8.13 to 15.35) | 11.48 (7.68 to 15.28) | 12.65 (8.94 to 17.29) |

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

BMI indicates body mass index; GBD, Global Burden of Disease Study; PAF, population attributable fraction; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[127]

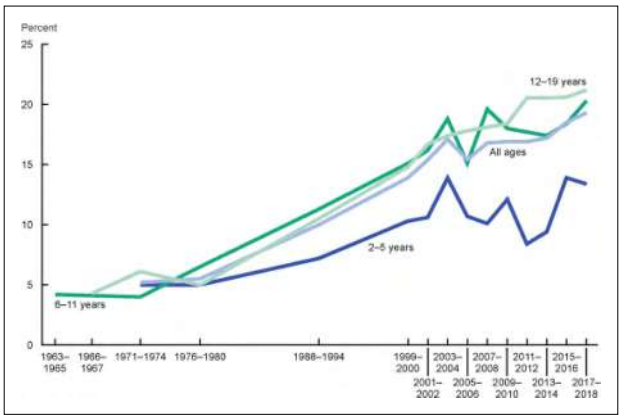



**Chart 6-1. Trends in obesity among children and adolescents 2 to 19 years of age, by age, United States, 1963 to 1965 through 2017 to 2018.**
Source: Reprinted from Fryar et al[4] using National Health and Nutrition Examination Survey.[126]

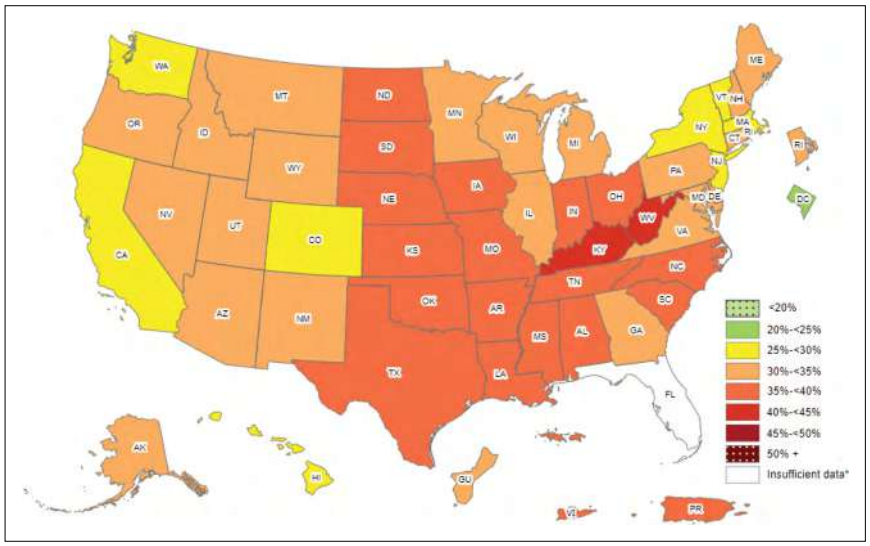



**Chart 6-2. Prevalence of self-reported obesity among US adults by state and territory, BRFSS, 2021.**
BRFSS indicates Behavioral Risk Factor Surveillance System.
Source: Reprinted from Centers for Disease Control and Prevention obesity prevalence map using BRFSS.[15,128]

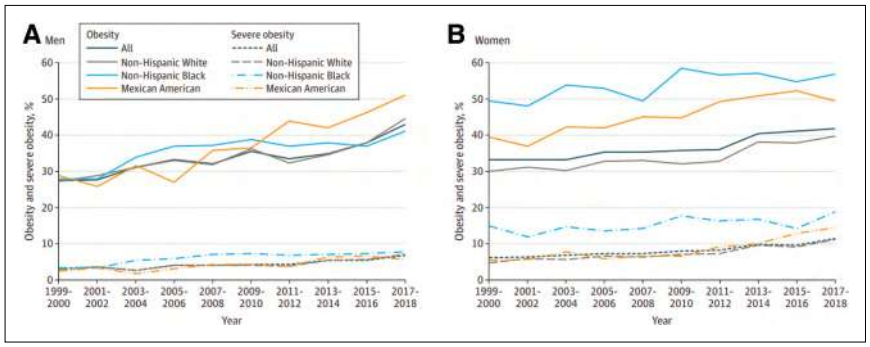



**Chart 6-3. Age-adjusted prevalence of obesity and severe obesity in US adults.**
**A**, Men. **B**, Women.
Source: Reproduced with permission from Ogden et al.[18] Copyright © 2020 American Medical Association. All rights reserved.

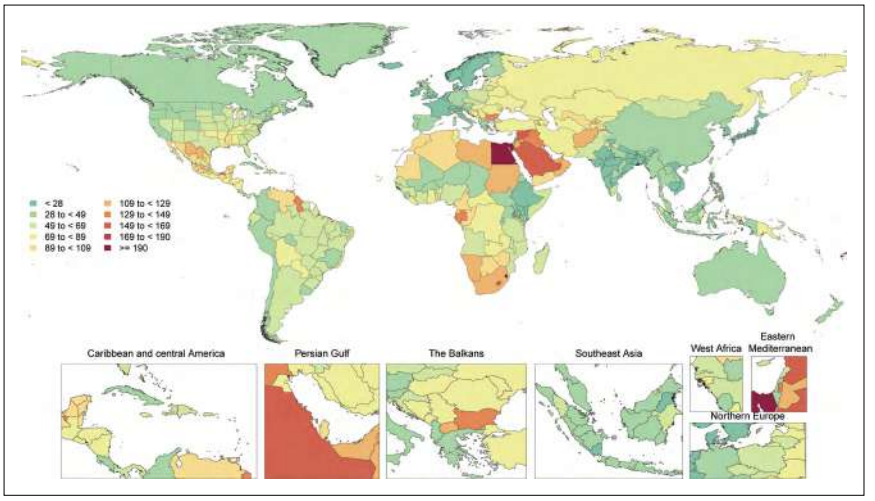



**Chart 6-4. Age-standardized global mortality rates attributable to high BMI per 100 000, both sexes, 2021.**
During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.
BMI indicates body mass index; and GBD, Global Burden of Disease.
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[127]

## REFERENCES


1. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity and severe obesity among adults: United States, 2017-2018. *NCHS Data Brief*. 2020:1–8.
2. Bianchettin RG, Lavie CJ, Lopez-Jimenez F. Challenges in cardiovascular evaluation and management of obese patients: JACC state-of-the-art review. *J Am Coll Cardiol*. 2023;81:490–504. doi: 10.1016/j.jacc.2022.11.031
3. Defining adult overweight & obesity. Accessed March 19, 2023. https://www.cdc.gov/obesity/adult/defining.html
4. Fryar CD, Carroll MD, Afful J. Health E-Stats: prevalence of overweight, obesity, and severe obesity among children and adolescents aged 2–19 years: United States, 1963–1965 through 2017–2018. Centers for Disease Control and Prevention, National Center for Health Statistics. 2020. Accessed October 17, 2023. https://cdc.gov/nchs/data/hestat/obesity-child-17-18/obesity-child.htm
5. Ross R, Neeland IJ, Yamashita S, Shai I, Seidell J, Magni P, Santos RD, Arsenault B, Cuevas A, Hu FB, et al. Waist circumference as a vital sign in clinical practice: a consensus statement from the IAS and ICCR Working Group on Visceral Obesity. *Nat Rev Endocrinol*. 2020;16:177–189. doi: 10.1038/s41574-019-0310-7
6. Lopez-Jimenez F, Almahmeed W, Bays H, Cuevas A, Di Angelantonio E, le Roux CW, Sattar N, Sun MC, Wittert G, Pinto FJ, et al. Obesity and cardiovascular disease: mechanistic insights and management strategies: a joint position paper by the World Heart Federation and World Obesity Federation. *Eur J Prev Cardiol*. 2022;29:2218–2237. doi: 10.1093/eurjpc/zwac187
7. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, Collins BS, Hilliard ME, Isaacs D, Johnson EL, et al; American Diabetes Association. 2: Classification and diagnosis of diabetes: Standards of Care in Diabetes–2023. *Diabetes Care*. 2023;46:S19–S40. doi: 10.2337/dc23-S002
8. Rao G, Powell-Wiley TM, Ancheta I, Hairston K, Kirley K, Lear SA, North KE, Palaniappan L, Rosal MC; on behalf of the American Heart Association Obesity Committee of the Council on Lifestyle and Cardiometabolic Health. Identification of obesity and cardiovascular risk in ethnically and racially diverse populations: a scientific statement from the American Heart Association [published correction appears in *Circulation*. 2015;132:e130]. *Circulation*. 2015;132:457–472. doi: 10.1161/CIR.0000000000000223
9. Caleyachetty R, Barber TM, Mohammed NI, Cappuccio FP, Hardy R, Mathur R, Banerjee A, Gill P. Ethnicity-specific BMI cutoffs for obesity based on type 2 diabetes risk in England: a population-based cohort study. *Lancet Diabetes Endocrinol*. 2021;9:419–426. doi: 10.1016/S2213-8587(21)00088-7
10. Stierman B, Afful J, Carroll MD, Chen TC, Davy O, Fink S, Fryar CD, Gu S, Hales CM, Hughes JP, et al. National Health and Nutrition Examination Survey 2017–March 2020 prepandemic data files: development of files and prevalence estimates for selected health outcomes: National Health Statistics Reports. Centers for Disease Control and Prevention. 2021. Accessed October 17, 2023. https://stacks.cdc.gov/view/cdc/106273
11. Martin CB, Stierman B, Yanovski JA, Hales CM, Sarafrazi N, Ogden CL. Body fat differences among US youth aged 8-19 by race and Hispanic origin, 2011-2018. *Pediatr Obes*. 2022;17:e12898. doi: 10.1111/ijpo.12898
12. DeBoer MD, Filipp SL, Gurka MJ. Geographical variation in the prevalence of obesity and metabolic syndrome among US adolescents. *Pediatr Obes*. 2019;14:e12483. doi: 10.1111/ijpo.12483
13. Bekelman TA, Dabelea D, Ganiban JM, Law A, McGovern Reilly A, Althoff KN, Mueller N, Camargo CA Jr, Duarte CS, Dunlop AL, et al; Program Collaborators for Environmental influences on Child Health Outcomes (ECHO). Regional and sociodemographic differences in average BMI among US children in the ECHO program. *Obesity (Silver Spring)*. 2021;29:2089–2099. doi: 10.1002/oby.23235
14. Ward ZJ, Bleich SN, Cradock AL, Barrett JL, Giles CM, Flax C, Long MW, Gortmaker SL. Projected U.S. state-level prevalence of adult obesity and severe obesity. *N Engl J Med*. 2019;381:2440–2450. doi: 10.1056/NEJMsa1909301
15. Centers for Disease Control and Prevention and National Center for Chronic Disease Prevention and Health Promotion. Behavioral Risk Factor Surveillance System (BRFSS): BRFSS prevalence & trends data. Accessed March 27, 2023. https://cdc.gov/brfss/brfssprevalence/
16. Unpublished NHLBI tabulation from the Behavioral Risk Factor Surveillance System (BRFSS) 2021. 2021. Accessed May 12, 2023. https://cdc.gov/obesity/data/prevalence-maps.html
17. Simmonds M, Llewellyn A, Owen CG, Woolacott N. Predicting adult obesity from childhood obesity: a systematic review and meta-analysis. *Obes Rev*. 2016;17:95–107. doi: 10.1111/obr.12334
18. Ogden CL, Fryar CD, Martin CB, Freedman DS, Carroll MD, Gu Q, Hales CM. Trends in obesity prevalence by race and Hispanic origin: 1999-2000 to 2017-2018. *JAMA*. 2020;324:1208–1210. doi: 10.1001/jama.2020.14590
19. Restrepo BJ. Obesity prevalence among U.S. adults during the COVID-19 pandemic. *Am J Prev Med*. 2022;63:102–106. doi: 10.1016/j.amepre.2022.01.012
20. Hales CM, Fryar CD, Carroll MD, Freedman DS, Aoki Y, Ogden CL. Differences in obesity prevalence by demographic characteristics and urbanization level among adults in the United States, 2013-2016. *JAMA*. 2018;319:2419–2429. doi: 10.1001/jama.2018.7270
21. Johnson JA 3rd, Johnson AM. Urban-rural differences in childhood and adolescent obesity in the United States: a systematic review and meta-analysis. *Child Obes*. 2015;11:233–241. doi: 10.1089/chi.2014.0085
22. Contreras DA, Martoccio TL, Brophy-Herb HE, Horodynski M, Peterson KE, Miller AL, Senehi N, Sturza J, Kaciroti N, Lumeng JC. Rural-urban differences in body mass index and obesity-related behaviors among low-income preschoolers. *J Public Health (Oxf)*. 2021;43:e637–e644. doi: 10.1093/pubmed/fdaa162
23. Javed Z, Valero-Elizondo J, Maqsood MH, Mahajan S, Taha MB, Patel KV, Sharma G, Hagan K, Blaha MJ, Blankstein R, et al. Social determinants of health and obesity: findings from a national study of US adults. *Obesity (Silver Spring)*. 2022;30:491–502. doi: 10.1002/oby.23336
24. Riveros-McKay F, Mistry V, Bounds R, Hendricks A, Keogh JM, Thomas H, Henning E, Corbin LJ, O'Rahilly S, Zeggini E, et al; Understanding Society Scientific Group. Genetic architecture of human thinness compared to severe obesity. *PLoS Genet*. 2019;15:e1007603. doi: 10.1371/journal.pgen.1007603

25. Herrera BM, Lindgren CM. The genetics of obesity. *Curr Diab Rep*. 2010;10:498–505. doi: 10.1007/s11892-010-0153-z
26. Kaur Y, de Souza RJ, Gibson WT, Meyre D. A systematic review of genetic syndromes with obesity. *Obes Rev*. 2017;18:603–634. doi: 10.1111/obr.12531
27. Loos RJF, Yeo GSH. The genetics of obesity: from discovery to biology. *Nat Rev Genet*. 2022;23:120–133. doi: 10.1038/s41576-021-00414-z
28. Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR, Powell C, Vedantam S, Buchkovich ML, Yang J, et al; LifeLines Cohort Study; ADIPOGen Consortium; AGEN-BMI Working Group; CARDIOGRAMplusC4D Consortium; CKDGen Consortium; GLGC; ICBP; MAGIC Investigators; MuTHER Consortium; MIGen Consortium; PAGE Consortium; ReproGen Consortium; GENIE Consortium; International Endogene Consortium. Genetic studies of body mass index yield new insights for obesity biology. *Nature*. 2015;518:197–206. doi: 10.1038/nature14177
29. Ng MCY, Graff M, Lu Y, Justice AE, Mudgal P, Liu CT, Young K, Yanek LR, Feitosa MF, Wojczynski MK, et al; Bone Mineral Density in Childhood Study (BMDCS) Group. Discovery and fine-mapping of adiposity loci using high density imputation of genome-wide association studies in individuals of African ancestry: African Ancestry Anthropometry Genetics Consortium. *PLoS Genet*. 2017;13:e1006719. doi: 10.1371/journal.pgen.1006719
30. Felix JF, Bradfield JP, Monnereau C, van der Valk RJ, Stergiakouli E, Chesi A, Gaillard R, Feenstra B, Thiering E, Kreiner-Moller E, et al; Bone Mineral Density in Childhood Study (BMDCS); Early Genetics and Lifecourse Epidemiology (EAGLE) Consortium. Genome-wide association analysis identifies three new susceptibility loci for childhood body mass index. *Hum Mol Genet*. 2016;25:389–403. doi: 10.1093/hmg/ddv472
31. Speakman JR. The "fat mass and obesity related" (*FTO*) gene: mechanisms of impact on obesity and energy balance. *Curr Obes Rep*. 2015;4:73–91. doi: 10.1007/s13679-015-0143-1
32. Loos RJ, Yeo GS. The bigger picture of *FTO*: the first GWAS-identified obesity gene. *Nat Rev Endocrinol*. 2014;10:51–61. doi: 10.1038/nrendo.2013.227
33. Cho YS, Go MJ, Kim YJ, Heo JY, Oh JH, Ban HJ, Yoon D, Lee MH, Kim DJ, Park M, et al. A large-scale genome-wide association study of Asian populations uncovers genetic factors influencing eight quantitative traits. *Nat Genet*. 2009;41:527–534. doi: 10.1038/ng.357
34. Wen W, Cho YS, Zheng W, Dorajoo R, Kato N, Qi L, Chen CH, Delahanty RJ, Okada Y, Tabara Y, et al; Genetic Investigation of ANthropometric Traits (GIANT) Consortium. Meta-analysis identifies common variants associated with body mass index in east Asians. *Nat Genet*. 2012;44:307–311. doi: 10.1038/ng.1087
35. Okada Y, Kubo M, Ohmiya H, Takahashi A, Kumasaka N, Hosono N, Maeda S, Wen W, Dorajoo R, Go MJ, et al; GIANT Consortium. Common variants at *CDKAL1* and *KLF9* are associated with body mass index in east Asian populations. *Nat Genet*. 2012;44:302–306. doi: 10.1038/ng.1086
36. Monda KL, Chen GK, Taylor KC, Palmer C, Edwards TL, Lange LA, Ng MC, Adeyemo AA, Allison MA, Bielak LF, et al; NABEC Consortium. A meta-analysis identifies new loci associated with body mass index in individuals of African ancestry. *Nat Genet*. 2013;45:690–696. doi: 10.1038/ng.2608
37. Akbari P, Gilani A, Sosina O, Kosmicki JA, Khrimian L, Fang YY, Persaud T, Garcia V, Sun D, Li A, et al; Regeneron Genetics Center; DiscovEHR Collaboration. Sequencing of 640,000 exomes identifies *GPR75* variants associated with protection from obesity. *Science*. 2021;373:eabf8683. doi: 10.1126/science.abf8683
38. Khera AV, Chaffin M, Wade KH, Zahid S, Brancale J, Xia R, Distefano M, Senol-Cosar O, Haas ME, Bick A, et al. Polygenic prediction of weight and obesity trajectories from birth to adulthood. *Cell*. 2019;177:587–596.e9. doi: 10.1016/j.cell.2019.03.028
39. Sulc J, Mounier N, Gunther F, Winkler T, Wood AR, Frayling TM, Heid IM, Robinson MR, Kutalik Z. Quantification of the overall contribution of gene-environment interaction for obesity-related traits. *Nat Commun*. 2020;11:1385. doi: 10.1038/s41467-020-15107-0
40. Ding Y, Hou K, Burch KS, Lapinska S, Prive F, Vilhjalmsson B, Sankararaman S, Pasaniuc B. Large uncertainty in individual polygenic risk score estimation impacts PRS-based risk stratification. *Nat Genet*. 2022;54:30–39. doi: 10.1038/s41588-021-00961-5
41. Sakaue S, Kanai M, Karjalainen J, Akiyama M, Kurki M, Matoba N, Takahashi A, Hirata M, Kubo M, Matsuda K, et al. Trans-biobank analysis with 676,000 individuals elucidates the association of polygenic risk scores of complex traits with human lifespan. *Nat Med*. 2020;26:542–548. doi: 10.1038/s41591-020-0785-8
42. He C, Zhang M, Li J, Wang Y, Chen L, Qi B, Wen J, Yang J, Lin S, Liu D, et al. Novel insights into the consequences of obesity: a phenotype-wide mendelian randomization study. *Eur J Hum Genet*. 2022;30:540–546. doi: 10.1038/s41431-021-00978-8
43. Valsesia A, Wang QP, Gheldof N, Carayol J, Ruffieux H, Clark T, Shenton V, Oyston LJ, Lefebvre G, Metairon S, et al. Genome-wide gene-based analyses of weight loss interventions identify a potential role for *NKX6.3* in metabolism. *Nat Commun*. 2019;10:540. doi: 10.1038/s41467-019-08492-8
44. Papandonatos GD, Pan Q, Pajewski NM, Delahanty LM, Peter I, Erar B, Ahmad S, Harden M, Chen L, Fontanillas P, et al; Diabetes Prevention Program and the Look AHEAD Research Groups. Genetic predisposition to weight loss and regain with lifestyle intervention: analyses from the Diabetes Prevention Program and the Look AHEAD Randomized Controlled Trials. *Diabetes*. 2015;64:4312–4321. doi: 10.2337/db15-0441
45. Lee WJ, Lim JE, Kang JO, Ha TW, Jung HU, Kim DJ, Baek EJ, Kim HK, Chung JY, Oh B. Smoking-interaction loci affect obesity traits: a gene-smoking stratified meta-analysis of 545,131 Europeans. *Lifestyle Genom*. 2022;15:87–97. doi: 10.1159/000525749
46. Kichaev G, Bhatia G, Loh PR, Gazal S, Burch K, Freund MK, Schoech A, Pasaniuc B, Price AL. Leveraging polygenic functional enrichment to improve GWAS power. *Am J Hum Genet*. 2019;104:65–75. doi: 10.1016/j.ajhg.2018.11.008
47. Liu M, Jiang Y, Wedow R, Li Y, Brazel DM, Chen F, Datta G, Davila-Velderrain J, McGuire D, Tian C, et al; 23andMe Research Team; HUNT All-In Psychiatry. Association studies of up to 1.2 million individuals yield new insights into the genetic etiology of tobacco and alcohol use. *Nat Genet*. 2019;51:237–244. doi: 10.1038/s41588-018-0307-5
48. Chen Y, Dawes PT, Mattey DL. Polymorphism in the vascular endothelial growth factor A (*VEGFA*) gene is associated with serum VEGF-A level and disease activity in rheumatoid arthritis: differential effect of cigarette smoking. *Cytokine*. 2012;58:390–397. doi: 10.1016/j.cyto.2012.02.018
49. Dick KJ, Nelson CP, Tsaprouni L, Sandling JK, Aissi D, Wahl S, Meduri E, Morange PE, Gagnon F, Grallert H, et al. DNA methylation and body-mass index: a genome-wide analysis. *Lancet*. 2014;383:1990–1998. doi: 10.1016/S0140-6736(13)62674-4
50. Liu Z, Xu HM, Wen LM, Peng YZ, Lin LZ, Zhou S, Li WH, Wang HJ. A systematic review and meta-analysis of the overall effects of school-based obesity prevention interventions and effect differences by intervention components. *Int J Behav Nutr Phys Act*. 2019;16:95. doi: 10.1186/s12966-019-0848-8
51. Fowler LA, Grammer AC, Staiano AE, Fitzsimmons-Craft EE, Chen L, Yaeger LH, Wilfley DE. Harnessing technological solutions for childhood obesity prevention and treatment: a systematic review and meta-analysis of current applications. *Int J Obes (Lond)*. 2021;45:957–981. doi: 10.1038/s41366-021-00765-x
52. Martin JC, Awoke MA, Misso ML, Moran LJ, Harrison CL. Preventing weight gain in adults: a systematic review and meta-analysis of randomized controlled trials. *Obes Rev*. 2021;22:e13280. doi: 10.1111/obr.13280
53. Liu J, Zhang Y, Lavie CJ, Moran AE. Trends in metabolic phenotypes according to body mass index among US adults, 1999-2018. *Mayo Clin Proc*. 2022;97:1664–1679. doi: 10.1016/j.mayocp.2022.02.013
54. Mongraw-Chaffin M, Foster MC, Anderson CAM, Burke GL, Haq N, Kalyani RR, Ouyang P, Sibley CT, Tracy R, Woodward M, et al. Metabolically healthy obesity, transition to metabolic syndrome, and cardiovascular risk. *J Am Coll Cardiol*. 2018;71:1857–1865. doi: 10.1016/j.jacc.2018.02.055
55. Lin L, Zhang J, Jiang L, Du R, Hu C, Lu J, Wang T, Li M, Zhao Z, Xu Y, et al. Transition of metabolic phenotypes and risk of subclinical atherosclerosis according to BMI: a prospective study. *Diabetologia*. 2020;63:1312–1323. doi: 10.1007/s00125-020-05116-5
56. Ma C, Avenell A, Bolland M, Hudson J, Stewart F, Robertson C, Sharma P, Fraser C, MacLennan G. Effects of weight loss interventions for adults who are obese on mortality, cardiovascular disease, and cancer: systematic review and meta-analysis. *BMJ*. 2017;359:j4849. doi: 10.1136/bmj.j4849
57. LeBlanc ES, Patnode CD, Webber EM, Redmond N, Rushkin M, O'Connor EA. Behavioral and pharmacotherapy weight loss interventions to prevent obesity-related morbidity and mortality in adults: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2018;320:1172–1191. doi: 10.1001/jama.2018.7777
58. Look AHEAD Research Group, Gregg EW, Jakicic JM, Blackburn G, Bloomquist P, Bray GA, Clark JM, Coday M, Curtis JM, Egan C, Evans M, et al. Association of the magnitude of weight loss and changes in physical fitness with long-term cardiovascular disease outcomes in overweight or obese people with type 2 diabetes: a post-hoc analysis of the Look AHEAD randomised clinical trial. *Lancet Diabetes Endocrinol*. 2016;4:913–921. doi: 10.1016/S2213-8587(16)30162-0

59. Arterburn DE, Telem DA, Kushner RF, Courcoulas AP. Benefits and risks of bariatric surgery in adults: a review. *JAMA*. 2020;324:879–887. doi: 10.1001/jama.2020.12567
60. Eisenberg D, Shikora SA, Aarts E, Aminian A, Angrisani L, Cohen RV, De Luca M, Faria SL, Goodpaster KPS, Haddad A, et al. 2022 American Society for Metabolic and Bariatric Surgery (ASMBS) and International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO): indications for metabolic and bariatric surgery. *Surg Obes Relat Dis*. 2022;18:1345–1356. doi: 10.1016/j.soard.2022.08.013
61. O'Brien PE, Hindle A, Brennan L, Skinner S, Burton P, Smith A, Crosthwaite G, Brown W. Long-term outcomes after bariatric surgery: a systematic review and meta-analysis of weight loss at 10 or more years for all bariatric procedures and a single-centre review of 20-year outcomes after adjustable gastric banding. *Obes Surg*. 2019;29:3–14. doi: 10.1007/s11695-018-3525-0
62. Syn NL, Cummings DE, Wang LZ, Lin DJ, Zhao JJ, Loh M, Koh ZJ, Chew CA, Loo YE, Tai BC, et al. Association of metabolic-bariatric surgery with long-term survival in adults with and without diabetes: a one-stage meta-analysis of matched cohort and prospective controlled studies with 174 772 participants. *Lancet*. 2021;397:1830–1841. doi: 10.1016/S0140-6736(21)00591-2
63. van Veldhuisen SL, Gorter TM, van Woerden G, de Boer RA, Rienstra M, Hazebroek EJ, van Veldhuisen DJ. Bariatric surgery and cardiovascular disease: a systematic review and meta-analysis. *Eur Heart J*. 2022;43:1955–1969. doi: 10.1093/eurheartj/ehac071
64. Pu R, Shi D, Gan T, Ren X, Ba Y, Huo Y, Bai Y, Zheng T, Cheng N. Effects of metformin in obesity treatment in different populations: a meta-analysis. *Ther Adv Endocrinol Metab*. 2020;11:2042018820926000. doi: 10.1177/2042018820926000
65. Chakhtoura M, Haber R, Ghezzawi M, Rhayem C, Tcheroyan R, Mantzoros CS. Pharmacotherapy of obesity: an update on the available medications and drugs under investigation. *EClinicalMedicine*. 2023;58:101882. doi: 10.1016/j.eclinm.2023.101882
66. Frieling K, Monte SV, Jacobs D, Albanese NP. Weight loss differences seen between glucagon-like peptide–1 receptor agonists and sodium–glucose cotransporter–2 inhibitors for treatment of type 2 diabetes. *J Am Pharm Assoc (2003)*. 2021;61:772–777. doi: 10.1016/j.japh.2021.06.015
67. Cheong AJY, Teo YN, Teo YH, Syn NL, Ong HT, Ting AZH, Chia AZQ, Chong EY, Chan MY, Lee CH, et al. SGLT inhibitors on weight and body mass: a meta-analysis of 116 randomized-controlled trials. *Obesity (Silver Spring)*. 2022;30:117–128. doi: 10.1002/oby.23331
68. Htike ZZ, Zaccardi F, Papamargaritis D, Webb DR, Khunti K, Davies MJ. Efficacy and safety of glucagon-like peptide-1 receptor agonists in type 2 diabetes: a systematic review and mixed-treatment comparison analysis. *Diabetes Obes Metab*. 2017;19:524–536. doi: 10.1111/dom.12849
69. Potts JE, Gray LJ, Brady EM, Khunti K, Davies MJ, Bodicoat DH. The effect of glucagon-like peptide 1 receptor agonists on weight loss in type 2 diabetes: a systematic review and mixed treatment comparison meta-analysis. *PLoS One*. 2015;10:e0126769. doi: 10.1371/journal.pone.0126769
70. Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, McGowan BM, Rosenstock J, Tran MTD, Wadden TA, et al; STEP 1 Study Group. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med*. 2021;384:989–1002. doi: 10.1056/NEJMoa2032183
71. Wilding JPH, Jacob S. Cardiovascular outcome trials in obesity: a review. *Obes Rev*. 2021;22:e13112. doi: 10.1111/obr.13112
72. Wadden TA, Bailey TS, Billings LK, Davies M, Frias JP, Koroleva A, Lingvay I, O'Neil PM, Rubino DM, Skovgaard D, et al; STEP 3 Investigators. Effect of subcutaneous semaglutide vs placebo as an adjunct to intensive behavioral therapy on body weight in adults with overweight or obesity: the STEP 3 randomized clinical trial. *JAMA*. 2021;325:1403–1413. doi: 10.1001/jama.2021.1831
73. Vosoughi K, Atieh J, Khanna L, Khoshbin K, Prokop LJ, Davitkov P, Murad MH, Camilleri M. Association of glucagon-like peptide 1 analogs and agonists administered for obesity with weight loss and adverse events: a systematic review and network meta-analysis. *EClinicalMedicine*. 2021;42:101213. doi: 10.1016/j.eclinm.2021.101213
74. Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery L, Alves B, Kiyosue A, Zhang S, Liu B, Bunck MC, et al; SURMOUNT-1 Investigators. Tirzepatide once weekly for the treatment of obesity. *N Engl J Med*. 2022;387:205–216. doi: 10.1056/nejmoa2206038
75. US Food and Drug Administration. FDA approves new drug treatment for chronic weight management, first since 2014. Accessed April 15, 2023. https://fda.gov/news-events/press-announcements/fda-approves-new-drug-treatment-chronic-weight-management-first-2014
76. Wilding JPH, Batterham RL, Davies M, Van Gaal LF, Kandler K, Konakli K, Lingvay I, McGowan BM, Oral TK, Rosenstock J, et al; STEP 1 Study Group. Weight regain and cardiometabolic effects after withdrawal of semaglutide: the STEP 1 trial extension. *Diabetes Obes Metab*. 2022;24:1553–1564. doi: 10.1111/dom.14725
77. Nowrouzi-Sohrabi P, Rezaei S, Jalali M, Ashourpour M, Ahmadipour A, Keshavarz P, Akbari H. The effects of glucagon-like peptide-1 receptor agonists on glycemic control and anthropometric profiles among diabetic patients with non-alcoholic fatty liver disease: a systematic review and meta-analysis of randomized controlled trials. *Eur J Pharmacol*. 2021;893:173823. doi: 10.1016/j.ejphar.2020.173823
78. Mantovani A, Petracca G, Beatrice G, Csermely A, Lonardo A, Targher G. Glucagon-like peptide-1 receptor agonists for treatment of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: an updated meta-analysis of randomized controlled trials. *Metabolites*. 2021;11:73. doi: 10.3390/metabo11020073
79. Ryan PM, Seltzer S, Hayward NE, Rodriguez DA, Sless RT, Hawkes CP. Safety and efficacy of glucagon-like peptide-1 receptor agonists in children and adolescents with obesity: a meta-analysis. *J Pediatr*. 2021;236:137–147.e13. doi: 10.1016/j.jpeds.2021.05.009
80. Uneda K, Kawai Y, Yamada T, Kinguchi S, Azushima K, Kanaoka T, Toya Y, Wakui H, Tamura K. Systematic review and meta-analysis for prevention of cardiovascular complications using GLP-1 receptor agonists and SGLT-2 inhibitors in obese diabetic patients. *Sci Rep*. 2021;11:10166. doi: 10.1038/s41598-021-89620-7
81. Leite AR, Angélico-Gonçalves A, Vasques-Nóvoa F, Borges-Canha M, Leite-Moreira A, Neves JS, Ferreira JP. Effect of glucagon-like peptide-1 receptor agonists on cardiovascular events in overweight or obese adults without diabetes: a meta-analysis of placebo-controlled randomized trials. *Diabetes Obes Metab*. 2022;24:1676–1680. doi: 10.1111/dom.14707
82. Oxlund CS, Pareek M, Rasmussen BSB, Vaduganathan M, Biering-Sorensen T, Byrne C, Almarzooq Z, Olsen MH, Bhatt DL. Body mass index, intensive blood pressure management, and cardiovascular events in the SPRINT trial. *Am J Med*. 2019;132:840–846. doi: 10.1016/j.amjmed.2019.01.024
83. Aune D, Sen A, Prasad M, Norat T, Janszky I, Tonstad S, Romundstad P, Vatten LJ. BMI and all cause mortality: systematic review and non-linear dose-response meta-analysis of 230 cohort studies with 3.74 million deaths among 30.3 million participants. *BMJ*. 2016;353:i2156. doi: 10.1136/bmj.i2156
84. Jayedi A, Khan TA, Aune D, Emadi A, Shab-Bidar S. Body fat and risk of all-cause mortality: a systematic review and dose-response meta-analysis of prospective cohort studies. *Int J Obes (Lond)*. 2022;46:1573–1581. doi: 10.1038/s41366-022-01165-5
85. Chen H, Deng Y, Li S. Relation of body mass index categories with risk of sudden cardiac death. *Int Heart J*. 2019;60:624–630. doi: 10.1536/ihj.18-155
86. Organisation for Economic Co-Operation and Development. *The Heavy Burden of Obesity: The Economics of Prevention*. OECD Publishing; 2019.
87. Kim MS, Kim WJ, Khera AV, Kim JY, Yon DK, Lee SW, Shin JI, Won HH. Association between adiposity and cardiovascular outcomes: an umbrella review and meta-analysis of observational and mendelian randomization studies. *Eur Heart J*. 2021;42:3388–3403. doi: 10.1093/eurheartj/ehab454
88. Khan SS, Ning H, Wilkins JT, Allen N, Carnethon M, Berry JD, Sweis RN, Lloyd-Jones DM. Association of body mass index with lifetime risk of cardiovascular disease and compression of morbidity. *JAMA Cardiol*. 2018;3:280–287. doi: 10.1001/jamacardio.2018.0022
89. Gill D, Zuber V, Dawson J, Pearson-Stuttard J, Carter AR, Sanderson E, Karhunen V, Levin MG, Wootton RE, Klarin D, et al. Risk factors mediating the effect of body mass index and waist-to-hip ratio on cardiovascular outcomes: mendelian randomization analysis. *Int J Obes (Lond)*. 2021;45:1428–1438. doi: 10.1038/s41366-021-00807-4
90. Lu Y, Hajifathalian K, Ezzati M, Woodward M, Rimm EB, Danaei G; Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration (BMI Mediated Effects). Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1.8 million participants. *Lancet*. 2014;383:970–983. doi: 10.1016/S0140-6736(13)61836-X
91. Bangalore S, Fayyad R, Laskey R, DeMicco DA, Messerli FH, Waters DD. Body-weight fluctuations and outcomes in coronary disease. *N Engl J Med*. 2017;376:1332–1340. doi: 10.1056/NEJMoa1606148
92. Liu X, Zhang D, Liu Y, Sun X, Hou Y, Wang B, Ren Y, Zhao Y, Han C, Cheng C, et al. A J-shaped relation of BMI and stroke: systematic review and dose-response meta-analysis of 4.43 million participants. *Nutr Metab Cardiovasc Dis*. 2018;28:1092–1099. doi: 10.1016/j.numecd.2018.07.004

93. Mahajan R, Stokes M, Elliott A, Munawar DA, Khokhar KB, Thiyagarajah A, Hendriks J, Linz D, Gallagher C, Kaye D, et al. Complex interaction of obesity, intentional weight loss and heart failure: a systematic review and meta-analysis. *Heart*. 2020;106:58–68. doi: 10.1136/heartjnl-2019-314770
94. Ndumele CE, Matsushita K, Lazo M, Bello N, Blumenthal RS, Gerstenblith G, Nambi V, Ballantyne CM, Solomon SD, Selvin E, et al. Obesity and subtypes of incident cardiovascular disease. *J Am Heart Assoc*. 2016;5:e003921. doi: 10.1161/JAHA.116.003921
95. Fliotsos M, Zhao D, Rao VN, Ndumele CE, Guallar E, Burke GL, Vaidya D, Delaney JCA, Michos ED. Body mass index from early-, mid-, and older-adulthood and risk of heart failure and atherosclerotic cardiovascular disease: MESA. *J Am Heart Assoc*. 2018;7:e009599. doi: 10.1161/JAHA.118.009599
96. Rao VN, Fudim M, Mentz RJ, Michos ED, Felker GM. Regional adiposity and heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2020;22:1540–1550. doi: 10.1002/ejhf.1956
97. Rao VN, Zhao D, Allison MA, Guallar E, Sharma K, Criqui MH, Cushman M, Blumenthal RS, Michos ED. Adiposity and incident heart failure and its subtypes: MESA (Multi-Ethnic Study of Atherosclerosis). *JACC Heart Fail*. 2018;6:999–1007. doi: 10.1016/j.jchf.2018.07.009
98. Salah HM, Pandey A, Van Spall HGC, Michos ED, McGarrah RW, Fudim M. Meta-analysis of nonalcoholic fatty liver disease and incident heart failure. *Am J Cardiol*. 2022;171:180–181. doi: 10.1016/j.amjcard.2022.02.012
99. Sharma A, Lavie CJ, Borer JS, Vallakati A, Goel S, Lopez-Jimenez F, Arbab-Zadeh A, Mukherjee D, Lazar JM. Meta-analysis of the relation of body mass index to all-cause and cardiovascular mortality and hospitalization in patients with chronic heart failure. *Am J Cardiol*. 2015;115:1428–1434. doi: 10.1016/j.amjcard.2015.02.024
100. Chung MK, Eckhardt LL, Chen LY, Ahmed HM, Gopinathannair R, Joglar JA, Noseworthy PA, Pack QR, Sanders P, Trulock KM; on behalf of the American Heart Association Electrocardiography and Arrhythmias Committee and Exercise, Cardiac Rehabilitation, and Secondary Prevention Committee of the Council on Clinical Cardiology; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular and Stroke Nursing; and Council on Lifestyle and Cardiometabolic Health. Lifestyle and risk factor modification for reduction of atrial fibrillation: a scientific statement from the American Heart Association. *Circulation*. 2020;141:e750–e772. doi: 10.1161/CIR.0000000000000748
101. Chatterjee NA, Giulianini F, Geelhoed B, Lunetta KL, Misialek JR, Niemeijer MN, Rienstra M, Rose LM, Smith AV, Arking DE, et al. Genetic obesity and the risk of atrial fibrillation: causal estimates from mendelian randomization. *Circulation*. 2017;135:741–754. doi: 10.1161/CIRCULATIONAHA.116.024921
102. Aune D, Sen A, Schlesinger S, Norat T, Janszky I, Romundstad P, Tonstad S, Riboli E, Vatten LJ. Body mass index, abdominal fatness, fat mass and the risk of atrial fibrillation: a systematic review and dose-response meta-analysis of prospective studies. *Eur J Epidemiol*. 2017;32:181–192. doi: 10.1007/s10654-017-0232-4
103. Park DY, An S, Murthi M, Kattoor AJ, Kaur A, Ravi V, Huang HD, Vij A. Effect of weight loss on recurrence of atrial fibrillation after ablative therapy: a systematic review and meta-analysis. *J Interv Card Electrophysiol*. 2022;64:763–771. doi: 10.1007/s10840-022-01168-2
104. Sattar N, McInnes IB, McMurray JJV. Obesity is a risk factor for severe COVID-19 infection: multiple potential mechanisms. *Circulation*. 2020;142:4–6. doi: 10.1161/CIRCULATIONAHA.120.047659
105. Mahamat-Saleh Y, Fiolet T, Rebeaud ME, Mulot M, Guihur A, El Fatouhi D, Laouali N, Peiffer-Smadja N, Aune D, Severi G. Diabetes, hypertension, body mass index, smoking and COVID-19-related mortality: a systematic review and meta-analysis of observational studies. *BMJ Open*. 2021;11:e052777. doi: 10.1136/bmjopen-2021-052777
106. Hendren NS, de Lemos JA, Ayers C, Das SR, Rao A, Carter S, Rosenblatt A, Walchok J, Omar W, Khera R, et al. Association of body mass index and age with morbidity and mortality in patients hospitalized with COVID-19: results from the American Heart Association COVID-19 Cardiovascular Disease Registry. *Circulation*. 2021;143:135–144. doi: 10.1161/CIRCULATIONAHA.120.051936
107. Vasbinder A, Meloche C, Azam TU, Anderson E, Catalan T, Shadid H, Berlin H, Pan M, O'Hayer P, Padalia K, et al; STOP-COVID Investigators. Relationship between preexisting cardiovascular disease and death and cardiovascular outcomes in critically ill patients with COVID-19. *Circ Cardiovasc Qual Outcomes*. 2022;15:e008942. doi: 10.1161/CIRCOUTCOMES.122.008942
108. Skinner AC, Perrin EM, Moss LA, Skelton JA. Cardiometabolic risks and severity of obesity in children and young adults. *N Engl J Med*. 2015;373:1307–1317. doi: 10.1056/NEJMoa1502821
109. Umer A, Kelley GA, Cottrell LE, Giacobbi P Jr, Innes KE, Lilly CL. Childhood obesity and adult cardiovascular disease risk factors: a systematic review with meta-analysis. *BMC Public Health*. 2017;17:683. doi: 10.1186/s12889-017-4691-z
110. Llewellyn A, Simmonds M, Owen CG, Woolacott N. Childhood obesity as a predictor of morbidity in adulthood: a systematic review and meta-analysis. *Obes Rev*. 2016;17:56–67. doi: 10.1111/obr.12316
111. Meyer JF, Larsen SB, Blond K, Damsgaard CT, Bjerregaard LG, Baker JL. Associations between body mass index and height during childhood and adolescence and the risk of coronary heart disease in adulthood: a systematic review and meta-analysis. *Obes Rev*. 2021;22:e13276. doi: 10.1111/obr.13276
112. Twig G, Yaniv G, Levine H, Leiba A, Goldberger N, Derazne E, Ben-Ami Shor D, Tzur D, Afek A, Shamiss A, et al. Body-mass index in 2.3 million adolescents and cardiovascular death in adulthood. *N Engl J Med*. 2016;374:2430–2440. doi: 10.1056/NEJMoa1503840
113. Ge WX, Han D, Ding ZY, Yi LP, Yang ZQ, Wang XN, Xiao Y, Liang F, Hai B, Lv HL, et al. Pediatric body mass index trajectories and the risk of hypertension among adolescents in China: a retrospective cohort study. *World J Pediatr*. 2023;19:76–86. doi: 10.1007/s12519-022-00626-1
114. Ward ZJ, Bleich SN, Long MW, Gortmaker SL. Association of body mass index with health care expenditures in the United States by age and sex. *PLoS One*. 2021;16:e0247307. doi: 10.1371/journal.pone.0247307
115. Cawley J, Biener A, Meyerhoefer C, Ding Y, Zvenyach T, Smolarz BG, Ramasamy A. Direct medical costs of obesity in the United States and the most populous states. *J Manag Care Spec Pharm*. 2021;27:354–366. doi: 10.18553/jmcp.2021.20410
116. Boutari C, Mantzoros CS. A 2022 update on the epidemiology of obesity and a call to action: as its twin COVID-19 pandemic appears to be receding, the obesity and dysmetabolism pandemic continues to rage on. *Metabolism*. 2022;133:155217. doi: 10.1016/j.metabol.2022.155217
117. World Obesity Federation. World Obesity Atlas 2023. Accessed March 30, 2023. https://worldobesity.org/resources/resource-library/world-obesity-atlas-2023
118. World Health Organization. Obesity and overweight. Accessed April 15, 2023. https://int/news-room/fact-sheets/detail/obesity-and-overweight#
119. Ritchie H, Roser M. Obesity 2017. Accessed April 15, 2023. https://ourworldindata.org/obesity
120. Vaduganathan M, Mensah GA, Turco JV, Fuster V, Roth GA. The global burden of cardiovascular diseases and risk: a compass for future health. *J Am Coll Cardiol*. 2022;80:2361–2371. doi: 10.1016/j.jacc.2022.11.005
121. Chong B, Jayabaskaran J, Kong G, Chan YH, Chin YH, Goh R, Kannan S, Ng CH, Loong S, Kueh MTW, et al. Trends and predictions of malnutrition and obesity in 204 countries and territories: an analysis of the Global Burden of Disease Study 2019. *EClinicalMedicine*. 2023;57:101850. doi: 10.1016/j.eclinm.2023.101850
122. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, Barengo NC, Beaton AZ, Benjamin EJ, Benziger CP, et al; GBD-NHLBI-JACC Global Burden of Cardiovascular Diseases Writing Group. Global burden of cardiovascular diseases and risk factors, 1990-2019: update from the GBD 2019 Study. *J Am Coll Cardiol*. 2020;76:2982–3021. doi: 10.1016/j.jacc.2020.11.010
123. NCD Risk Factor Collaboration. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults. *Lancet*. 2017;390:2627–2642. doi: 10.1016/S0140-6736(17)32129-3
124. NCD Risk Factor Collaboration. Rising rural body-mass index is the main driver of the global obesity epidemic in adults. *Nature*. 2019;569:260–264. doi: 10.1038/s41586-019-1171-x
125. Okunogbe A, Nugent R, Spencer G, Powis J, Ralston J, Wilding J. Economic impacts of overweight and obesity: current and future estimates for 161 countries. *BMJ Glob Health*. 2022;7:e009773. doi: 10.1136/bmjgh-2022-009773
126. Centers for Disease Control and Prevention and National Center for Health Statistics. National Health and Nutrition Examination Survey (NHANES) public use data files. Accessed April 1, 2023. https://cdc.gov/nchs/nhanes/
127. Global Burden of Disease Study and Institute for Health Metrics and Evaluation. University of Washington. Accessed August 2, 2023. http://ghdx.healthdata.org/
128. Centers for Disease Control and Prevention. Adult obesity prevalence maps. Accessed April 15, 2023. https://cdc.gov/obesity/data/prevalence-maps.html

# 7. HIGH BLOOD CHOLESTEROL AND OTHER LIPIDS

*See Tables 7-1 and 7-2 and Charts 7-1 through 7-5*

Click here to return to the Table of Contents

Click here to return to the Abbreviations

Cholesterol is a primary causal risk factor for the development of atherosclerosis and CVD. TC levels in the blood have traditionally been one of the primary metrics used to define CVH in children and adults. LDL-C is the component of TC that is most closely associated with CVD risk and is therefore the target of both lifestyle and pharmacological treatment. HDL-C is inversely associated with CVD risk, and high triglyceride levels are associated with increased risk. More recently, AHA's Life's Essential 8 has adopted non–HDL-C (TC minus HDL-C) as a key metric to assess lipid health.[1] However, a full lipid panel, including TC, LDL-C, HDL-C, and triglycerides, is normally recommended to best assess lipid-related CVD risk. Lipoprotein(a), an LDL particle with an added apolipoprotein(a), is a genetically determined factor, with elevated levels associated with increased CVD risk. The multisociety 2018 Cholesterol Clinical Practice Guideline and the 2019 CVD Primary Prevention Clinical Practice Guidelines focus predominantly on the use of LDL-C–lowering therapy to reduce ASCVD risk.[2,3] The 2022 ACC expert consensus decision pathway discusses the role of nonstatin therapy in the management of ASCVD risk.[4]

## Prevalence of High TC

### Youth

#### (See Chart 7-1)

- Among children 6 to 11 years of age, the mean TC level in 2017 to 2020 was 157.4 mg/dL. For males, it was 157.5 mg/dL; for females, it was 157.2 mg/dL. Mean TC levels among racial and ethnic groups in NHANES 2017 to 2020 were as follows (unpublished NHLBI tabulation using NHANES[5]):
  - For NH White children, 156.3 mg/dL for males and 159.5 mg/dL for females
  - For NH Black children, 159.3 mg/dL for males and 155.3 mg/dL for females
  - For Hispanic children, 156.5 mg/dL for males and 153.1 mg/dL for females
  - For NH Asian children, 169.6 mg/dL for males and 166.0 mg/dL for females
- Among adolescents 12 to 19 years of age, the mean TC level in 2017 to 2020 was 154.8 mg/dL; for males, it was 150.1; for females, it was 159.7 mg/dL. Mean TC levels among racial and ethnic groups in NHANES 2017 to 2020 were as follows (unpublished NHLBI tabulation using NHANES[5]):
  - For NH White adolescents, 148.8 mg/dL for males and 162.4 mg/dL for females
  - For NH Black adolescents, 153.1 mg/dL for males and 156.8 mg/dL for females
  - For Hispanic adolescents, 149.8 mg/dL for males and 154.9 mg/dL for females
  - For NH Asian adolescents, 156.3 mg/dL for males and 161.0 mg/dL for females
- Among youth 6 to 19 years of age, the prevalence of elevated TC levels (TC ≥200 mg/dL) in 2009 to 2016 was 7.1% (95% CI, 6.4%–7.8%; Chart 7-1A). Among youth 6 to 19 years of age, the prevalence of ideal TC levels (TC <170 mg/dL) in 2015 to 2016 was 71.4% (95% CI, 69.0%–73.8%; Chart 7-1B).[6]

### Adults (≥20 Years of Age)

#### (See Table 7-1 and Charts 7-2 through 7-4)

- Among adults ≥20 years of age, the mean TC level in 2017 to 2020 was 187.2 mg/dL. For males, it was 183.9 mg/dL; for females, it was 190.0 mg/dL. Across 3 NHANES time periods (1999–2002, 2007–2010, and 2017–2020), NH Black adults had the lowest serum TC compared with NH White adults and Mexican American adults (Chart 7-2). Mean TC levels among racial and ethnic groups in 2017 to 2020 were as follows (unpublished NHLBI tabulation using NHANES[5]):
  - For NH White adults, 183.3 mg/dL for males and 191.6 mg/dL for females
  - For NH Black adults, 179.5 mg/dL for males and 182.6 mg/dL for females
  - For Hispanic adults, 185.3 mg/dL for males and 187.4 mg/dL for females
  - For NH Asian adults, 191.4 mg/dL for males and 190.8 mg/dL for females
- The prevalence of TC ≥200 mg/dL and ≥240 mg/dL among US adults ≥20 years of age in 2017 to 2020 (unpublished NHLBI tabulation using NHANES[5]) is shown overall and by sex and race and ethnicity in Table 7-1 and Charts 7-3 and 7-4.
- The US Department of Health and Human Services Healthy People 2030 target is a mean population TC level of 186.4 mg/dL for adults,[7] which was

The 2024 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2024. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

achieved by NH Black US adults (males and females combined) and Mexican American US adults (males and females combined) in NHANES 2017 to 2020 (Chart 7-2).[5,7]

## Prevalence of Abnormal Levels of Lipid Subfractions

### LDL-C

#### Youth

*(See Chart 7-1)*

- Among adolescents 12 to 19 years of age, the mean LDL-C level in 2017 to 2020 was 88.1 mg/dL (males, 85.1 mg/dL; females, 91.3 mg/dL). Mean LDL-C levels among racial and ethnic groups were as follows (unpublished NHLBI tabulation using NHANES[5]):
  - For NH White adolescents, 83.2 mg/dL for males and 92.0 mg/dL for females
  - For NH Black adolescents, 84.8 mg/dL for males and 97.6 mg/dL for females
  - For Hispanic adolescents, 89.0 mg/dL for males and 88.1 mg/dL for females
  - For NH Asian adolescents, 83.0 mg/dL for males and 83.2 mg/dL for females; however, these values are based on data from small sample sizes (39 NH Asian males and 27 NH Asian females). Further specification of NH Asian subgroups is not available.
- LDL-C levels ≥130 mg/dL were present in 5.0% of male adolescents and 4.6% of female adolescents during 2017 to 2020 (unpublished NHLBI tabulation using NHANES[5]).

#### Adults

*(See Table 7-1)*

- In 2017 to 2020 (unpublished NHLBI tabulation using NHANES[5]), the mean level of LDL-C for American adults ≥20 years of age was 110.1 mg/dL. The racial and ethnic breakdown was as follows:
  - Among NH White adults, 109.5 mg/dL for males and 109.3 mg/dL for females
  - Among NH Black adults, 109.8 mg/dL for males and 106.0 mg/dL for females
  - Among Hispanic adults, 110.5 mg/dL for males and 111.5 mg/dL for females
  - Among NH Asian adults, 114.8 mg/dL for males and 109.6 mg/dL for females
- In 2017 to 2020, the age-adjusted prevalence of high LDL-C (≥130 mg/dL) in US adults was 25.5% (unpublished NHLBI tabulation using NHANES[5]; Table 7-1).
- Among adults who reported CAD between 2015 and 2020, age-adjusted mean LDL-C was 94.4 mg/dL (95% CI, 90.3–98.5).[8] In these adults, 73.5% (95% CI, 68.2%–78.8%) had an LDL-C ≥70 mg/dL, and 88.1% (95% CI, 83.6%–92.6%) had an LDL-C ≥55 mg/dL.

### Lipoprotein(a)

Lipoprotein(a) is an LDL-like particle, an apolipoprotein(a) covalently bound to apolipoprotein $B_{100}$ by disulfide bonds. Some professional societies recommend screening of lipoprotein(a) in individuals with a personal or family history of ASCVD or who are at high risk of ASCVD, with some societies (eg, in Europe and Canada) recommending universal screening for all people at least once in a person's lifetime.

- Elevated lipoprotein(a), which is defined as ≥125 nmol/L or ≥50 mg/dL and is present in up to 20% of the population, is associated with increased risk of CHD, stroke, valvular aortic stenosis, and even HF and AF. Levels above this point are defined as a risk-enhancing factor by the National Lipid Association and by the 2018 Cholesterol Clinical Practice Guideline to further inform the decision to initiate or intensify preventive treatment such as with statins.
- Among ≈460 000 middle-aged adults in the UK Biobank enrolled between 2006 and 2010, median serum lipoprotein(a) concentration was 19.6 nmol/L (25th–75th percentile, 7.6–74.8 nmol/L) overall, with median values of 21.8 nmol/L in females and 17.4 nmol/L in males, as well as 19 nmol/L in White, 31 nmol/L in South Asian, 75 nmol/L in Black, and 16 nmol/L in Chinese adults.[9]

### HDL Cholesterol

#### Youth

*(See Chart 7-1)*

- Among children 6 to 11 years of age, the mean HDL-C level in 2017 to 2020 was 55.5 mg/dL. For males, it was 56.6 mg/dL, and for females, it was 54.3 mg/dL. Mean HDL-C levels among racial and ethnic groups were as follows (unpublished NHLBI tabulation using NHANES[5]):
  - For NH White children, 56.8 mg/dL for males and 54.8 mg/dL for females
  - For NH Black children, 58.5 mg/dL for males and 55.9 mg/dL for females
  - For Hispanic children, 55.6 mg/dL for males and 51.3 mg/dL for females
  - For NH Asian children, 59.3 mg/dL for males and 58.1 mg/dL for females
- Among children 6 to 11 years of age, low levels of HDL-C (<40 mg/dL) were present in 5.9% of males and 8.9% of females in 2017 to 2020 (unpublished NHLBI tabulation using NHANES[5]).
- Among adolescents 12 to 19 years of age, the mean HDL-C level was 51.7 mg/dL. For males, it was 49.0 mg/dL, and for females, it was 54.6 mg/dL. Mean HDL-C levels among racial and ethnic

groups were as follows (NHANES,[5] unpublished NHLBI tabulation):
  - For NH White adolescents, 48.2 mg/dL for males and 55.2 mg/dL for females
  - For NH Black adolescents, 53.8 mg/dL for males and 55.9 mg/dL for females
  - For Hispanic adolescents, 48.2 mg/dL for males and 52.2 mg/dL for females
  - For NH Asian adolescents, 51.1 mg/dL for males and 55.3 mg/dL for females
- Low levels of HDL-C (<40 mg/dL) were present in 19.3% of male adolescents and 8.6% of female adolescents in 2017 to 2020 (unpublished NHLBI tabulation using NHANES[5]).

### *Adults*

*(See Table 7-1)*

- HDL-C is considered low and associated with increased ASCVD risk if <40 mg/dL in males or <50 mg/dL in females. In 2017 to 2020 (unpublished NHLBI tabulation using NHANES[5]), the mean level of HDL-C for American adults ≥20 years of age was 53.6 mg/dL. Mean HDL-C levels among racial and ethnic groups were as follows:
  - Among NH White adults, 48.4 mg/dL for males and 59.5 mg/dL for females
  - Among NH Black adults, 52.7 mg/dL for males and 59.2 mg/dL for females
  - Among Hispanic adults, 45.4 mg/dL for males and 55.4 mg/dL for females
  - Among NH Asian adults, 46.8 mg/dL for males and 59.8 mg/dL for females
- Age-adjusted prevalence rates of low HDL-C (<40 mg/dL) for 2017 to 2020 are shown overall and by sex and race and ethnicity in Table 7-1. Prevalence rates were higher among males than females and were highest among Hispanic males.

## *Triglycerides*

### *Youth*

*(See Chart 7-1)*

- Limited data are available on triglycerides for children 6 to 11 years of age.
- Among adolescents 12 to 19 years of age, the geometric mean triglyceride level in 2017 to 2020 was 62.3 mg/dL. For males, it was 61.6 mg/dL, and for females, it was 63.1 mg/dL. Levels among racial and ethnic groups were as follows (unpublished NHLBI tabulation using NHANES[5]):
  - Among NH White adolescents, 65.0 mg/dL for males and 66.8 mg/dL for females
  - Among NH Black adolescents, 48.1 mg/dL for males and 44.5 mg/dL for females
  - Among Hispanic adolescents, 63.1 mg/dL for males and 70.7 mg/dL for females
  - Among NH Asian adolescents, 52.8 mg/dL for males and 67.9 mg/dL for females
- Elevated triglycerides (≥90 mg/dL) occurred in 20.8% of male adolescents and 23.5% of female adolescents during 2017 to 2020 (unpublished NHLBI tabulation using NHANES[5]).

### *Adults*

- Triglyceride levels of 150 to 199 mg/dL are generally considered borderline, and levels ≥200 mg/dL are considered elevated, although increases in risk of ASCVD have been demonstrated at levels even <100 mg/dL.[10] Among American adults ≥20 years of age, the geometric mean triglyceride level in 2017 to 2020 was 91.6 mg/dL (unpublished NHLBI tabulation using NHANES[5]). The geometric mean triglyceride levels were 98.5 mg/dL for males and 85.5 mg/dL for females. Levels among racial and ethnic groups were as follows:
  - Among NH White adults, 99.0 mg/dL for males and 85.9 mg/dL for females
  - Among NH Black adults, 74.1 mg/dL for males and 67.5 mg/dL for females
  - Among Hispanic adults, 108.2 mg/dL for males and 96.2 mg/dL for females
  - Among NH Asian adults, 110.2 mg/dL for males and 84.3 mg/dL for females
- In 2017 to 2020, 19.9% of adults had high triglyceride levels (≥150 mg/dL; unpublished NHLBI tabulation using NHANES[5]).

## *Secular Trends in TC and Lipid Subfractions*

### *Youth*

*(See Chart 7-1)*

- Between 1999 and 2016, trends in mean levels of TC, HDL-C, and non–HDL-C among youth 6 to 19 years of age demonstrated improved levels. Levels of LDL-C, triglycerides, and apolipoprotein B also improved among adolescents 12 to 19 years of age over a similar period (data not available for younger children; Chart 7-1).
- The proportion of youths 6 to 19 years of age with ideal levels of 3 cholesterol measures (TC, HDL-C, and non–HDL-C) increased significantly from 42.1% (95% CI, 39.6%–44.7%) in 2007 to 2008 to 51.4% (95% CI, 48.5%–54.2%) in 2015 to 2016, and the proportion with at least 1 adverse level decreased from 23.1% (95% CI, 21.5%–24.7%) in 2007 to 2010 to 19.2% (95% CI, 17.6%–20.8%) in 2013 to 2016 (Chart 7-1).
- The proportion of adolescents 12 to 19 years of age with ideal levels of 6 cholesterol measures (TC, HDL-C, non–HDL-C, LDL-C, triglycerides, and apolipoprotein B) did not change significantly, from 39.6% (95% CI, 33.7%–45.4%) in 2007 to

2008 to 46.8% (95% CI, 40.9%–52.6%) in 2013 to 2014 (Chart 7-1).

### *Adults (≥20 Years of Age)*

*(See Chart 7-2)*

- Mean age-adjusted TC levels decreased in the US population from 197 mg/dL in 2007 to 2008 to 189 mg/dL in 2017 to 2018.[11] In females, mean TC decreased from 199 mg/dL in 2007 to 2008 to 192 mg/dL in 2017 to 2018. In males, mean TC decreased from 195 mg/dL in 2007 to 2008 to 185 mg/dL in 2017 to 2018.
- The prevalence of high TC (≥240 mg/dL) has decreased over time, from 18.3% (95% CI, 16.3%–20.3%) of adults in 1999 to 2000 to 10.5% (95% CI, 9.7%–11.3%) in 2017 to 2018.[12]
  - From 1999 to 2020, mean serum TC for adults ≥20 years of age decreased across all subgroups of race and ethnicity (Chart 7-2).
  - Declines in mean TC levels were also observed among adults receiving lipid-lowering medication, from 206 mg/dL in 2005 to 2006 to 187 mg/dL in 2015 to 2016.[13]
  - Among adults 20 to 44 years of age in the United States, prevalence of hyperlipidemia (defined as TC ≥200 mg/dL or a health care diagnosis of high cholesterol) decreased from 40.5% in 2009 to 2010 to 36.1% in 2017 to 2020.[14]
  - In ≈350 000 patients who were 40 to 79 years of age in the Kaiser Permanente Southern California health system with lipid information before (March 2019–March 2020) and during (December 2020–December 2021) the COVID-19 pandemic, the proportion with elevated TC ≥240 mg/dL increased from 9.9% to 10.8%.[15]
- Age-adjusted mean LDL-C decreased among US adults from 116 mg/dL in 2007 to 2008 to 111 mg/dL in 2017 to 2018, with similar patterns in females and males.[11]
- The age-adjusted prevalence of high LDL-C (≥130 mg/dL) decreased from 42.9% during 1999 to 2000 to 26.2% during 2017 to 2018 (unpublished NHLBI tabulation using NHANES[5]).
- Mean HDL-C levels increased statistically significantly between 2007 to 2008 and 2017 to 2018 in female (from 57 to 58 mg/dL, $P_{trend}$=0.002) and male (from 46 to 48 mg/dL, $P_{trend}$=0.001) adults in the United States.[11]
- The prevalence of low HDL-C (<40 mg/dL) among US adults declined from 22.2% in 2007 to 2008 to 16.0% in 2017 to 2018.[12]
- Geometric mean triglyceride levels decreased between 2007 to 2008 and 2017 to 2018 in female (from 104 to 86 mg/dL) and male (from 122 to 98 mg/dL) adults in the United States.[11]
- Among males, age-adjusted levels of apolipoprotein B declined from 98 mg/dL in 2005 to 2006 to 93 mg/dL in 2011 to 2012 and did not change subsequently through 2015 to 2016; among females, age-adjusted mean apolipoprotein B declined from 94 mg/dL in 2005 to 2006 to 91 mg/dL in 2015 to 2016.[16]

## Family History and Genetics

- GWASs in hundreds of thousands of individuals of diverse ancestry, in addition to the use of electronic health record–based samples and whole-exome sequencing (which offers more comprehensive coverage of the coding regions of the genome), have identified >200 lipid loci.[17–21]
- A recent multiancestry GWAS in 1.65 million individuals has identified 941 lipid-associated genomic regions harboring >1700 distinct variants, with 355 novel genomic loci identified.[22] The notable findings also highlight that multiancestry PRSs leveraging the GWAS findings from multiple ethnicities are more informative for lipid traits across multiple population groups.[22]
- With the use of whole-genome sequencing across diverse ancestries in 66 000 individuals, 428 million variants were interrogated, and a rare noncoding variant model for blood lipids was characterized.[23] Novel associations were replicated in 45 000 independent samples with array-based genotyping.
- Lipoprotein(a), a causal risk factor for CAD, is a highly heritable trait. Whole-genome sequencing (which provides a comprehensive coverage of the entire genome, including both coding and noncoding regions) analysis combining structural variants (mainly LPA KIV2-CN) with sequence variations has elucidated that genetic heritability of lipoprotein(a) is ≈85% in Black individuals and ≈75% in European individuals.[24]
- The loci associated with blood lipid levels are often associated with cardiovascular and metabolic traits, including CAD, type 2 diabetes, hypertension, waist-hip ratio, and BMI.[25] Mendelian randomization studies confirm causal associations between LDL-C, triglycerides, non–HDL-C, apolipoprotein B, and CAD and coronary events but do not support a causal role for apolipoprotein A1 or HDL-C.[26–31]

## Familial Hypercholesterolemia

- FH is an autosomal codominant genetic disorder that has been associated with pathogenic variants in *LDLR*, *APOB*, *LDLRAP1*, and *PCSK9*, which affect uptake and clearance of LDL-C.[32,33] Fewer than 10% of patients with FH have actually been diagnosed.[34]

- According to a meta-analysis of data from 11 million individuals worldwide, the pooled estimate of heterozygous FH prevalence was 0.32% (95% CI, 0.26%–0.39%), or 1 in 313 individuals worldwide. The prevalence of homozygous FH was estimated as 1 in 400 000.[32,35]
- According to a meta-analysis of data from 11 million individuals worldwide, the pooled estimate of heterozygous FH prevalence was 0.32% (95% CI, 0.26%–0.39%), or 1 in 313 individuals worldwide. The prevalence of homozygous FH was estimated as 1 in 400 000.[36]
- Individuals with the FH phenotype (LDL-C ≥190 mg/dL) experience an acceleration in CHD risk by 10 to 20 years in males and 20 to 30 years in females.[37] However, individuals with LDL-C ≥190 mg/dL and a confirmed pathogenic variant for FH representing lifelong elevation of LDL-C levels have substantially higher odds for CAD than individuals with LDL-C ≥190 mg/dL without pathogenic variants.[32]
  - Compared with individuals with LDL-C <130 mg/dL and no pathogenic variant, those with both LDL-C ≥190 mg/dL and a pathogenic variant for FH had a 22-fold increased risk for CAD (OR, 22.3 [95% CI, 10.7–53.2]).
  - Compared with individuals with LDL-C <130 mg/dL and no pathogenic variant, individuals with LDL-C ≥190 mg/dL and no pathogenic variant for FH had a 6-fold increased risk for CAD (OR, 6.0 [95% CI, 5.2–6.9]).
- In a Norwegian registry–based cohort, adults with genetic FH also had a significantly higher incidence of severe aortic stenosis requiring replacement at a mean of 65 years of age (standardized incidence ratio, 7.7 [95% CI, 5.2–11.5] during 18 300 person-years of follow-up) compared with the total Norwegian population (24 incident cases compared with 3.1 expected cases).[38]
- Among 48 741 individuals 40 to 69 years of age with genotyping array and exome sequencing data from the UK Biobank, a pathogenic variant associated with FH was identified in 0.6%.[39] Among participants with a pathogenic variant associated with FH compared with those without a pathogenic variant associated with FH, risk of premature ASCVD (≤55 years of age) was higher (HR, 3.17 [95% CI, 1.96–5.12]).
- Among 2404 adult patients (mean, 45.5 years of age [SD, 15.4 years]) with FH in a multicenter, nationwide cohort study (SAFEHEART), independent predictors of ASCVD over a mean follow-up of 5.5 years (SD, 3.2 years) included traditional clinical risk factors for ASCVD (age [30–59 years versus <30 years: 2.92 (95% CI, 1.14–7.52); ≥60 years versus <30 years: 4.27 (95% CI, 1.60–11.48)], male sex [2.01 (95% CI, 1.33–3.04)], HBP [1.99 (95% CI, 1.26–3.15)], overweight [2.40 (95% CI, 1.36–4.23)] or obesity [2.67 (95% CI, 1.47–4.85)], smoking [1.62 (95% CI, 1.08–2.44)], and lipoprotein[a] level >50 mg/dL [1.52 (95% CI, 1.05–2.21)]).[40]
- In a 20-year follow-up study, early initiation of statin treatment among 214 children with FH was associated with a decrease in LDL-C by 32%, slowed progression of subclinical atherosclerosis (carotid IMT change, 0.0056 mm/y, not significantly different from unaffected siblings), and lower cumulative incidence of cardiovascular events (1% versus 26%) and death resulting from cardiovascular causes (0% versus 7%) by 39 years of age compared with affected parents.[41]
- In NHANES 1999 to 2014, despite a high frequency of cholesterol screening and awareness (>80%), statin use was low in adults with definite/probable FH (52.3% [SE, 8.2%]) and with severe dyslipidemia (37.6% [SE, 1.2%]).[42] Among adults with diagnosed FH in the CASCADE FH Registry, 25% achieved LDL-C <100 mg/dL and 41% achieved LDL-C reduction ≥50%. Factors associated with ≥50% reduction from untreated LDL-C levels were high-intensity statin use (OR, 7.33 [95% CI, 1.86–28.86]; used in 42%) and use of >1 medication to lower LDL-C (OR, 1.80 [95% CI, 1.34–2.41]; used in 45%).[43]
- Among 493 children with diagnosed FH in the CASCADE FH Registry, the mean age at diagnosis was 9.4 years (SD, 4.0 years); the mean highest pretreatment LDL-C was 238 mg/dL (SD, 61 mg/dL); 1 or ≥2 additional CVD risk factors were present in 35.1% and 8.7%, respectively; and 64% of participants used lipid-lowering therapy (56% used a statin) with a mean age at initiation of 11.1 years (SD, 3.2 years). Among 315 participants ≥10 years of age with either pretreatment LDL-C ≥190 mg/dL or pretreatment LDL-C ≥160 mg/dL plus family history of premature CVD, 76.5% were using lipid-lowering therapy (statin in 71.6%, nutraceutical in 7.3%). Only 27.6% of children overall and 39% of children receiving lipid-lowering therapy achieved the recommended LDL-C of either ≥50% decrease from baseline or <130 mg/dL.[44] These figures are similar to the medians reported for 8 European countries, although there is substantial variation between countries.[45]
- Cascade screening, meaning cholesterol testing for all first-degree relatives of patients with FH, can be an effective strategy to identify affected family members who would benefit from therapeutic intervention.[46] A systematic review of 10 studies of cascade testing for FH identified that the average yield {diagnostic yield=[positive cases (n)/total tested (n)]×100} was 44.8%, and the mean number of new cases per index case was 1.65.[47]

- A 2020 modeling study found that child-parent cascade screening, consisting of universal screening of children at 1 year of age during immunizations followed by cascade screening of relatives, was more effective than either cascade or child-parent screening in isolation at shortening the time to identify 25%, 50%, and 75% of FH cases in the population; the estimates for the United States were 6, 16, and 30 years of age, respectively, to reach these proportions.[48]
- In a report of 24 pediatric patients with biallelic (homozygous or compound heterozygous) FH in Germany, mean age at diagnosis was 6.3 years (SD, 3.4 years), and mean LDL-C at diagnosis was 752 mg/dL (SD, 193 mg/dL). Twenty-one patients were diagnosed on the basis of clinical lipid deposits (xanthomas/xanthelasmas), and 3 were diagnosed after screening on the basis of family history of biallelic FH. Diet and medications alone reduced LDL-C by 32.2% (SD, 18.0%) to a mean of 510 mg/dL (SD, 201 mg/dL), whereas weekly or twice-weekly lipoprotein apheresis resulted in an additional reduction of 63.9% (SD, 15.5%) to a mean LDL-C of 184 mg/dL (SD, 83 mg/dL) between apheresis treatments. After apheresis was started at a mean age of 8.5 years (SD, 3.1 years), 67% of patients remained clinically stable (no ASCVD events or interventions) over a mean follow-up of 17.2 years (SD, 5.6 years).[49]

## Familial Combined Hyperlipidemia

- Familial combined hyperlipidemia is a complex oligogenic disorder that affects 1% to 3% of the general population, which makes it the most prevalent primary dyslipidemia. In individuals with premature CAD, the prevalence is as high as 14%. Familial combined hyperlipidemia has a heterogeneous clinical presentation within families and within individuals, including fluctuating elevations in LDL-C or triglycerides, as well as elevated apolipoprotein B levels. Environmental interactions are important in familial combined hyperlipidemia, and metabolic comorbidities are common. Familial combined hyperlipidemia remains underdiagnosed.[50]

## Screening

- According to BRFSS 2021, the median crude prevalence of adults reporting that they had their blood cholesterol checked within the past 5 years across all states and the District of Columbia was 85.2%. In addition, 10.8% reported that they never had it checked, and 3.5% reported that it was not checked in the past 5 years. The highest age-adjusted percentages of adults who had their blood cholesterol checked in the past 5 years were in the District of Columbia (90.1%) and Puerto Rico (93.5%), whereas the state with the lowest percentage was Maine (64.7%).[51]
- In 2017 to 2018, the proportion of US adults who had cholesterol levels screened in the preceding 5 years was 65.8% for Hispanic adults, 75.0% for NH Asian adults, 70.7% for NH Black adults, and 74.1% for NH White adults.[52]
- In the United States, universal cholesterol screening with a lipid profile is recommended for all children between 9 and 11 years of age and again between 17 and 21 years of age, and reverse-cascade screening of family members is recommended for children found to have moderate to severe hypercholesterolemia.[2,53]
  - In a survey of 472 clinicians in the United States, 64.8% of pediatricians and 34.1% of family medicine physicians reported completing lipid screening of eligible pediatric-age patients within the preceding year.[54]
  - It has been estimated that in the United States the numbers of children 10 years of age needed to universally screen to identify 1 case of severe hyperlipidemia (LDL-C ≥190 mg/dL or LDL-C ≥160 mg/dL plus family history) or any hyperlipidemia (LDL-C ≥130 mg/dL) were 111 and 12, respectively. These numbers were 49 and 7, respectively, for a targeted screening program based on parental dyslipidemia or early CVD in a first-degree relative. The incremental costs of detection per case for universal (versus targeted) screening were $32 170 for severe and $1980 for any hyperlipidemia, and the universal (versus targeted) strategy would annually detect ≈8000 more children with severe hyperlipidemia and 126 000 more children with any hyperlipidemia.[55]
- In a cross-sectional analysis of primary care visits from the IQVIA National Disease and Therapeutic Index, a nationally representative audit of outpatient practices in the United States, a 36.9% decrease was noted in cholesterol level measurements in the second quarter of 2020 during the COVID-19 pandemic compared with the same time frame in 2018 to 2019.[56]
- Screening for lipoprotein(a) is uncommon. An analysis of health claims data for >9000 patients showed that only 0.6% of primary prevention and 0.7% of secondary prevention patients with laboratory data had lipoprotein(a) levels measured.[57]

## Awareness

- According to BRFSS 2021 data, 35.6% of US adults report having been told that they have high cholesterol (although objective lipid levels are not available for comparison in this sample).[51] The age-adjusted percentage of adults reporting that they have been

told they have high cholesterol was highest in Puerto Rico (36.9%), West Virginia (34.1%), and Virginia (34.1%) and lowest in Montana (25.1%).
- Among US adults with a history of clinical ASCVD, the proportion who were aware of high cholesterol levels increased from 51.5% to 67.7% between 2005 to 2006 and 2015 to 2016 ($P_{\text{linear trend}}$=0.07).[13]
- According to NHANES 2005 to 2014 data, awareness among young adults 18 to 39 years of age with high (≥240 mg/dL) or borderline high (200–239 mg/dL) TC was 56.9% (SE, 2.4%) and 22.5% (SE, 1.4%), respectively.[58]
- Among young adults in the United States who were 20 to 39 years of age with LDL-C at least 130 mg/dL, 23.3% were aware of having high cholesterol in NHANES 2015 to 2020.[59]
- Among US adults assessed in NHANES 2007 to 2016, awareness of high blood cholesterol (defined as being told by a health care professional that they had high blood cholesterol) was 25.2% in heterosexual females, 26.2% in lesbian females, 14.5% in bisexual females, and 18.9% in females who reported another sexual identity, as well as 27.1% in heterosexual males, 28.2% in gay males, 19.0% in bisexual males, and 8.4% in males who reported another sexual identity.[60]

## Treatment

- The Healthy People 2030 target for cholesterol treatment is 54.9% of eligible adults treated. In 2013 to 2016, 44.9% of eligible adults ≥21 years of age received treatment for blood cholesterol.[7]
- Among 49 447 patients with LDL-C ≥190 mg/dL in the ACC NCDR PINNACLE registry of cardiology practices between 2013 and 2016, the proportions documented as receiving medications were as follows: 58.5% statin, 31.9% high-intensity statin, 34.6% any lipid-lowering therapy associated with ≥50% reduction in LDL-C level, 8.5% ezetimibe, and 8.5% PCSK9 inhibitor. Treatment rates were even lower among the subset of individuals without preexisting ASCVD.[61]
- Among US adults with TC ≥240 mg/dL, rates of treatment with lipid-lowering therapy have increased over time but remain persistently lower in females compared with males (40% compared with 48% in 2001–2004 and 56% compared with 67% in 2013–2016 in females versus males, respectively).[62]
- Among 63 576 adult patients in the Veterans Affairs Health System between 2011 and 2014 with LDL-C ≥190 mg/dL but no diabetes or ASCVD, 52% received statin therapy and 9.7% received high-intensity statin therapy, with lower treatment rates among females (versus males) and patients <35 or >75 years of age (versus 35–75 years of age). High-intensity statin use increased over time from 8.6% in 2011 to 13.6% in 2014 ($P$<0.001).[63]
- In a study of lipid-lowering therapy after 81 372 events in US adults in the Veterans Affairs Health System, lipid-lowering therapy intensification was most common (82.5%) among those not taking lipid-lowering therapy before the coronary event.[64] Having higher baseline LDL-C, having lipid levels checked, and attending a cardiology visit after the event were associated with a greater likelihood of intensification of lipid-lowering therapy.
- Among US adults with diabetes who were 40 to 75 years of age, statin use increased from 48.5% in 2011 to 2014 to 53.0% in 2015 to 2018.[65]
- Among US adults with a 10-year predicted ASCVD risk ≥7.5%, the proportion taking a statin increased from 27.9% to 32.5% between 2005 to 2006 and 2015 to 2016.[13]
- In US adults without a history of CVD at borderline (5%–7.5%) or intermediate (7.5%–20%) 10-year ASCVD risk, 55% and 53%, respectively, had at least 1 ASCVD risk-enhancing factor, as defined by the 2019 CVD Primary Prevention Clinical Practice Guidelines.[3,66] Among those with any risk-enhancing factors, only 23% were on a statin for primary prevention.
- Among 2963 visits of patients with a history of stroke or TIA in the NAMCS, statin therapy was initiated or continued in 35.7% of office visits.[67] Among factors associated with statin prescription, office visits in rural areas were associated with a lower likelihood of statin prescription compared with office visits in urban areas (OR, 0.64 [95% CI, 0.41–0.99]).
- In an analysis of adults with IHD in the NAMCS from 2006 to 2018, 46.6% of patients were using or prescribed a statin.[68] Higher odds of statin use were observed among middle-aged (50–74 years of age: OR, 1.65 [95% CI, 1.28–2.13]) and older (≥75 years of age: OR, 1.66 [95% CI, 1.26–2.19]) patients compared with younger patients (18–49 years of age) and among patients who were male (OR, 1.35 [95% CI, 1.23–1.48]) compared with female. Lower odds of statin use were observed among patients who were of NH Black (OR, 0.75 [95% CI, 0.61–0.91]) and Hispanic (OR, 0.74 [95% CI, 0.60–0.92]) race and ethnicity compared with NH White patients. In this database, there was no significant change in statin use from 2006 (44.1%) to 2018 (46.2%).
- Among US adults assessed in NHANES 2007 to 2016, use of lipid-lowering medication was 7.7% in heterosexual females, 0% in lesbian females, 1.1% in bisexual females, and 5.5% in females who reported another sexual identity, as well as 9.6% in heterosexual males, 8.5% in gay males, 9.6% in bisexual males, and 0% in males who reported another sexual identity.[60]

- In ≈350 000 patients who were 40 to 79 years of age in the Kaiser Permanente Southern California health system with lipid information before (March 2019–March 2020) and during (December 2020–December 2021) the COVID-19 pandemic, statin use increased from 37.7% to 42.4%.[15]
- In an analysis of adults in NHANES from 2017 to 2020 examining statin use in different ASCVD risk groups, the proportion not on statin therapy was highest in those with LDL-C ≥190 mg/dL (92.8%) and those with intermediate ASCVD risk plus risk-enhancing factors (74.6%), followed by those with high ASCVD risk (59.4%), those with diabetes (54.8%), and those with established ASCVD (41.5%).[69]
- Among 81 332 participants with diabetes in the All of Us Program, 49.8% were not on statin therapy.[70] Only 18.2% of those with diabetes and ASCVD were on high-intensity statins. Overall, 5.1% were using ezetimibe and 0.6% were using PCSK9 inhibitors. Overall, 1.9% of participants with triglycerides ≥150 mg/dL were on icosapent ethyl.
- In the PROMINENT trial of >10 000 patients with type 2 diabetes, mild to moderate hypertriglyceridemia (200–499 mg/dL), and HDL-C ≤40 mg/dL; on guideline-directed lipid-lowering therapy; or with adverse reactions to statins who were randomized to receive pemafibrate or placebo, there was no significant difference between groups in the primary outcome of MACEs (HR, 1.03 [95% CI, 0.91–1.15]). The group receiving pemafibrate showed an increase in LDL-C and apolipoprotein B levels.[71]
- In a patient-level analysis of 3655 patients in the ORION-9, -10, and -11 trials who had heterozygous FH, ASCVD, or ASCVD risk equivalent on maximally tolerated statin therapy randomized to receive inclisiran versus placebo, over 18 months, the participants on inclisiran had a lower likelihood of MACEs (7.1% versus 9.4% receiving placebo: OR, 0.74 [95% CI, 0.58–0.94]), although there was no significant difference in incidence of fatal and nonfatal MI (1.8% versus 2.3%) or fatal and nonfatal stroke (0.7% versus 0.8%).[72]
- In the CLEAR Outcomes trial of 13 970 patients who had or at were high risk for CVD, who were unable to take statins, or who were statin intolerant randomized to receive bempedoic acid or placebo, the incidence of MACEs was lower among patients who received bempedoic acid (11.7%) compared with placebo (13.3%; HR, 0.87 [95% CI, 0.79–0.96]), although no significant differences in fatal or nonfatal stroke, death resulting from cardiovascular causes, or all-cause mortality were observed.[73]

## Control

- Among US adults receiving statin therapy, age-adjusted rates of lipid control (TC ≤200 mg/dL) did not significantly change over time, from 78.5% in 2007 to 2008 to 79.5% in 2017 to 2018, with similar patterns by sex.[11] Between 2007 to 2008 and 2017 to 2018, lipid control statistically significantly improved among Mexican American adults (73.0% to 86.5%) but did not significantly change among Black adults (67.4% to 73.1%), White adults (79.9% to 82.0%), or Asian adults (78.5% in 2011 to 2012 to 75.2% in 2017 to 2018).
- During 2013 to 2016, among US adults with type 2 diabetes, LDL-C <100 mg/dL was present in 56.8% without ASCVD, and LDL-C <70 mg/dL was achieved in 26.4% with ASCVD.[74]
- An analysis of the Truven Marketscan Database showed that among patients with ASCVD, 74.2% had an LDL-C level of ≥70 mg/dL, with more than half of these patients not on statins or ezetimibe. In addition, only 9.2% of patients with ASCVD and LDL-C ≥70 mg/dL were on a high-intensity statin.[75]

## Mortality and Complications

- Among 18 288 healthy young and middle-aged adults in 4 US cohorts (ARIC, FHS Offspring, CARDIA, MESA) followed up for a median of 16 years, the highest quartiles of cumulative LDL-C exposure level and time-weighted average LDL-C were associated with incident CHD (aHR, 1.57 [95% CI, 1.10–2.23] for cumulative LDL-C level; aHR, 1.69 [95% CI, 1.23–2.31] for time-weighted average LDL-C) relative to the lowest quartile of each measure, adjusted for demographic and clinical risk factors and index visit LDL-C.[76]
- In 589 participants in the Cardiovascular Risk in Young Finns Study with non–HDL-C measured in adolescence (12–18 years of age), young adulthood (21–30 years of age), and midadulthood (33–45 years of age), a 38.61–mg/dL higher non–HDL-C at each life stage was associated with higher odds of CAC in midadulthood, adjusted for cardiovascular risk factors (adolescence aOR, 1.16 [95% credible interval, 1.01–1.46]; young adulthood aOR, 1.14 [95% credible interval, 1.01–1.43]; midadulthood aOR, 1.12 [95% credible interval 1.01–1.34]), with an accumulated aOR for CAC of 1.50 (95% credible interval, l.14-1.92).[77]
- In a large study of the National Health Insurance Service in Korea (N=15 860 253) starting in 2009 to 2010 that evaluated 555 802 deaths resulting from all causes during a mean of 8.4 years of follow-up through 2018, a U-shaped association of HDL-C with all-cause mortality was observed. Relative to HDL-C levels of 50 to 59 mg/dL, individuals at the lowest HDL-C levels (<20 mg/dL) had higher risk for all-cause mortality (aHR for males, 3.03 [95% CI, 2.84–3.24]; aHR for females, 2.10 [95% CI, 1.84–2.40]), and individuals at the highest

HDL-C levels (≥110 mg/dL) also had higher risk for all-cause mortality (aHR for males, 1.30 [95% CI, 1.23–1.38]; aHR for females, 1.21 [95% CI, 1.11–1.31]).[78]

- A mendelian randomization analysis of data from 654 783 participants including 91 129 cases of CHD demonstrated that triglyceride-lowering variants in the lipoprotein lipase gene and LDL-C–lowering variants in the LDL receptor gene were associated with similarly lower CHD risk when evaluated per 10–mg/dL lower apolipoprotein B level (OR, 0.771 [95% CI, 0.741–0.802] and 0.773 [95% CI, 0.747–0.801]), respectively. This suggested that the clinical benefit of both triglyceride and LDL-C lowering might be related to the absolute reduction in apolipoprotein B–containing lipoprotein particles (very-low-density lipoprotein and LDL particles, respectively).[30]
- In a systematic review and trial-level meta-regression analysis that included 197 270 participants from 24 nonstatin trials and 25 statin trials, the RR of major vascular events was 0.80 (95% CI, 0.76–0.85) per 1–mmol/L reduction in LDL-C (or 0.79 per 40 mg/dL) and 0.84 (95% CI, 0.75–0.94) per 1–mmol/L reduction in triglycerides (0.92 per 40 mg/dL).[79]
- A meta-analysis of 21 RCTs of lipid-lowering therapies, including statins, ezetimibe, and PCSK9 inhibitors, comprising 184 012 patients with mean 4.4 years of follow-up showed greater RR reduction of major vascular events with increasing duration of treatment: each 1 mmol/L of LDL-C lowered was associated with a 12% (95% CI, 8%–16%) RR reduction for year 1, 20% (95% CI, 16%–24%) reduction for year 3, 23% (95% CI, 18%–27%) reduction for year 5, and 29% (95% CI, 14%–42%) reduction for year 7.[80]
- Among 20 490 adults who had an MI or coronary revascularization in Stockholm, Sweden, between 2012 and 2018 and initiated lipid-lowering therapy, the risk of MACEs was significantly lower for each 10% increase in 1-year adherence (HR, 0.94 [95% CI, 0.93–0.96]), intensity (HR, 0.92 [95% CI, 0.88–0.96]), and adherence-adjusted intensity (HR, 0.91 [95% CI, 0.89–0.94]).[81]
- In >460 000 individuals from the UK Biobank, the risk of incident ASCVD per 50 nmol/L lipoprotein(a) was similar across ethnicity, with an HR of 1.11 (95% CI, 1.10–1.12) in White, 1.10 (95% CI, 1.04–1.16) in South Asian, and 1.07 (95% CI, 1.00–1.15) in Black individuals.[9] Lipoprotein(a) ≥150 nmol/L was present in 12.2% of those without and 20.3% of those with preexisting ASCVD and was associated with an HR of 1.50 (95% CI, 1.44–1.56) and 1.16 (95% CI, 1.05–1.27) for incident ASCVD, respectively.
- In an analysis among >435 000 adults in the U.K. Biobank, each 50-nmol/L-higher lipoprotein(a) was associated with a higher risk of AF (HR, 1.03 [95% CI, 1.02–1.04]).[82] Only 39% (95% CI, 27%–73%) of the lipoprotein(a)-associated risk was mediated through ASCVD, suggesting that lipoprotein(a) may increase risk of AF independently of its effect on ASCVD risk.
- Among 502 655 adults 40 to 69 years of age in the UK Biobank, a linear association between higher prepandemic HDL-C level and later COVID-19–related hospitalization was observed.[83] Each 0.2–mmol/L higher HDL-C level was associated with 7% lower odds of hospitalization (aOR, 0.93 [95% CI, 0.90–0.96]).

## Cost

- In an analysis of 2016 US health care spending, hyperlipidemia ranked the 35th most expensive health condition, with estimated spending of $26.4 billion (95% CI, $24.3–$29.4 billion) overall.[84] Costs were split relatively evenly between younger and older adults (51.0% for 20–64 years of age, 48.4% for ≥65 years of age, 0.6% for <20 years of age), were higher for public versus private insurance (49.1% public insurance, 43.8% private insurance, 7.1% out-of-pocket payments), and were concentrated in prescription medications and ambulatory visits (45.6% prescribed pharmaceuticals, 33.4% ambulatory care, 5.9% inpatient care, 4.7% nursing care facility, 0.5% ED). Hyperlipidemia was among the conditions with the highest annual spending growth for public insurance from 1999 to 2016 at 9.3% (95% CI, 8.2%–10.4%) per year; annual spending growth for hyperlipidemia was 5.2% overall, 4.0% for private insurance, and −0.9% for out-of-pocket payments.
- Among Medicare Part D beneficiaries in the United States from 2014 to 2018, Medicare expenditure for LDL-C–lowering therapy decreased 46% from $6.3 billion in 2014 to $3.3 billion in 2018.[85]

## Global Burden of Hypercholesterolemia (See Chart 7-5 and Table 7-2)

- Among the GBD data, global years of life lost attributable to high LDL-C totaled 5.71 million (95% UI, 3.68–8.27) in 2019. LDL-C was the third highest contributor to CVD DALYs in 2019, after high SBP and dietary risks.[86]
- Based on 204 countries and territories, age-standardized mortality rates attributable to high LDL cholesterol were highest in central Asia and eastern Europe, followed by North Africa and the Middle East in 2021 (Chart 7-5). There were 3.72 (95% UI, 2.16-5.30) million deaths attributable to high LDL cholesterol in 2021. The PAF was 5.39% (95% UI, 3.09%–7.60%; Table 7-2).

**Table 7-1. High TC and LDL-C and Low HDL-C, United States (≥20 Years of Age), 2017 to 2020**

| Population group | Prevalence of TC ≥200 mg/dL | Prevalence of TC ≥240 mg/dL | Prevalence of LDL-C ≥130 mg/ dL | Prevalence of HDL-C <40 mg/dL |
|---|---|---|---|---|
| Both sexes | 86 400 000 (34.7) | 24 700 000 (10.0) | 63 100 000 (25.5) | 41 300 000 (16.9) |
| Males | 38 900 000 (32.8) | 11 000 000 (9.5) | 30 300 000 (25.6) | 29 900 000 (24.9) |
| Females | 47 500 000 (36.2) | 13 700 000 (10.4) | 32 800 000 (25.4) | 11 400 000 (9.3) |
| NH White males | 32.5 | 9.6 | 25.0 | 25.0 |
| NH White females | 37.2 | 10.7 | 24.0 | 8.8 |
| NH Black males | 27.5 | 6.9 | 26.4 | 15.3 |
| NH Black females | 29.6 | 9.3 | 22.5 | 7.9 |
| Hispanic males | 32.8 | 9.3 | 23.7 | 29.5 |
| Hispanic females | 33.6 | 10.0 | 27.5 | 11.8 |
| NH Asian males | 40.7 | 13.0 | 31.5 | 25.4 |
| NH Asian females | 37.7 | 8.7 | 25.3 | 6.9 |

Values are number (percent) or percent. Prevalence of TC ≥200 mg/dL includes people with TC ≥240 mg/dL. In adults, levels of 200 to 239 mg/dL are considered borderline high, and levels of ≥240 mg/dL are considered high. Data for TC, LDL-C, and HDL-C are age adjusted. In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.[87]

COVID-19 indicates coronavirus disease 2019; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NH, non-Hispanic; NHANES, National Health and Nutrition Examination Survey; and TC, total cholesterol.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES,[5] applied to 2020 population estimates.

**Table 7.2. Deaths Caused by High LDL-C Worldwide, by Sex, 2021**

| | Deaths | | |
|---|---|---|---|
| | Both sexes (95% UI) | Male (95% UI) | Female (95% UI) |
| Total number of deaths (millions), 2021 | 3.72 (2.16 to 5.30) | 2.05 (1.26 to 2.86) | 1.68 (0.94 to 2.42) |
| Percent change in total number, 1990–2021 | 51.53 (44.63 to 60.09) | 60.77 (50.26 to 73.74) | 41.58 (32.02 to 50.49) |
| Percent change in total number, 2010–2021 | 19.82 (15.48 to 26.38) | 20.86 (13.28 to 29.77) | 18.58 (12.01 to 24.51) |
| Mortality rate per 100 000, age standardized, 2021 | 44.10 (25.49 to 63.04) | 53.18 (31.66 to 74.92) | 35.73 (20.03 to 51.57) |
| Percent change in rate, age standardized, 1990–2021 | −38.53 (−41.23 to −34.96) | −34.94 (−38.76 to −29.96) | −42.47 (−46.27 to −38.97) |
| Percent change in rate, age standardized, 2010–2021 | −14.81 (−18.19 to −10.12) | −13.11 (−18.25 to −7.05) | −16.45 (−21.03 to 12.09) |
| PAF, all ages, 2021, % | 5.39 (3.09 to 7.60) | 5.35 (3.24 to 7.41) | 5.44 (2.98 to 7.87) |
| Percent change in PAF, all ages, 1990–2021 | 1.56 (−2.59 to 5.62) | 4.40 (−1.02 to 9.46) | −1.46 (−6.74 to 2.56) |
| Percent change in PAF, all ages, 2010–2021 | −7.99 (−10.26 to −5.65) | −8.36 (−11.34 to −5.16) | −7.54 (−10.58 to −4.94) |

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Disease; LDL-C, low-density lipoprotein cholesterol; PAF, population attributable fraction; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[88]

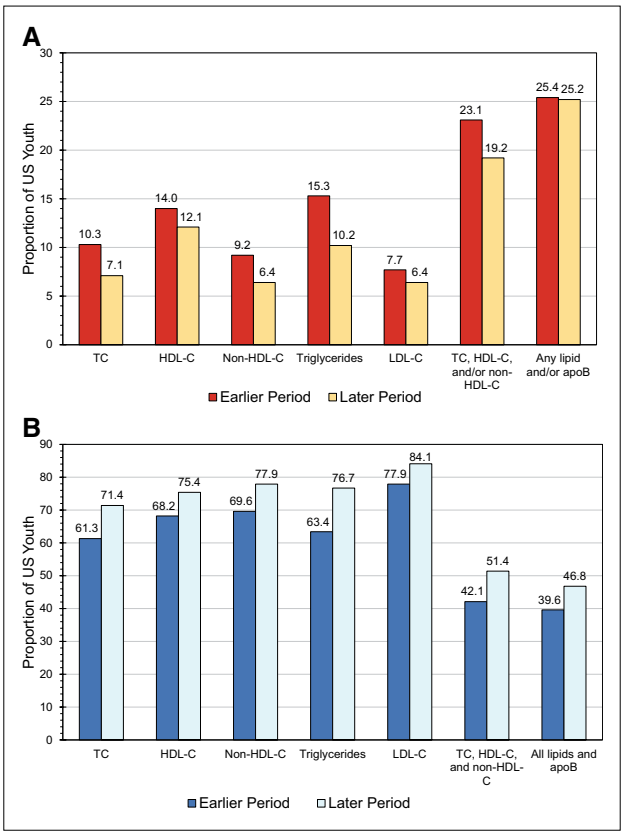



**Chart 7-1. Proportions of US youth with guideline-defined high (or, for HDL-C, low) and acceptable lipid levels in the period of 1999 to 2016, NHANES.**

**A**, High (or, for HDL-C, low) lipid levels. **B**, Acceptable lipid levels. TC, HDL-C, and non–HDL-C are shown for all youth 6 to 19 years of age, and triglycerides, LDL-C, and any or all lipids plus apoB are shown for fasting adolescents 12 to 19 years of age. **A**, For high (or, for HDL-C, low) lipid levels, the earlier and later periods shown for each lipid are as follows: 1999 to 2006 and 2009 to 2016 for TC; 2007 to 2010 and 2013 to 2016 for HDL-C; 2007 to 2010 and 2013 to 2016 for non–HDL-C; 1999 to 2006 and 2007 to 2014 for triglycerides; 1999 to 2006 and 2007 to 2014 for LDL-C; 2007 to 2010 and 2013 to 2016 for any of TC, HDL-C, or non–HDL-C; and 2007 to 2010 and 2011 to 2014 for any lipid or apoB. **B**, For acceptable lipid levels, the earlier and later periods shown for each lipid are as follows: 1999 to 2000 and 2015 to 2016 for TC; 2007 to 2008 and 2015 to 2016 for HDL-C; 2007 to 2008 and 2015 to 2016 for non–HDL-C; 1999 to 2000 and 2013 to 2014 for triglycerides; 1999 to 2000 and 2013 to 2014 for LDL-C; 2007 to 2008 and 2015 to 2016 for TC, HDL-C, and non–HDL-C; and 2007 to 2008 and 2013 to 2014 for all lipids and apoB. High (or, for HDL-C, low) and acceptable levels were defined according to the 2011 National Heart, Lung, and Blood Institute pediatric guideline[53] as follows: for TC, ≥200 and <170 mg/dL, respectively; for LDL-C, ≥130 and <110 mg/dL; for HDL-C, <40 and >45 mg/dL; for non–HDL-C, ≥145 and <120 mg/dL; for triglycerides, ≥130 and <90 mg/dL; and for apoB, ≥110 and <90 mg/dL.

apoB indicates apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NHANES, National Health and Nutrition Examination Survey; and TC, total cholesterol.

Source: Data derived from Perak et al.[6]

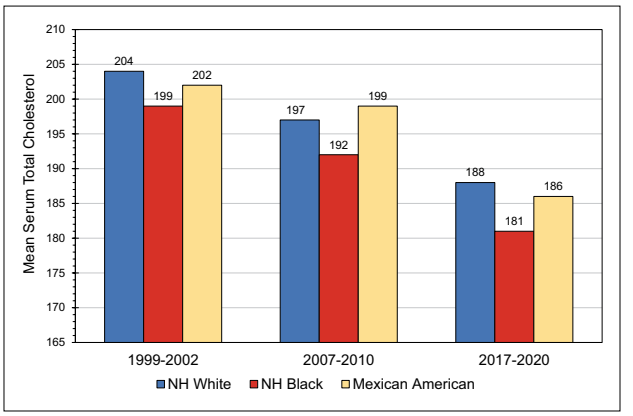



**Chart 7-2. Age-adjusted trends in mean serum TC among US adults ≥20 years of age, by race and ethnicity and survey year (NHANES 1999–2002, 2007–2010, and 2017–2020).**

Values are in milligrams per deciliter. In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.[87]

COVID-19 indicates coronavirus disease 2019; NH, non-Hispanic; NHANES, National Health and Nutrition Examination Survey; and TC, total cholesterol.

*Data for the category of Mexican American people were consistently collected in all NHANES years, but the combined category of Hispanic people was used starting only in 2007. Consequently, for long-term trend data, the category of Mexican American people is used.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.[5]

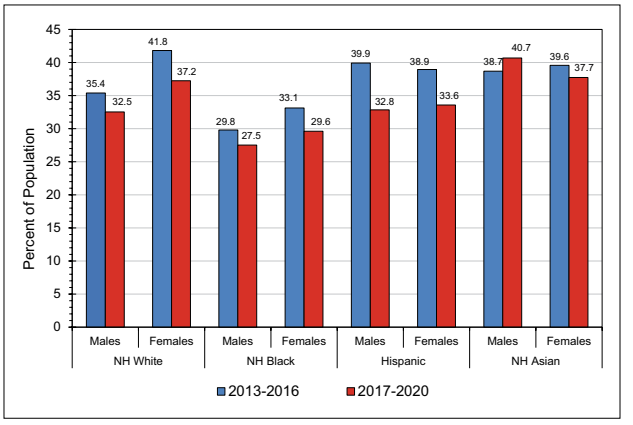



**Chart 7-3. Age-adjusted trends in the prevalence of serum TC ≥200 mg/dL in US adults ≥20 years of age, by race and ethnicity, sex, and survey year (NHANES 2013–2016 and 2017–2020).**

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.[87]

COVID-19 indicates coronavirus disease 2019; NH, non-Hispanic; NHANES, National Health and Nutrition Examination Survey; and TC, total cholesterol.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.[5]

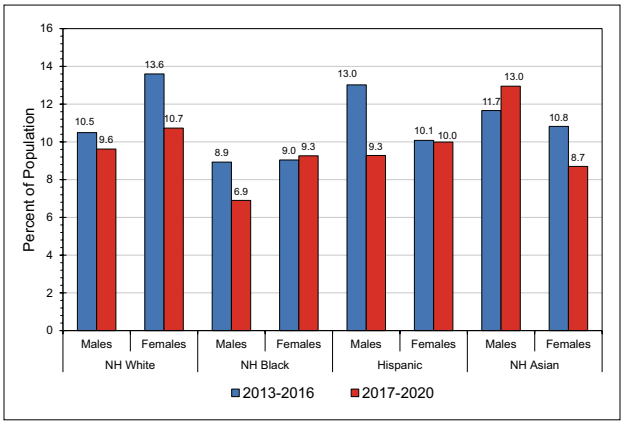



**Chart 7-4. Age-adjusted trends in the prevalence of serum TC ≥240 mg/dL in US adults ≥20 years of age, by race and ethnicity, sex, and survey year (NHANES 2013–2016 and 2017–2020).**

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.[87]

COVID-19 indicates coronavirus disease 2019; NH, non-Hispanic; NHANES, National Health and Nutrition Examination Survey; and TC, total cholesterol.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.[5]

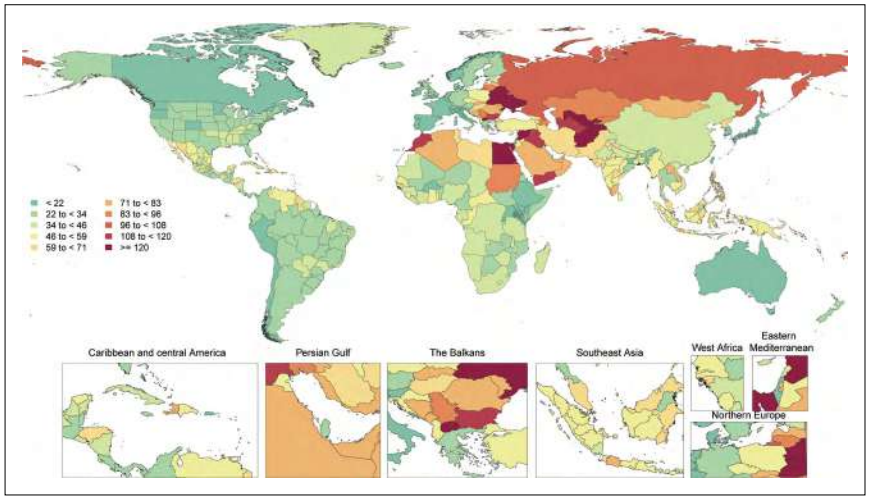



**Chart 7-5. Age-standardized global mortality rates attributable to high LDL-C per 100 000, both sexes, 2021.**

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Disease; and LDL-C, low-density lipoprotein cholesterol.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[88]

## REFERENCES


1. Lloyd-Jones DM, Allen NB, Anderson CAM, Black T, Brewer LC, Foraker RE, Grandner MA, Lavretsky H, Perak AM, Sharma G, et al; on behalf of the American Heart Association. Life's Essential 8: updating and enhancing the American Heart Association's construct of cardiovascular health: a presidential advisory from the American Heart Association. *Circulation*. 2022;146:e18–e43. doi: 10.1161/CIR.0000000000001078
2. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol [published corrections appear in *Circulation*. 2019;139:e1182–e1186 and *Circulation*. 2023;148:e5]. *Circulation*. 2019;139:e1082–e1143. doi: 10.1161/CIR.0000000000000625
3. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease [published corrections appear in *Circulation*. 2019;140:e649–e650, *Circulation*. 2020;141:e60, and *Circulation*. 2020;141:e774]. *Circulation*. 2019;140:e596–e646. doi: 10.1161/CIR.0000000000000678
4. Lloyd-Jones DM, Morris PB, Ballantyne CM, Birtcher KK, Covington AM, DePalma SM, Minissian MB, Orringer CE, Smith SC Jr, Waring AA, et al; Writing Committee. 2022 ACC expert consensus decision pathway on the role of nonstatin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2022;80:1366–1418. doi: 10.1016/j.jacc.2022.07.006
5. Centers for Disease Control and Prevention and National Center for Health Statistics. National Health and Nutrition Examination Survey (NHANES) public use data files. Accessed April 1, 2023. https://cdc.gov/nchs/nhanes/
6. Perak AM, Ning H, Kit BK, de Ferranti SD, Van Horn LV, Wilkins JT, Lloyd-Jones DM. Trends in levels of lipids and apolipoprotein B in US youths aged 6 to 19 years, 1999-2016. *JAMA*. 2019;321:1895–1905. doi: 10.1001/jama.2019.4984
7. US Department of Health and Human Services. Healthy People 2030. Accessed March 14, 2023. https://health.gov/healthypeople/objectives-and-data/browse-objectives/heart-disease-and-stroke
8. Aggarwal R, Chiu N, Libby P, Boden WE, Bhatt DL. Low-density lipoprotein cholesterol levels in adults with coronary artery disease in the US, January 2015 to March 2020. *JAMA*. 2023;330:80–82. doi: 10.1001/jama.2023.8646
9. Patel AP, Wang M, Pirruccello JP, Ellinor PT, Ng K, Kathiresan S, Khera AV. Lp(a) (Lipoprotein[a]) concentrations and incident atherosclerotic cardiovascular disease: new insights from a large national biobank. *Arterioscler Thromb Vasc Biol*. 2021;41:465–474. doi: 10.1161/ATVBAHA.120.315291
10. Aberra T, Peterson ED, Pagidipati NJ, Mulder H, Wojdyla DM, Philip S, Granowitz C, Navar AM. The association between triglycerides and incident cardiovascular disease: What is "optimal"? *J Clin Lipidol*. 2020;14:438–447.e3. doi: 10.1016/j.jacl.2020.04.009
11. Aggarwal R, Bhatt DL, Rodriguez F, Yeh RW, Wadhera RK. Trends in lipid concentrations and lipid control among US adults, 2007-2018. *JAMA*. 2022;328:737–745. doi: 10.1001/jama.2022.12567
12. Carroll MD, Fryar CD. Total and high-density lipoprotein cholesterol in adults: United States, 2015-2018. *NCHS Data Brief*. 2020:1–8.
13. Patel N, Bhargava A, Kalra R, Parcha V, Arora G, Muntner P, Arora P. Trends in lipid, lipoproteins, and statin use among U.S. adults: impact of 2013 cholesterol guidelines. *J Am Coll Cardiol*. 2019;74:2525–2528. doi: 10.1016/j.jacc.2019.09.026
14. Aggarwal R, Yeh RW, Joynt Maddox KE, Wadhera RK. Cardiovascular risk factor prevalence, treatment, and control in US adults aged 20 to 44 years, 2009 to March 2020. *JAMA*. 2023;329:899–909. doi: 10.1001/jama.2023.2307
15. Lee MS, Chen A, Zhou H, Herald J, Nayak R, Shen YA. Control of atherosclerotic risk factors during the COVID-19 pandemic in the U.S. *Am J Prev Med*. 2023;64:125–128. doi: 10.1016/j.amepre.2022.08.007
16. Carroll MD, Kruszon-Moran D, Tolliver E. Trends in apolipoprotein B, non-high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol for adults aged 20 and over, 2005-2016. *Natl Health Stat Rep*. 2019;127:1–16.
17. Willer CJ, Schmidt EM, Sengupta S, Peloso GM, Gustafsson S, Kanoni S, Ganna A, Chen J, Buchkovich ML, Mora S, et al; Global Lipids Genetics Consortium. Discovery and refinement of loci associated with lipid levels. *Nat Genet*. 2013;45:1274–1283. doi: 10.1038/ng.2797
18. Peloso G, Auer P, Bis J, Voorman A, Morrison A, Stitziel N, Brody J, Khetarpal S, Crosby J, Fornage M. Association of low-frequency and rare coding-sequence variants with blood lipids and coronary heart disease in 56,000 Whites and Blacks. *Am J Hum Genet*. 2014;94:223–232. doi: 10.1016/j.ajhg.2014.01.009
19. Dewey FE, Murray MF, Overton JD, Habegger L, Leader JB, Fetterolf SN, O'Dushlaine C, Van Hout CV, Staples J, Gonzaga-Jauregui C, et al. Distribution and clinical impact of functional variants in 50,726 whole-exome sequences from the DiscovEHR study. *Science*. 2016;354:aaf6814. doi: 10.1126/science.aaf6814
20. Natarajan P, Peloso GM, Zekavat SM, Montasser M, Ganna A, Chaffin M, Khera AV, Zhou W, Bloom JM, Engreitz JM, et al; NHLBI TOPMed Lipids Working Group. Deep-coverage whole genome sequences and blood lipids among 16,324 individuals. *Nat Commun*. 2018;9:3391. doi: 10.1038/s41467-018-05747-8
21. Klarin D, Damrauer SM, Cho K, Sun YV, Teslovich TM, Honerlaw J, Gagnon DR, DuVall SL, Li J, Peloso GM, et al; Global Lipids Genetics Consortium. Genetics of blood lipids among ~300,000 multi-ethnic participants of the Million Veteran Program. *Nat Genet*. 2018;50:1514–1523. doi: 10.1038/s41588-018-0222-9
22. Graham SE, Clarke SL, Wu KH, Kanoni S, Zajac GJM, Ramdas S, Surakka I, Ntalla I, Vedantam S, Winkler TW, et al. The power of genetic diversity in genome-wide association studies of lipids. *Nature*. 2021;600:675–679. doi: 10.1038/s41586-021-04064-3
23. Selvaraj MS, Li X, Li Z, Pampana A, Zhang DY, Park J, Aslibekyan S, Bis JC, Brody JA, Cade BE, et al; NHLBI Trans-Omics for Precision Medicine (TOPMed) Consortium. Whole genome sequence analysis of blood lipid levels in >66,000 individuals. *Nat Commun*. 2022;13:5995. doi: 10.1038/s41467-022-33510-7
24. Zekavat SM, Ruotsalainen S, Handsaker RE, Alver M, Bloom J, Poterba T, Seed C, Ernst J, Chaffin M, Engreitz J, et al; NHLBI TOPMed Lipids Working Group. Deep coverage whole genome sequences and plasma lipoprotein(a) in individuals of European and African ancestries. *Nat Commun*. 2018;9:2606. doi: 10.1038/s41467-018-04668-w
25. Khera AV, Chaffin M, Zekavat SM, Collins RL, Roselli C, Natarajan P, Lichtman JH, D'Onofrio G, Mattera J, Dreyer R, et al. Whole-genome sequencing to characterize monogenic and polygenic contributions in patients hospitalized with early-onset myocardial infarction. *Circulation*. 2019;139:1593–1602. doi: 10.1161/CIRCULATIONAHA.118.035658
26. Allara E, Morani G, Carter P, Gkatzionis A, Zuber V, Foley CN, Rees JMB, Mason AM, Bell S, Gill D, et al; INVENT Consortium. Genetic determinants of lipids and cardiovascular disease outcomes: a wide-angled mendelian randomization investigation. *Circ Genom Precis Med*. 2019;12:e002711. doi: 10.1161/CIRCGEN.119.002711
27. Bjornsson E, Thorleifsson G, Helgadottir A, Guethnason T, Guethbjartsson T, Andersen K, Gretarsdottir S, Olafsson I, Tragante V, Olafsson OH, et al. Association of genetically predicted lipid levels with the extent of coronary atherosclerosis in Icelandic adults. *JAMA Cardiol*. 2019;5:13–20. doi: 10.1001/jamacardio.2019.2946
28. Karjalainen MK, Holmes MV, Wang Q, Anufrieva O, Kahonen M, Lehtimaki T, Havulinna AS, Kristiansson K, Salomaa V, Perola M, et al. Apolipoprotein A-I concentrations and risk of coronary artery disease: a mendelian randomization study. *Atherosclerosis*. 2020;299:56–63. doi: 10.1016/j.atherosclerosis.2020.02.002
29. Ference BA, Bhatt DL, Catapano AL, Packard CJ, Graham I, Kaptoge S, Ference TB, Guo Q, Laufs U, Ruff CT, et al. Association of genetic variants related to combined exposure to lower low-density lipoproteins and lower systolic blood pressure with lifetime risk of cardiovascular disease. *JAMA*. 2019;322:1381–1391. doi: 10.1001/jama.2019.14120
30. Ference BA, Kastelein JJP, Ray KK, Ginsberg HN, Chapman MJ, Packard CJ, Laufs U, Oliver-Williams C, Wood AM, Butterworth AS, et al. Association of triglyceride-lowering LPL variants and LDL-C-lowering LDLR variants with risk of coronary heart disease. *JAMA*. 2019;321:364–373. doi: 10.1001/jama.2018.20045
31. Richardson TG, Sanderson E, Palmer TM, Ala-Korpela M, Ference BA, Davey Smith G, Holmes MV. Evaluating the relationship between circulating lipoprotein lipids and apolipoproteins with risk of coronary heart disease: a multivariable mendelian randomisation analysis. *PLoS Med*. 2020;17:e1003062. doi: 10.1371/journal.pmed.1003062
32. Khera AV, Won HH, Peloso GM, Lawson KS, Bartz TM, Deng X, van Leeuwen EM, Natarajan P, Emdin CA, Bick AG, et al. Diagnostic yield and clinical utility of sequencing familial hypercholesterolemia genes in patients with severe hypercholesterolemia. *J Am Coll Cardiol*. 2016;67:2578–2589. doi: 10.1016/j.jacc.2016.03.520

33. Defesche JC, Stefanutti C, Langslet G, Hopkins PN, Seiz W, Baccara-Dinet MT, Hamon SC, Banerjee P, Kastelein JJP. Efficacy of alirocumab in 1191 patients with a wide spectrum of mutations in genes causative for familial hypercholesterolemia. *J Clin Lipidol*. 2017;11:1338–1346.e7. doi: 10.1016/j.jacl.2017.08.016
34. Banda JM, Sarraju A, Abbasi F, Parizo J, Pariani M, Ison H, Briskin E, Wand H, Dubois S, Jung K, et al. Finding missed cases of familial hypercholesterolemia in health systems using machine learning. *NPJ Digit Med*. 2019;2:23. doi: 10.1038/s41746-019-0101-5
35. Zhang Y, Dron JS, Bellows BK, Khera AV, Liu J, Balte PP, Oelsner EC, Amr SS, Lebo MS, Nagy A, et al. Association of severe hypercholesterolemia and familial hypercholesterolemia genotype with risk of coronary heart disease. *Circulation*. 2023;147:1556–1559. doi: 10.1161/CIRCULATIONAHA.123.064168
36. Beheshti SO, Madsen CM, Varbo A, Nordestgaard BG. Worldwide prevalence of familial hypercholesterolemia: meta-analyses of 11 million subjects. *J Am Coll Cardiol*. 2020;75:2553–2566. doi: 10.1016/j.jacc.2020.03.057
37. Perak AM, Ning H, de Ferranti SD, Gooding HC, Wilkins JT, Lloyd-Jones DM. Long-term risk of atherosclerotic cardiovascular disease in US adults with the familial hypercholesterolemia phenotype. *Circulation*. 2016;134:9–19. doi: 10.1161/CIRCULATIONAHA.116.022335
38. Mundal LJ, Hovland A, Igland J, Veierod MB, Holven KB, Bogsrud MP, Tell GS, Leren TP, Retterstol K. Association of low-density lipoprotein cholesterol with risk of aortic valve stenosis in familial hypercholesterolemia. *JAMA Cardiol*. 2019;4:1156. doi: 10.1001/jamacardio.2019.3903
39. Trinder M, Francis GA, Brunham LR. Association of monogenic vs polygenic hypercholesterolemia with risk of atherosclerotic cardiovascular disease. *JAMA Cardiol*. 2020;5:390–399. doi: 10.1001/jamacardio.2019.5954
40. Perez de Isla L, Alonso R, Mata N, Fernandez-Perez C, Muniz O, Diaz-Diaz JL, Saltijeral A, Fuentes-Jimenez F, de Andres R, Zambon D, et al. Predicting cardiovascular events in familial hypercholesterolemia: the SAFEHEART Registry (Spanish Familial Hypercholesterolemia Cohort Study). *Circulation*. 2017;135:2133–2144. doi: 10.1161/CIRCULATIONAHA.116.024541
41. Luirink IK, Wiegman A, Kusters DM, Hof MH, Groothoff JW, de Groot E, Kastelein JJP, Hutten BA. 20-Year follow-up of statins in children with familial hypercholesterolemia. *N Engl J Med*. 2019;381:1547–1556. doi: 10.1056/NEJMoa1816454
42. Bucholz EM, Rodday AM, Kolor K, Khoury MJ, De Ferranti SD. Prevalence and predictors of cholesterol screening, awareness, and statin treatment among US adults with familial hypercholesterolemia or other forms of severe dyslipidemia (1999-2014). *Circulation*. 2018;137:2218–2230. doi: 10.1161/CIRCULATIONAHA.117.032321
43. deGoma EM, Ahmad ZS, O'Brien EC, Kindt I, Shrader P, Newman CB, Pokharel Y, Baum SJ, Hemphill LC, Hudgins LC, et al. Treatment gaps in adults with heterozygous familial hypercholesterolemia in the United States: data from the CASCADE-FH Registry. *Circ Cardiovasc Genet*. 2016;9:240–249. doi: 10.1161/CIRCGENETICS.116.001381
44. de Ferranti SD, Shrader P, Linton MF, Knowles JW, Hudgins LC, Benuck I, Kindt I, O'Brien EC, Peterson AL, Ahmad ZS, et al. Children with heterozygous familial hypercholesterolemia in the United States: data from the Cascade Screening for Awareness and Detection-FH Registry. *J Pediatr*. 2021;229:70–77. doi: 10.1016/j.jpeds.2020.09.042
45. Ramaswami U, Futema M, Bogsrud MP, Holven KB, Roeters van Lennep J, Wiegman A, Descamps OS, Vrablik M, Freiberger T, Dieplinger H, et al. Comparison of the characteristics at diagnosis and treatment of children with heterozygous familial hypercholesterolaemia (FH) from eight European countries. *Atherosclerosis*. 2020;292:178–187. doi: 10.1016/j.atherosclerosis.2019.11.012
46. Knowles JW, Rader DJ, Khoury MJ. Cascade screening for familial hypercholesterolemia and the use of genetic testing. *JAMA*. 2017;318:381–382. doi: 10.1001/jama.2017.8543
47. Lee C, Rivera-Valerio M, Bangash H, Prokop L, Kullo IJ. New case detection by cascade testing in familial hypercholesterolemia: a systematic review of the literature. *Circ Genom Precis Med*. 2019;12:e002723. doi: 10.1161/CIRCGEN.119.002723
48. Wald DS, Bestwick JP. Reaching detection targets in familial hypercholesterolaemia: comparison of identification strategies. *Atherosclerosis*. 2020;293:57–61. doi: 10.1016/j.atherosclerosis.2019.11.028
49. Taylan C, Driemeyer J, Schmitt CP, Pape L, Büscher R, Galiano M, König J, Schürfeld C, Spitthöver R, Versen A, et al. Cardiovascular outcome of pediatric patients with bi-allelic (homozygous) familial hypercholesterolemia before and after initiation of multimodal lipid lowering therapy including lipoprotein apheresis. *Am J Cardiol*. 2020;136:38–48. doi: 10.1016/j.amjcard.2020.09.015
50. Bello-Chavolla OY, Kuri-Garcia A, Rios-Rios M, Vargas-Vazquez A, Cortes-Arroyo JE, Tapia-Gonzalez G, Cruz-Bautista I, Aguilar-Salinas CA. Familial combined hyperlipidemia: current knowledge, perspectives, and controversies. *Rev Invest Clin*. 2018;70:224–236. doi: 10.24875/RIC.18002575
51. Centers for Disease Control and Prevention and National Center for Chronic Disease Prevention and Health Promotion. Behavioral Risk Factor Surveillance System (BRFSS): BRFSS prevalence & trends data. Accessed March 27, 2023. https://cdc.gov/brfss/brfssprevalence/
52. Gao Y, Shah LM, Ding J, Martin SS. US trends in cholesterol screening, lipid levels, and lipid-lowering medication use in US adults, 1999 to 2018. *J Am Heart Assoc*. 2023;12:e028205. doi: 10.1161/JAHA.122.028205
53. National Heart, Lung, and Blood Institute. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: summary report. *Pediatrics*. 2011;128(suppl 5):S213–S256. doi: 10.1542/peds.2009-2107C
54. Zhang X, DeSantes K, Dodge A, Larson M, Eickhoff J, Moreno M, Peterson A. Practices and attitudes regarding pediatric cholesterol screening recommendations differ between pediatricians and family medicine clinicians. *Pediatr Cardiol*. 2022;43:631–635. doi: 10.1007/s00246-021-02767-y
55. Smith AJ, Turner EL, Kinra S, Bodurtha JN, Chien AT. A cost analysis of universal versus targeted cholesterol screening in pediatrics. *J Pediatr*. 2018;196:201–207.e2. doi: 10.1016/j.jpeds.2018.01.027
56. Alexander GC, Tajanlangit M, Heyward J, Mansour O, Qato DM, Stafford RS. Use and content of primary care office-based vs telemedicine care visits during the COVID-19 pandemic in the US. *JAMA Netw Open*. 2020;3:e2021476. doi: 10.1001/jamanetworkopen.2020.21476
57. Hu X, Cristino J, Gautam R, Mehta R, Amari D, Heo JH, Wang S, Wong ND. Characteristics and lipid lowering treatment patterns in patients tested for lipoprotein(a): a real-world US study. *Am J Prev Cardiol*. 2023;14:100476. doi: 10.1016/j.ajpc.2023.100476
58. Bucholz EM, Gooding HC, de Ferranti SD. Awareness of cardiovascular risk factors in U.S. young adults aged 18-39 years. *Am J Prev Med*. 2018;54:e67–e77. doi: 10.1016/j.amepre.2018.01.022
59. Zhang Y, An J, Reynolds K, Safford MM, Muntner P, Moran AE. Trends of elevated low-density lipoprotein cholesterol, awareness, and screening among young adults in the US, 2003-2020. *JAMA Cardiol*. 2022;7:1079–1080. doi: 10.1001/jamacardio.2022.2641
60. Caceres BA, Sharma Y, Ravindranath R, Ensari I, Rosendale N, Doan D, Streed CG. Differences in ideal cardiovascular health between sexual minority and heterosexual adults. *JAMA Cardiol*. 2023;8:335–346. doi: 10.1001/jamacardio.2022.5660
61. Virani SS, Kennedy KF, Akeroyd JM, Morris PB, Bittner VA, Masoudi FA, Stone NJ, Petersen LA, Ballantyne CM. Variation in lipid-lowering therapy use in patients with low-density lipoprotein cholesterol >/=190 mg/dl: insights from the National Cardiovascular Data Registry-Practice Innovation and Clinical Excellence Registry. *Circ Cardiovasc Qual Outcomes*. 2018;11:e004652. doi: 10.1161/CIRCOUTCOMES.118.004652
62. Peters SAE, Muntner P, Woodward M. Sex differences in the prevalence of, and trends in, cardiovascular risk factors, treatment, and control in the United States, 2001 to 2016. *Circulation*. 2019;139:1025–1035. doi: 10.1161/CIRCULATIONAHA.118.035550
63. Rodriguez F, Knowles JW, Maron DJ, Virani SS, Heidenreich PA. Frequency of statin use in patients with low-density lipoprotein cholesterol >/=190 mg/dl from the Veterans Affairs Health System. *Am J Cardiol*. 2018;122:756–761. doi: 10.1016/j.amjcard.2018.05.008
64. Zheutlin AR, Derington CG, Herrick JS, Rosenson RS, Poudel B, Safford MM, Brown TM, Jackson EA, Woodward M, Reading S, et al. Lipid-lowering therapy use and intensification among United States veterans following myocardial infarction or coronary revascularization between 2015 and 2019. *Circ Cardiovasc Qual Outcomes*. 2022;15:e008861. doi: 10.1161/CIRCOUTCOMES.121.008861
65. Leino AD, Dorsch MP, Lester CA. Changes in statin use among U.S. adults with diabetes: a population-based analysis of NHANES 2011-2018. *Diabetes Care*. 2020;43:3110–3112. doi: 10.2337/dc20-1481
66. Hammond MM, Cameron NA, Ning H, Bah I, Beltrame K, Khan SS, Shah NS. Statin use and eligibility for primary prevention of atherosclerotic cardiovascular disease among adults at borderline or intermediate risk in the United States. *J Am Heart Assoc*. 2023;12:e029263. doi: 10.1161/JAHA.122.029263
67. Snyder BM, Soric MM. National trends in statin medication prescribing in patients with a history of stroke or transient ischemic attack. *J Pharm Pract*. 2021;34:216–223. doi: 10.1177/0897190019865147
68. Minhas AMK, Ijaz SH, Javed N, Sheikh AB, Jain V, Michos ED, Greene SJ, Fudim M, Warraich HJ, Shapiro MD, et al. National trends and disparities

in statin use for ischemic heart disease from 2006 to 2018: insights from National Ambulatory Medical Care Survey. *Am Heart J.* 2022;252:60–69. doi: 10.1016/j.ahj.2022.05.015
69. Chobufo MD, Regner SR, Zeb I, Lacoste JL, Virani SS, Balla S. Burden and predictors of statin use in primary and secondary prevention of atherosclerotic vascular disease in the US: from the National Health and Nutrition Examination Survey 2017-2020. *Eur J Prev Cardiol.* 2022;29:1830–1838. doi: 10.1093/eurjpc/zwac103
70. Akbarpour M, Devineni D, Gong Y, Wong ND. Dyslipidemia treatment and lipid control in US adults with diabetes by sociodemographic and cardiovascular risk groups in the NIH Precision Medicine Initiative All of Us Research Program. *J Clin Med.* 2023;12:1668. doi: 10.3390/jcm12041668
71. Das Pradhan A, Glynn RJ, Fruchart JC, MacFadyen JG, Zaharris ES, Everett BM, Campbell SE, Oshima R, Amarenco P, Blom DJ, et al; PROMINENT Investigators. Triglyceride lowering with pemafibrate to reduce cardiovascular risk. *N Engl J Med.* 2022;387:1923–1934. doi: 10.1056/NEJMoa2210645
72. Ray KK, Raal FJ, Kallend DG, Jaros MJ, Koenig W, Leiter LA, Landmesser U, Schwartz GG, Lawrence D, Friedman A, et al; ORION Phase III Investigators. Inclisiran and cardiovascular events: a patient-level analysis of phase III trials. *Eur Heart J.* 2023;44:129–138. doi: 10.1093/eurheartj/ehac594
73. Nissen SE, Lincoff AM, Brennan D, Ray KK, Mason D, Kastelein JJP, Thompson PD, Libby P, Cho L, Plutzky J, et al; CLEAR Outcomes Investigators. Bempedoic acid and cardiovascular outcomes in statin-intolerant patients. *N Engl J Med.* 2023;388:1353–1364. doi: 10.1056/NEJMoa2215024
74. Andary R, Fan W, Wong ND. Control of cardiovascular risk factors among US adults with type 2 diabetes with and without cardiovascular disease. *Am J Cardiol.* 2019;124:522–527. doi: 10.1016/j.amjcard.2019.05.035
75. Klimchak AC, Patel MY, Iorga SR, Kulkarni N, Wong ND. Lipid treatment and goal attainment characteristics among persons with atherosclerotic cardiovascular disease in the United States. *Am J Prev Cardiol.* 2020;1:100010. doi: 10.1016/j.ajpc.2020.100010
76. Zhang Y, Pletcher MJ, Vittinghoff E, Clemons AM, Jacobs DR Jr, Allen NB, Alonso A, Bellows BK, Oelsner EC, Zeki Al Hazzouri A, et al. Association between cumulative low-density lipoprotein cholesterol exposure during young adulthood and middle age and risk of cardiovascular events. *JAMA Cardiol.* 2021;6:1406–1413. doi: 10.1001/jamacardio.2021.3508
77. Armstrong MK, Fraser BJ, Hartiala O, Buscot MJ, Juonala M, Wu F, Koskinen J, Hutri-Kahonen N, Kahonen M, Laitinen TP, et al. Association of non-high-density lipoprotein cholesterol measured in adolescence, young adulthood, and mid-adulthood with coronary artery calcification measured in mid-adulthood. *JAMA Cardiol.* 2021;6:661–668. doi: 10.1001/jamacardio.2020.7238
78. Yi SW, Park SJ, Yi JJ, Ohrr H, Kim H. High-density lipoprotein cholesterol and all-cause mortality by sex and age: a prospective cohort study among 15.8 million adults. *Int J Epidemiol.* 2021;50:902–913. doi: 10.1093/ije/dyaa243
79. Marston NA, Giugliano RP, Im K, Silverman MG, O'Donoghue ML, Wiviott SD, Ference BA, Sabatine MS. Association between triglyceride lowering and reduction of cardiovascular risk across multiple lipid-lowering therapeutic classes: a systematic review and meta-regression analysis of randomized controlled trials. *Circulation.* 2019;140:1308–1317. doi: 10.1161/CIRCULATIONAHA.119.041998
80. Wang N, Woodward M, Huffman MD, Rodgers A. Compounding benefits of cholesterol-lowering therapy for the reduction of major cardiovascular events: systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes.* 2022;15:e008552. doi: 10.1161/CIRCOUTCOMES.121.008552
81. Mazhar F, Hjemdahl P, Clase CM, Johnell K, Jernberg T, Sjölander A, Carrero JJ. Intensity of and adherence to lipid-lowering therapy as predictors of major adverse cardiovascular outcomes in patients with coronary heart disease. *J Am Heart Assoc.* 2022;11:e025813. doi: 10.1161/JAHA.122.025813
82. Mohammadi-Shemirani P, Chong M, Narula S, Perrot N, Conen D, Roberts JD, Thériault S, Bossé Y, Lanktree MB, Pigeyre M, et al. Elevated lipoprotein(a) and risk of atrial fibrillation: an observational and mendelian randomization study. *J Am Coll Cardiol.* 2022;79:1579–1590. doi: 10.1016/j.jacc.2022.02.018
83. Lassale C, Hamer M, Hernaez A, Gale CR, Batty GD. Association of prepandemic high-density lipoprotein cholesterol with risk of COVID-19 hospitalisation and death: the UK Biobank cohort study. *Prev Med Rep.* 2021;23:101461. doi: 10.1016/j.pmedr.2021.101461
84. Dieleman JL, Cao J, Chapin A, Chen C, Li Z, Liu A, Horst C, Kaldjian A, Matyasz T, Scott KW, et al. US health care spending by payer and health condition, 1996-2016. *JAMA.* 2020;323:863–884. doi: 10.1001/jama.2020.0734
85. Sumarsono A, Lalani HS, Vaduganathan M, Navar AM, Fonarow GC, Das SR, Pandey A. Trends in utilization and cost of low-density lipoprotein cholesterol-lowering therapies among Medicare beneficiaries: an analysis from the Medicare Part D database. *JAMA Cardiol.* 2021;6:92–96. doi: 10.1001/jamacardio.2020.3723
86. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, Barengo NC, Beaton AZ, Benjamin EJ, Benziger CP, et al; GBD-NHLBI-JACC Global Burden of Cardiovascular Diseases Writing Group. Global burden of cardiovascular diseases and risk factors, 1990-2019: update from the GBD 2019 Study. *J Am Coll Cardiol.* 2020;76:2982–3021. doi: 10.1016/j.jacc.2020.11.010
87. Stierman B, Afful J, Carroll M, Chen T, Davy O, Fink S, Fryar C, Gu Q, Hales C, Hughes J, et al. National Health and Nutrition Examination Survey 2017-March 2020 prepandemic data files-development of files and prevalence estmates for selected health outcomes. *Natl Health Stat Rep.* 2021. Accessed October 18, 2023. https://stacks.cdc.gov/view/cdc/106273
88. Global Burden of Disease Study and Institute for Health Metrics and Evaluation. University of Washington. Accessed August 2, 2023. http://ghdx.healthdata.org/

# 8. HIGH BLOOD PRESSURE

***ICD-9 401 to 404; ICD-10 I10 to I15. See Tables 8-1 and 8-2 and Charts 8-1 through 8-6***

Click here to return to the Table of Contents

Click here to return to the Abbreviations

HBP is a major risk factor for CHD, HF, and stroke.[1,2] The AHA has identified untreated BP <90th percentile (for children) and <120/<80 mm Hg (for adults ≥20 years of age) as 1 of the 7 components of ideal CVH.[3]

## Prevalence

## (See Table 8-1 and Charts 8-1 and 8-2)

- Although surveillance definitions vary widely in the published literature, including for the CDC and NHLBI, as of the 2017 Hypertension Clinical Practice Guidelines, the following definition of hypertension has been proposed for surveillance[4]:
  - SBP ≥130 mm Hg, DBP ≥80 mm Hg, self-reported antihypertensive medicine use, or having been told previously, at least twice, by a physician or other health professional that one has HBP.
- Other important BP classifications, or phenotypes, assessed by 24-hour ambulatory BP monitoring include the following:
  - Sustained hypertension, defined as elevated clinic BP with elevated 24-hour ambulatory BP
  - White-coat hypertension, defined as elevated clinic BP with normal 24-hour ambulatory BP
  - Masked hypertension, defined as normal clinic BP with elevated 24-hour ambulatory BP
- With the use of the most recent 2017 definition, the age-adjusted prevalence of hypertension among US adults ≥20 years of age was estimated to be 46.7% in NHANES in 2017 to 2020 (50.4% for males and 43.0% for females). This equates to an estimated 122.4 million adults ≥20 years of age who have hypertension (62.8 million males and 59.6 million females; Table 8-1).
- In NHANES 2017 to 2020,[5] the prevalence of hypertension was 28.5% among those 20 to 44 years of age, 58.6% among those 45 to 64 years of age, and 76.5% among those ≥65 years of age (unpublished NHLBI tabulation).
- In NHANES 2017 to 2020,[5] a higher percentage of males than females had hypertension up to 64 years of age. For those ≥65 years of age, the percentage of females with hypertension was higher than for males (unpublished NHLBI tabulation; Chart 8-1).
- The prevalence of hypertension in adults ≥20 years of age is presented by both age and sex in Chart 8-1.
- Data from NHANES 2017 to 2020[5] indicate that 38.0% of US adults with hypertension are not aware that they have it (unpublished NHLBI tabulation).
- The age-adjusted prevalence of hypertension in 1999 to 2002, 2007 to 2010, and 2017 to 2020 is shown in race and ethnicity and sex subgroups in Chart 8-2.
- In 2021, the prevalence of HBP in US adults was highest in Mississippi (40.2%) and lowest in Colorado (24.6%; unpublished NHLBI tabulation using BRFSS[6]).
- In a meta-analysis of 42 studies and 71 353 patients with apparent treatment-resistant hypertension, the overall pooled prevalence of nonadherence was 37% (95% CI, 27%–47%).[7] The prevalence was higher with direct methods of assessment (such as direct observed therapy test, or therapeutic drug monitoring) at 46% (95% CI, 40%–52%) than indirect methods (pill counts or questionnaires) at 20% (95% CI, 11%–35%).

### *Children and Adolescents*

- According to the 2017 guidelines from the American Academy of Pediatrics,[8] hypertension in children and adolescents is defined as follows:
  - Elevated BP as ≥90th to <95th percentile or 120/80 mm Hg to <95th percentile (whichever is lower) for children 1 to <13 years of age and 120/<80 to 129/<80 mm Hg for those ≥13 years of age
  - Stage 1 hypertension as ≥95th to <95th percentile+12 mm Hg or 130/80 to 139/89 mm Hg (whichever is lower) for children 1 to <13 years of age and 130/80 to 139/89 mm Hg for those >13 years of age
  - Stage 2 hypertension as ≥95th percentile+12 mm Hg or ≥140/90 mm Hg (whichever is lower) for children 1 to <13 years of age and ≥140/90 mm Hg for those ≥13 years of age
- In NHANES 2015 to 2016, 13.3% (SE, 1.3%) of children and adolescents 8 to 17 years of age had elevated BP, and 4.9% (SE, 0.7%) had hypertension (defined according to the 2017 guidelines from the

The 2024 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2024. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

American Academy of Pediatrics[8]). Rates of elevated BP were higher among youth 13 to 17 years of age compared with those 8 to 12 years of age (15.6% and 10.8%, respectively). However, rates of hypertension were slightly higher among youth at younger ages, with a prevalence of 4.4% among youth 13 to 17 years of age and 5.3% in youth 8 to 12 years of age.[9]

- In NHANES 2015 to 2016, among youth 8 to 17 years of age, hypertension (defined according to the 2017 guidelines from the American Academy of Pediatrics[8]) was more common among males (5.9%) than females (3.8%) and among Mexican American youth (9.0%) compared with NH Black youth (4.7%) and NH White youth (2.7%). Having elevated BP was more common among males (16.9%) than females (9.8%). In addition, Mexican American youth (16.9%) and NH Black youth (16.4%) were more likely to have elevated BP than NH White youth (10.7%).[9]
- In a systematic review of 60 studies of pediatric patients (defined as individuals ≤18 years of age) with type 2 diabetes, the prevalence of hypertension among 3463 participants was 25.3% (95% CI, 19.6%–31.5%).[10] Male participants had higher hypertension risk than female participants (OR, 1.42 [95% CI, 1.10–1.83]), with Pacific Islander and Indigenous (referring to the indigenous populations of North America) youth having the highest prevalence of all racial and ethnic groups (Pacific Islander youth, 26.7% [95% CI, 14.5%–40.7%]; Indigenous youth, 26.5% [95% CI, 17.3%–36.7%]; White youth, 21.0% [95% CI, 12.7%–30.6%]; Black youth, 19.0% [95% CI, 12.0%–27.2%]; Hispanic/Latino youth, 15.1% [95% CI, 6.6%–26.3%]; Asian youth, 18.4% [95% CI, 9.5%–29.2%]).
- In an analysis from SHIP AHOY, a cross-sectional cohort study of 397 adolescents 11 to 19 years of age, the prevalence of hypertension with awake ambulatory BP using the 95th percentile was 17% and 11% for SBP and DBP, respectively.[11] With the use of the 2017 ACC/AHA adult thresholds of ≥130/80 mm Hg, the prevalence was higher at 27% and 13% for SBP and DBP, respectively.
- Among 30 565 children and adolescents (3–17 years of age) receiving health care between 2012 and 2015, 51.2% of those with a first BP reading ≥95th percentile for age, sex, and height who had a repeated BP measurement during the same visit had a mean BP based on 2 consecutive readings that was <95th percentile. Of those with a visit BP ≥95th percentile, 67.8% did not have a follow-up visit within 3 months, and only 2.3% of those individuals with a follow-up visit had a BP ≥95th percentile at this visit.[12]
- In a 2022 systematic review of 53 studies of pediatric populations from Africa, hypertension prevalence ranged from 0.2% to 38.9%.[13] In the meta-analysis, which included 41 studies and 52 918 participants 3 to 19 years of age from 10 countries, the pooled prevalence for hypertension (SBP or DBP ≥95th percentile) was 7.5% (95% CI, 5.3%–9.9%) and elevated BP (SBP or DBP ≥90th and <95th percentile) was 11.4% (95% CI, 8.0–15.3) with a high degree of statistical heterogeneity ($I^2$>99).
- A meta-analysis from 2022 of secondary hypertension in children included 19 prospective studies and 7 retrospective studies with 2575 children with hypertension.[14] The overall pooled prevalence of secondary hypertension was 8.0% (95% CI, 4.0%–13.0%) among otherwise healthy youths with hypertension. Studies conducted in primary care or school settings reported a lower prevalence of secondary hypertension (pooled prevalence, 3.7% [95% CI, 1.2%–7.2%]) compared with studies conducted in referral clinics (pooled prevalence, 20.1% [95% CI, 11.5%–30.3%]).

### Race and Ethnicity

#### (See Table 8-1 and Chart 8-2)

- Table 8-1 includes statistics on prevalence of HBP, mortality from HBP, hospital discharges for HBP, and cost of HBP for different race, ethnicity, and sex groups.
- The prevalence of hypertension in Black people in the United States is among the highest in the world. According to NHANES 2017 to 2020 data,[5] the age-adjusted prevalence of hypertension among NH Black people was 55.8% among males and 56.9% among females (Chart 8-2).
- In an analysis of NHANES participants 22 to 79 years of age from 2003 to 2014, foreign-born NH Black individuals (n=522) had lower adjusted odds of having hypertension than US-born NH Black individuals (n=4511; OR, 0.61 [95% CI, 0.49–0.77]).[15]
- Data from the NHIS 2018 showed that Black adults ≥18 years of age were more likely (32.2%) to have been told on ≥2 occasions that they had hypertension than American Indian/Alaska Native adults (27.2%), White adults (23.9%), Hispanic or Latino adults (23.7%), or Asian adults (21.9%).[16]
- Data from the National Longitudinal Study of Adolescent to Adult Health (1994-1995, 11–18 years of age; 2007–2008, 24–32 years of age), older ages, being NH Black or Asian, male sex, BMI, and current smoking were associated with higher incidence of hypertension (defined as SBP ≥140 or DBP ≥90 mm Hg).[17] At the individual level, compared with NH White, NH Black (OR, 1.21 [95% CI, 1.03–1.42]) and Asian (OR, 1.28 [95% CI, 1.02–1.62]) students had higher odds of hypertension. At the school level, however, hypertension was associated with the percentage of NH White students

(OR for 10% higher, 1.06 [95% CI, 1.01–1.09]). Parental education and neighborhood-level fixed effects were not associated with hypertension.

## Incidence and Lifetime Risk

- Data from 13 160 participants in cohorts in the Cardiovascular Lifetime Risk Pooling Project (ie, the Framingham Offspring Study, CARDIA, and ARIC) showed that the lifetime risk of hypertension from 20 to 85 years of age according to the 2017 Hypertension Clinical Practice Guidelines was 86.1% (95% CI, 84.1%–88.1%) for Black males, 85.7% (95% CI, 84.0%–87.5%) for Black females, 83.8% (95% CI, 82.5%–85.0%) for White males, and 69.3% (95% CI, 67.8%–70.7%) for White females.[18]

## Secular Trends

- In 51 761 participants from NHANES, according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure definition of hypertension (≥140/90 mm Hg), the age-adjusted estimated prevalence of hypertension in US adults >18 years of age (weighted to the US population) increased from 30.0% (95% CI, 27.1%–32.9%) in 1999 to 2000 to 32% (95% CI, 29.3%–34.6%) in 2017 to 2018. However, with the use of the 2017 Hypertension Clinical Practice Guidelines definition of hypertension (≥130/80 mm Hg), the age-adjusted estimated prevalence of hypertension in US adults >18 years of age was 48.6% (95% CI, 45.7%–51.5%) in 1999 to 2000 and 46.5% (95% CI, 44.0%–49.0%) in 2017 to 2018.[19]
- With the use of the 2017 guidelines from the American Academy of Pediatrics, analysis of data for children and adolescents 8 to 17 years of age (N=12 249) from NHANES 2003 to 2004 through NHANES 2015 to 2016 found that the prevalence of either elevated BP or hypertension (combined) significantly declined from 16.2% in 2003 to 2004 to 13.3% in 2015 to 2016 ($P_{trend}$<0.001) and the prevalence of hypertension declined from 6.6% to 4.5% ($P_{trend}$=0.005).[9]
- In NHANES, among youths with underweight or normal weight (8–17 years of age), there was a statistically significant decline in the prevalence of elevated BP/hypertension and hypertension (defined according to the 2017 guidelines from the American Academy of Pediatrics[8]) between 2003 to 2004 and 2015 to 2016. There were no changes in the prevalence of elevated BP/hypertension or hypertension among youths with overweight during this time period; among youths with obesity, there was a decline in the prevalence of elevated BP/hypertension ($P_{trend}$=0.03) but not hypertension. Among adolescents with underweight or normal weight, the unadjusted prevalence of elevated BP/hypertension was 12.9% (SE, 1.6%) and the prevalence of hypertension was 4.9% (SE, 0.9%) in 2003 to 2004; the prevalence of elevated BP/hypertension was 8.7% (SE, 1.7%) and that of hypertension was 2.7% (SE, 1%) in 2015 to 2016 ($P_{trend}$=0.001 and 0.002). Among youths with obesity, the unadjusted prevalence of elevated BP/hypertension was 30.1% (SE, 5.0%) and that of hypertension was 12.4% (SE, 3.3%) in 2003 to 2004; the unadjusted prevalence of prehypertension was 25.5% (SE, 2.4%) and that of hypertension was 11.6% (SE, 2.1%) in 2015 to 2016.[9]
- In NHDS data compiled by the CDC, chronic hypertension in pregnancy (defined as SBP ≥140 mm Hg or DBP ≥90 mm Hg either before pregnancy or up to the first 20 weeks during pregnancy) increased >13-fold between 1970 and 2010. Black females had a persistent 2-fold higher rate of chronic hypertension compared with White females over the 40-year period.[20]

## Risk Factors

- In NHANES 2015 to 2016, the prevalence of hypertension (defined according to the 2017 guidelines from the American Academy of Pediatrics[8]) was 11.6% among US adolescents with obesity (BMI ≥120% of 95th percentile of sex-specific BMI for age or BMI ≥35 kg/m$^2$) compared with 2.7% among children with normal weight or underweight. The prevalence of elevated BP among youths with obesity compared with youths with normal weight or underweight was 16.2% compared with 8.7%.[9]
- Among 60 027 participants in the Norwegian Mother and Child Cohort Study who were normotensive before pregnancy, the PAF for pharmacologically treated hypertension within 10 years postpartum was 28.6% (95% CI, 25.5%–30.3%) for complications of pregnancy (preeclampsia/eclampsia, gestational hypertension, preterm delivery, and pregestational or gestational diabetes).[21]
- In a cohort of 58 671 parous females participating in the Nurses' Health Study II without CVD or hypertension at baseline, gestational hypertension and preeclampsia during first pregnancy were associated with a higher rate of self-reported physician-diagnosed chronic hypertension over a 25- to 32-year follow-up (HR, 2.8 [95% CI, 2.6–3.0] for gestational hypertension; HR, 2.2 [95% CI, 2.1–2.3] for preeclampsia).[22]
- In an analysis of the Australian Longitudinal Study on Women's Health, 9508 females were followed

up for 145 159 person-years, and 1556 females (16.4%) developed hypertension during follow-up.[23] The incidence of hypertension was higher among females with polycystic ovarian syndrome (17 per 1000 person-years) compared with females without (10 per 1000 person-years). The incidence rate difference of hypertension was 4-fold higher (15.8 per 1000 person-years versus 4.3 per 1000 person-years) among females with obesity with polycystic ovarian syndrome compared with age-matched lean females with polycystic ovarian syndrome. Polycystic ovarian syndrome was independently associated with 37% greater risk of hypertension (HR, 1.37 [95% CI, 1.14–1.65]) after adjustment for BMI, family history of hypertension, occupation, and comorbidity with type 2 diabetes.

- In a systematic review of 11 cohort studies including 224 829 individuals, living or working in environments with noise exposure was significantly associated with increased risk of hypertension (RR, 1.18 [95% CI, 1.06–1.32]), and a linear dose-response was noted, with a risk ratio of hypertension of 1.13 (95% CI, 0.99–1.28) per 10-dB higher ambient noise.[24]
- In a study from the China Health and Nutrition Survey of 12 080 adults 18 to 65 years of age who were enrolled from 1989 and 2011, compared with the referent group of those who worked 35 to 49 h/wk, participants who worked no more than 34 h/wk (HR, 1.21 [95% CI, 1.03–1.41]) and at least 56 h/wk (HR, 1.38 [95% CI, 1.19–1.59]) had a higher risk of developing hypertension during follow-up after adjustment for sociodemographics, lifestyle factors, and occupation type.[25]
- Among 6897 Black and White individuals in the REGARDS cohort who were free of hypertension (SBP ≥140 mm Hg, DBP ≥90 mm Hg) at baseline, the Southern dietary pattern accounted for 51.6% (95% CI, 18.8%–84.4%) of the excess risk of incident hypertension in Black males compared with White males and 29.2% (95% CI, 13.4%–44.9%) of the risk in Black females compared with White females.[26]
- In a meta-analysis of 133 studies with 12 197 participants, each 50-mmol reduction in 24-hour sodium excretion (a marker of sodium consumption) was associated with a 1.10–mm Hg (95% CI, 0.66–1.54) reduction in SBP and a 0.33–mm Hg (95% CI, 0.04–0.63) reduction in DBP.[27] Greater SBP and DBP lowering from the same amount of sodium reduction was seen in populations with older age (−3.33/−1.23 mm Hg in those >65 years of age compared with −0.39/−0.18 mm Hg in those <35 years of age), individuals with higher baseline SBP (−2.97/−1.41 mm Hg in those with SBP >160 mm Hg compared with −0.39/−0.07 mm Hg in those with SBP <120 mm Hg), and Black individuals (−4.07/−2.37 mm Hg compared with −1.60/−0.82 mm Hg in White individuals).
- In an open-label, cluster-randomized trial involving 20 995 people from 600 villages in rural China, the use of a salt substitute (75% sodium chloride and 25% potassium chloride by mass) compared with the use of regular salt (100% sodium chloride) resulted in a lower incidence of stroke (RR, 0.86 [95% CI, 0.77–0.96]), all-cause mortality (RR, 0.88 [95% CI, 0.82–0.95]), and MACEs (RR, 0.87 [95% CI, 0.80–0.94]).[28] There was no increase in rates of hyperkalemia with the use of the salt substitute (RR, 1.04 [95% CI, 0.80–1.37]).
- In a population-based study from the Australian Longitudinal Study on Women's Health, which included 6599 middle-aged females and 6099 females of reproductive age, higher intakes of flavones (RR for highest versus lowest quintile of consumption, 0.82 [95% CI, 0.70–0.97]), isoflavones (RR, 0.86 [95% CI, 0.75–0.99]), and flavanones (RR, 0.83 [95% CI, 0.69–1.00]) were associated with a lower risk of hypertension in the middle-aged cohort.[29] In the cohort of reproductive age, higher intakes of flavanols (RR, 0.70 [95% CI, 0.49–0.99]) were associated with a lower risk of hypertension.
- In an analysis of the electronic FHS participants, higher daily habitual PA as measured by a smartwatch was associated with lower home BP. Every 1000-step increase in the average daily step count was associated with a 0.49–mm Hg lower home SBP ($P$=0.004) and 0.36 mm Hg lower home DBP ($P$=0.003), with no difference between males and females.[30]
- In the HCHS/SOL Sueño Sleep Ancillary Study of Hispanic people (N=2148), a 10% higher sleep fragmentation and frequent napping versus not napping were associated with a 5.2% and 11.6% higher prevalence of hypertension, respectively. A 10% higher sleep efficiency was associated with a 7.2% lower prevalence of hypertension.[31]
- In the JHS ancillary sleep study conducted from 2012 to 2016 among 913 participants, those with moderate or severe OSA had 2-fold higher odds (95% CI, 1.14–3.67) of resistant hypertension than participants without sleep apnea.[32]
- In a double-blind, placebo-controlled, crossover RCT, 110 individuals were randomized to receive 1 g acetaminophen 4 times daily or matched placebo for 2 weeks.[33] Use of acetaminophen resulted in a significant increase in mean daytime SBP with a placebo-corrected increase of 4.7 mm Hg (95% CI, 2.9–6.6) and mean daytime DBP with a placebo-corrected increase of 1.6 mm Hg (95% CI, 0.5–2.7).
- In an analysis from DEBATS of 1244 adults living near 3 major French airports, a 10-dB increase in

aircraft noise levels was associated with a higher incidence of hypertension (RR, 1.36 [95% CI, 1.02–1.82]).[34] Noise annoyance, or noise sensitivity, was not associated with higher incident hypertension.

- In a meta-analysis of 7 studies including 102 152 patients and 636 645 healthy individuals, male infertility was significantly associated with a slightly higher incidence of subsequent hypertension (RR, 1.08 [95% CI, 1.02–1.14]).[35] This risk persisted when only studies that adjusted for potential confounders were included (RR, 1.06 [95% CI, 1.03–1.09]).
- In the BWHS of 59 000 self-identified Black females from across the United States, a validated predicted vitamin D score relation to incident hypertension was reported.[36] Of the 42 239 participants who were free of CVD and cancer from 1995 to 2019, 19 505 incident cases of hypertension were identified during follow-up. An inverse dose-response association between predicted vitamin D score and hypertension risk was reported (HR, 0.66 [95% CI, 0.63–0.68]) for the highest quartile of predicted vitamin D relative to the lowest. This trend was mostly attenuated after controlling for potential confounders, including BMI, PA, and smoking status (HR, 0.91 [95% CI, 0.87–0.95]).

## Social Determinants/Health Equity

- In 1845 Black participants from the JHS without hypertension at baseline, medium (HR, 1.49 [95% CI, 1.18–1.89]) and high (HR, 1.34 [95% CI, 1.07–1.68]) exposure compared with low exposure to discrimination over the course of a lifetime was associated with a higher risk of incident hypertension after adjustment for demographics and hypertension risk factors.[37]
- In an analysis of the JHS cohort study of NH Black people, high (versus low) adult SES measures were associated with a lower prevalence of hypertension, with the exception of having a college degree (PR, 1.04 [95% CI, 1.01–1.07]) and upper-middle income (PR, 1.05 [95% CI, 1.01–1.09]).[38] Higher childhood SES was associated with a lower prevalence (PR, 0.83 [95% CI, 0.75–0.91]) and risk (HR, 0.76 [95% CI, 0.65–0.89]) of hypertension.
- In a subsample of 528 females and males 45 to 84 years of age who did not have hypertension at baseline from the Chicago, IL, MESA field center, higher levels of self-reported neighborhood safety were associated with lower levels of SBP (1.54 mm Hg per 1-SD increase [95% CI, 0.25–2.83]) in both sexes and lower levels of DBP (1.24 mm Hg [95% CI, 0.37–2.12]) among females only.[39]
- In a cohort of 3547 white collar workers from Quebec, in models adjusted for demographics and a range of other risk factors, the prevalence of masked hypertension was higher among individuals working 41 to 48 h/wk (PR, 1.51 [95% CI, 1.06–2.14]) and ≥49 h/wk (1.70 [95% CI, 1.09–2.64]) compared with those working ≤40 h/wk. Similarly, the prevalence of sustained hypertension was higher among those working 41 to 48 h/wk (PR, 1.33 [95% CI, 0.99–1.76]) and ≥49 h/wk (1.66 [95% CI, 1.15–2.50]) compared with those working ≤40 h/wk.[40]
- In a systematic review including 45 studies and involving 117 252 workers, an increase in both SBP and DBP among permanent night workers (2.52 mm Hg [95% CI, 0.75–4.29] and 1.76 mm Hg [95% CI, 0.41–3.12], respectively) compared with day workers was noted.[41] For rotational shift workers, both with and without night work, compared with day workers without rotations, an increase was noted only for SBP (0.65 mm Hg [95% CI, 0.07–1.22] and 1.28 mm Hg [95% CI, 0.18–2.39], respectively).

## Genetics/Family History

- Several large-scale GWASs and whole-exome and whole-genome sequencing studies in primarily European ancestry populations, with the interrogation of common and rare variants in >1.3 million individuals, have established >300 well-replicated hypertension loci, with several hundred additional suggestive loci.[42–52]
- Nine genetic loci have been identified for BP traits in African-ancestry populations.[53] Large-scale genomic discovery effort in non-European ancestry populations is needed to comprehensively understand the genetic architecture of hypertension.
- Mendelian randomization analysis suggests a causal role for higher BP in 14 cardiovascular conditions, including IHD (SBP per 10 mm Hg: OR, 1.33 [95% CI, 1.24–1.41]; DBP per 5 mm Hg: OR, 1.20 [95% CI, 1.14–1.27]) and stroke (SBP per 10 mm Hg: OR, 1.35 [95% CI, 1.24–1.48]; DBP per 5 mm Hg: OR, 1.20 [95% CI, 1.12–1.28]).[54]
- In a recent study, the multiancestry SBP PRS was constructed with 1.08 million variants identified from SBP GWAS data from >400 000 individuals of pan-ancestry in the UK Biobank. The SBP PRS was applied to 21 987 multiethnic US individuals who underwent whole-genome sequencing. The SBP PRS was associated with increased 10-year risk of incident cardiovascular events by 7% after accounting for traditional cardiovascular risk factors. These associations were seen across all racial and ethnic groups.[55]
- GWASs for BP variability and longitudinal BP traits have led to the discovery of novel loci.[56,57] Furthermore, females were noted to have rapid

progression of BP measures over a lifetime, which may indicate a sex-specific genetic burden for hypertension.[58,59]

- Given the strong effects of environmental factors on hypertension, gene-environment interactions are important in the pathophysiology of hypertension. Studies of several hundred thousand people have to date revealed several loci of interest that interact with smoking[60,61] and sodium.[62,63] In individuals of European ancestry, a high genetic risk for hypertension and CVD is offset by a favorable lifestyle. Large-scale gene-environment interaction studies in multiethnic populations have not yet been conducted.
- The clinical implications and utility of hypertension genes remain unclear, although some genetic variants have been shown to influence response to antihypertensive agents.[64] Pharmacogenomic studies in ethnically diverse populations have the potential to recognize potential adverse events and to inform personalized drug efficacy.[65]

## Prevention

### *Awareness, Treatment, and Control*

#### *(See Table 8-2 and Charts 8-3 through 8-5)*

- Based on NHANES 2017 to 2020 data,[5] the extent of awareness, treatment, and control of HBP is provided by race and ethnicity in Chart 8-3, by age in Chart 8-4, and by race and ethnicity and sex in Chart 8-5. Awareness, treatment, and control of hypertension were higher at older ages (Chart 8-4). In all race and ethnicity groups, females were more likely than males to be aware of their condition, under treatment, or in control of their hypertension (Chart 8-5).
- Analysis of NHANES 1999 to 2002, 2007 to 2010, and 2017 to 2020[5] found that hypertension awareness, treatment, and control increased in all racial and ethnic groups between 1999 to 2002 and 2007 to 2010. Changes in hypertension awareness, treatment, and control were more modest between 2007 to 2010 and 2017 to 2020, with some racial and ethnic subgroups experiencing declines (Table 8-2).
- In an analysis of 18 262 adults ≥18 years of age with hypertension (defined as ≥140/90 mm Hg) in NHANES, the estimated age-adjusted proportion with controlled BP increased from 31.8% (95% CI, 26.9%–36.7%) in 1999 to 2000 to 48.5% (95% CI, 45.5%–51.5%) in 2007 to 2008, remained relatively stable at 53.8% (95% CI, 48.7%–59.0%) in 2013 to 2014, but declined to 43.7% (95% CI, 40.2%–47.2%) in 2017 to 2018.[19] Controlled BP was less prevalent among NH Black individuals (41.5%) compared with NH White individuals (48.2%). In addition, compared with adults 18 to 44 years of age, controlled BP was more common in adults 45 to 64 years of age (36.7% and 49.7%, respectively).
- SPRINT demonstrated that an SBP goal of <120 mm Hg resulted in fewer CVD events and a greater reduction in mortality than an SBP goal of <140 mm Hg among people with SBP ≥130 mm Hg and increased cardiovascular risk.[66] From NHANES 2007 to 2012 data, it was estimated that 7.6% (95% CI, 7.0%–8.3%) of US adults (16.8 million [95% CI, 15.7–17.8 million]) met the SPRINT inclusion and exclusion criteria.[67]
- Among 3358 Black people taking antihypertensive medication in the JHS, 25.4% of participants reported not taking ≥1 of their prescribed antihypertensive medications within the 24 hours before their baseline study visit in 2000 to 2004. This percentage was 28.7% at examination 2 (2005–2008) and 28.5% at examination 3 (2009–2012). Nonadherence was associated with higher likelihood of having SBP ≥140 mm Hg or DBP ≥90 mm Hg (PR, 1.26 [95% CI, 1.16–1.37]).[68]
- In the UK Biobank, among 99 468 previously diagnosed, treated hypertensive individuals, 60 to 69 years of age (OR, 0.61 [95% CI, 0.58–0.64] compared with 40–50 years of age), alcohol consumption >30 units/wk (OR, 0.61 [95% CI, 0.58–0.64] compared with no alcohol use), Black ethnicity (OR, 0.73 [95% CI, 0.65–0.82] compared with White ethnicity), and obesity (OR, 0.73 [95% CI, 0.71–0.76] compared with normal BMI) were associated with lack of hypertension control.[69] Comorbidities associated with lack of BP control included CVD (OR, 2.11 [95% CI, 2.04–2.19]), migraines (OR, 1.68 [95% CI, 1.56–1.81]), diabetes (OR, 1.32 [95% CI, 1.27–1.36]), and depression (OR, 1.27 [95% CI, 1.20–1.34]).
- A longitudinal analysis of prospectively collected data from the UK Avon Longitudinal Study of Parents and Children cohort reported the association of self-reported alcohol intake and presence of hypertensive disorders in pregnancy.[70] Of the 8999 females in the study, 1490 (17%) had developed hypertensive disorders in pregnancy. Both maternal drinking and partner drinking were associated with decreased odds of hypertensive disorders in pregnancy (OR, 0.86 [95% CI, 0.77–0.96] and OR, 0.82 [95% CI, 0.70–0.97], respectively).
- In an analysis of 269 010 US veterans with apparent treatment-resistant hypertension from 2000 to 2017, 4277 (1.6%) were tested for primary aldosteronism.[71] Testing was associated with a 4-fold higher likelihood of initiating mineralocorticoid antagonist therapy (HR, 4.10 [95% CI, 3.68–4.55]).

After adjustment for patient-, health care professional–, and center-level covariates (including baseline BP), compared with no testing, testing for primary aldosteronism was associated with an average 1.47–mm Hg (95% CI, −1.64 to −1.29 mm Hg) lower SBP over time.

- In an analysis of 1590 health care professionals who completed the DocStyles survey, a web-based survey of health care professionals, 86.3% reported using a prescribing strategy to increase their patients' adherence to antihypertensive medications. The most common strategies were prescribing once-daily regimens (69.4%), prescribing medications covered by the patient's insurance (61.8%), and using longer fills (59.9%).[72]
- In a meta-analysis of 15 RCTs and 7415 patients with hypertension of app-based behavioral self-monitoring interventions, a small but significant reduction in SBP was reported (WMD, 1.6 mm Hg [95% CI, 2.7–0.6]). App-based interventions were also associated with an increase in adherence behavior (SMD, 0.78 [95% CI, 0.22–1.34]) compared with usual care or minimal intervention.
- A meta-analysis of 16 cohort studies with 2 769 700 participants analyzed the association of adherence to BP-lowering medications and subsequent CVD events.[73] The pooled RR of CVD events was 0.66 (95% CI, 0.56-0.78) for the highest versus lowest BP-lowering drug adherence categories. A linear dose-response association of adherence and CVD events was also reported ($P_{nonlinearity}$=0.89), and each 20% increase in adherence was associated with a 13% lower risk of CVD events (RR, 0.87 [95% CI, 0.83–0.92]).[74]
- A meta-analysis of 14 RCTs of renin-angiotensin system inhibitor continuation or initiation compared with no renin-angiotensin system inhibitor therapy included 11 trials and 1838 participants with a mean follow-up of 26 days.[75] There was no effect of renin-angiotensin system inhibitors compared with control on all-cause mortality (RR, 0.95 [95% CI, 0.69–1.30]) overall or in subgroups defined by COVID-19 severity or trial type. In a network meta-analysis, renin-angiotensin system inhibitor use was associated with a nonsignificant reduction in AMI (RR, 0.59 [95% CI, 0.33–1.06]) and a higher risk of acute kidney injury (RR, 1.82 [95% CI, 1.05–3.16]) in trials that initiated and continued renin-angiotensin system inhibitors.
- In a prospective RCT of 21 104 participants who were enrolled to take all of their usual antihypertensive medications in either the morning (6–10 AM) or in the evening (8 PM–midnight), the primary cardiovascular end-point event of vascular death or hospitalization for nonfatal MI or nonfatal stroke occurred in 362 participants (3.4%) assigned to evening treatment and 390 (3.7%) assigned to morning treatment (HR, 0.95 [95% CI, 0.83–1.10]).[76]

## Mortality

## (See Table 8-1)

- According to data from the NVSS, in 2021,[77] 124 508 deaths were attributable primarily to HBP (Table 8-1). The 2021 age-adjusted death rate attributable primarily to HBP was 31.3 per 100 000. Age-adjusted death rates attributable to HBP (per 100 000) in 2021 were 32.1 for NH White males, 69.7 for NH Black males, 26.9 for Hispanic males, 20.4 for NH Asian males, 39.3 for NH Native Hawaiian or other Pacific Islander males, 43.8 for NH American Indian/Alaska Native males, 26.4 for NH White females, 47.3 for NH Black females, 20.8 for Hispanic females, 16.7 for NH Asian females, 27.1 for NH Native Hawaiian or other Pacific Islander females, and 30.1 for NH American Indian/Alaska Native females (unpublished NHLBI tabulation using CDC WONDER[78]).
- From 2011 to 2021, the age-adjusted death rate attributable to HBP increased 65.6%, and the actual number of deaths attributable to HBP rose 91.2%. From 2018 to 2021, in NH White people, the HBP age-adjusted death rate increased 33.6%, whereas the actual number of deaths attributable to HBP increased 29.7%. In NH Black people, the HBP death rate increased 24.0%, whereas the actual number of deaths attributable to HBP increased 29.3%. In Hispanic people, the HBP death rate increased 20.8%, and the actual number of deaths attributable to HBP increased 31.6% (unpublished NHLBI tabulation using CDC WONDER[78]).
- When any mention of HBP was present, the overall age-adjusted death rate in 2021 was 172.2 per 100 000. Death rates were 193.9 for NH White males, 319.2 for NH Black males, 123.5 for NH Asian males, 225.1 for Native Hawaiian or other Pacific Islander males, 246.5 for NH American Indian or Alaska Native males (underestimated because of underreporting), and 182.9 for Hispanic males. In females, rates were 141.0 for NH White females, 219.4 for NH Black females, 90.6 for NH Asian females, 166.4 for NH Native Hawaiian or other Pacific Islander females, 174.7 for NH American Indian or Alaska Native females (underestimated because of underreporting), and 128.2 for Hispanic females (unpublished NHLBI tabulation using CDC WONDER[78]).
- In 3394 participants from the CARDIA study cohort, greater long-term visit-to-visit variability in SBP (eg, variability independent of the mean) from young adulthood through midlife was associated with

greater all-cause mortality (HR, 1.24 [95% CI, 1.09–1.41]) during a median follow-up of 20 years.[79]

- In a meta-analysis of 64 000 participants from 27 studies, untreated white-coat hypertension was associated with an increased risk of all-cause (HR, 1.33 [95% CI, 1.07–1.67]) and cardiovascular (HR, 2.09 [95% CI, 1.23–4.48]) mortality compared with normotension.[80] There was no evidence of increased risk among those with treated white-coat hypertension.
- In 1034 participants from the JHS completing ambulatory BP monitoring, each 1-SD higher level of mean nighttime SBP (15.5 mm Hg) was associated with all-cause mortality (HR, 1.24 [95% CI, 1.06–1.45]) after multivariable adjustment including clinic BP; however, there were no associations between daytime SBP, daytime DBP, or nighttime DBP and all-cause mortality.[81]

## Complications

- In the Blood Pressure Lowering Treatment Trialists Collaboration individual patient-level meta-analysis of 48 RCTs and 344 716 participants, a 5–mm Hg reduction of SBP reduced the risk of major cardiovascular events by ≈10%, regardless of previous diagnoses of CVD.[82] This effect was also seen at normal and high-normal BP values.
- In a cross-sectional analysis from SHIP AHOY of 397 adolescents 11 to 19 years of age, absolute mean systolic ambulatory BP cut points of 125 mm Hg during wake hours, 110 mm Hg during sleep, and 120 mm Hg over 24 hours were observed to have a balance of sensitivity (67%) and specificity (60%) for predicting LVH.[11]
- In a sample of 4851 adults 18 to 30 years of age at baseline from the CARDIA cohort, for those who developed hypertension before 40 years of age, incident CVD rates were 3.15 (95% CI, 2.47–4.02) for those with stage 1 hypertension (untreated SBP 130–139 mm Hg or DBP 80–89 mm Hg) per 1000 person-years and 8.04 (95% CI, 6.45–10.03) for those with stage 2 hypertension (≥140/90 mm Hg or taking antihypertensive medication) per 1000 person-years over the median follow-up of ≈19 years.[83] Over a median follow-up of 18.8 years in 4851 adults from the CARDIA cohort, among those who developed hypertension before 40 years of age, incident CVD rates were 2.74 (95% CI, 1.78–4.20) for those with elevated BP or prehypertension (untreated SBP 130–139 mm Hg or DBP 80–89 mm Hg) per 1000 person-years compared with 1.37 (95% CI, 1.07–1.75) among those who retained normal BP through 40 years of age.[83]
- Among 27 078 Black and White individuals in the Southern Community Cohort Study, hypertension was associated with an increased risk of HF in the full cohort (HR, 1.69 [95% CI, 1.56–1.84]), with a PAR of 31.8% (95% CI, 27.3%–36.0%).[84]
- In an RCT of 8511 older Chinese patients with hypertension (60–80 years of age), randomizing to a BP target of 110 to <130 mm Hg (intensive treatment) compared with a target of 130 to <150 mm Hg (standard treatment) reduced MACEs (HR, 0.74 [95% CI, 0.60–0.92]).[85]
- In a pooled cohort of 12 497 NH Black individuals from the JHS and REGARDS, over a maximum 14.3 years of follow-up, the multivariable-adjusted HR associated with hypertension (defined as ≥130/80 per the 2017 Hypertension Clinical Practice Guidelines[4] compared with normotension) was almost 2-fold higher (HR, 1.91 [95% CI, 1.48–2.46]) for composite incident CVD and was 2.41 (95% CI, 1.59–3.66) for incident CHD, 2.20 (95% CI, 1.44–3.36) for incident stroke, and 1.52 (95% CI, 1.01–2.30) for incident HF.[1] The PAR associated with hypertension was 32.5% (95% CI, 20.5%–43.6%) for composite incident CVD, 42.7% (95% CI, 24.0%–58.4%) for incident CHD, 38.9% (95% CI, 19.4%–55.6%) for incident stroke, and 21.6% (95% CI, 0.6%–40.8%) for incident HF. For composite CVD, the PAR for hypertension was 54.6% (95% CI, 37.2%–68.7%) among NH people <60 years of age but was significantly lower, at 32% (95% CI, 11.9%–48.1%), among NH Black people ≥60 years of age.
- In 8022 individuals from SPRINT with hypertension but without AF at baseline, those in the intensive BP-lowering arm (target SBP <120 mm Hg) had a 26% lower risk of developing AF over the 5.2 years of follow-up (28 322 person-years) than those in the standard BP-lowering arm (target SBP <140 mm Hg; HR, 0.74 [95% CI, 0.56–0.98]; $P$=0.037).[86]
- In 1034 adults from the JHS cohort of NH Black participants completing ambulatory BP monitoring, each 1-SD higher level of mean daytime SBP (13.5 mm Hg) was also associated with an increased incidence of CVD events (HR, 1.53 [95% CI, 1.24–1.88]) after multivariable adjustment that included clinic BP. Adjusted findings were similar for nighttime SBP (HR, 1.48 [95% CI, 1.22–1.80]) per 15.5 mm Hg, daytime DBP (HR, 1.25 [95% CI, 1.02–1.51]) per 9.3 mm Hg, and nighttime DBP (HR, 1.30 [95% CI, 1.06–1.59]) per 9.5 mm Hg.[81]
- Among adults with established CKD, apparent treatment-resistant hypertension has been associated with increased risk for CVD (HR, 1.38 [95% CI, 1.22–1.56]); renal outcomes, including a 50% decline in eGFR or ESRD (HR, 1.28 [95% CI, 1.11–1.46]); HF (HR, 1.66 [95% CI, 1.38–2.00]); and all-cause mortality (HR, 1.24 [95% CI, 1.06–1.45]).[87]
- In an analysis from the CRIC study of 3873 participants, 180 participants (4.6%) had orthostatic

hypotension and 81 (2.1%) had orthostatic hypertension.[88] Orthostatic hypotension was associated with high risk for cardiovascular outcomes, including HF, MI, stroke, or PAD (HR, 1.12 [95% CI, 1.03–1.21]), but not kidney outcomes or mortality. Orthostatic hypertension was independently associated with high risk for kidney outcomes, including incident ESRD or 50% decline in eGFR (HR, 1.51 [95% CI, 1.14–1.97]), but not cardiovascular outcomes or mortality.

- Among 3319 adults ≥65 years of age from the S.AGES cohort in France, higher SBP variability (assessed in 6-month intervals over the course of 3 years) was associated with poorer global cognition independently of baseline SBP (adjusted 1-SD increase of coefficient of variation: β=–0.12 [SE, 0.06]; *P*=0.04).[89] Similar results were observed for DBP variability (β=–0.20 [SE, 0.06]; *P*<0.001). Higher SBP variability was also associated with greater dementia risk (adjusted 1-SD increase of coefficient of variation: HR, 1.23 [95% CI, 1.01–1.50]; *P*=0.04).
- In a subsample of 191 participants from CARDIA, higher cumulative SBP from baseline through year 30 was associated with slower walking speed (*P*=0.010), smaller step length (*P*=0.011), and worse cognitive function in the executive (*P*=0.021), memory (*P*=0.015), and global (*P*=0.010) domains.[90] Associations between cumulative BP and both walking speed and step length were moderated by cerebral WMH burden ($P_{interaction}$<0.05).
- In a meta-analysis of 20 studies and 7 899 697 participants, higher SBP variability (OR, 1.25 [95% CI, 1.16–1.35]), mean SBP (OR, 1.12 [95% CI, 1.02–1.29]), DBP variability (OR, 1.20 [95% CI, 1.12–1.29]), and mean DBP (OR, 1.16 [95% CI, 1.04–1.29]) were associated with dementia and cognitive impairment.[91]
- A pooled individual participant data analysis of 5 RCTs from the Dementia Risk Reduction collaboration included 28 008 individuals recruited from 20 countries.[92] After a median follow-up of 4.3 years, there were 861 cases of incident dementia. The pooled mean BP difference between the antihypertensive and control arms was 9.6 mm Hg for SBP and 3.7 mm Hg for DBP. With multilevel logistic regression, BP-lowering treatment was associated with a lower risk of subsequent dementia (OR, 0.87 [95% CI, 0.75–0.99]).
- A meta-analysis included 5 cohort studies with a total of 183 874 females with and 2 309 705 females without hypertensive disorders in pregnancy to study the risk of subsequent dementia.[93] Any type of hypertensive disorder in pregnancy was associated with a higher risk of subsequent dementia (HR, 1.38 [95% CI, 1.18–1.61]). For dementia subtypes, any hypertensive disorder in pregnancy was associated with higher risk of vascular dementia (HR, 3.14 [95% CI, 2.32–4.24]).
- In an analysis of the ONTARGET study, the lowest risk of ESRD or doubling of serum creatinine (707 events overall) was seen at achieved SBP of 120 to <140 mm Hg; risk increased with higher (HR, 3.06 [95% CI, 1.90–3.32]) and lower (HR, 1.97 [95% CI, 1.7–3.32]) SBP, with similar RRs reported with or without diabetes.[94]
- In an analysis from the CKiD cohort, high mean arterial pressure >90th percentile was associated with progression, defined as time to renal replacement therapy or 50% decline in baseline renal function, in children (HR, 1.88 [95% CI, 1.03–3.44]) only after 4 years of follow-up.[95] Among those with glomerular CKD, higher risk for progression was noted from baseline with the highest risk in those with mean arterial pressure >90th percentile (HR, 3.23 [95% CI, 1.34–7.79]).
- In an individual patient meta-analysis of 33 trials including 260 447 participants with 15 012 cancer events, no associations were identified between any antihypertensive drug class and risk of any cancer (HR, 0.99 [95% CI, 0.95–1.04] for ACE inhibitors; HR, 0.96 [95% CI, 0.92–1.01] for ARBs; HR, 0.98 [95% CI, 0.89–1.07] for β-blockers; HR, 1.01 [95% CI, 0.95–1.07] for thiazides), except for calcium channel blockers (HR, 1.06 [95% CI, 1.01–1.11]).[96] In a network meta-analysis comparing each drug class with placebo, no drug class was associated with an excess cancer risk (HR, 1.00 [95% CI, 0.93–1.09] for ACE inhibitors; HR, 0.99 [95% CI, 0.92–1.06] for ARBs; HR, 0.99 [95% CI, 0.89–1.11] for β-blockers; HR, 1.04 [95% CI, 0.96–1.13] for calcium channel blockers; HR, 1.00 [95% CI, 0.90–1.10] for thiazides).
- A prospective observational cohort study of 906 patients from Italy with hypertension and CKD reported outcomes associated with baseline ambulatory BP patterns.[97] The absence of nocturnal dipping (defined as nighttime:daytime SBP ratio of <0.9) was associated with higher rates of cardiovascular events (HR, 2.79 [95% CI, 1.64–4.75]) and kidney disease progression (HR, 2.40 [95% CI, 1.58–3.65]) in participants whose daytime ambulatory SBP was not at goal (SBP >135 mm Hg). Similar results were also noted in those whose ambulatory daytime SBP was at goal (HR for cardiovascular events, 2.06 [95% CI, 1.15–3.68]; HR for kidney disease progression, 1.82 [95% CI, 1.17–2.82]).
- In an analysis of the FHS including 8198 participants with hypertension subtypes, the prevalence of nonhypertension (SBP <140 mm Hg and DBP <90 mm Hg) was 79%, isolated systolic hypertension

(SBP ≥140 mm Hg and DBP <90 mm Hg) was 8%, isolated diastolic hypertension (SBP <140 mm Hg and DBP ≥90 mm Hg) was 4%, and systolic-diastolic hypertension (SBP ≥140 mm Hg and DBP ≥90 mm Hg) was 9%.[98] Over the median 5.5-year follow-up, compared with the nonhypertensive group (referent), isolated diastolic hypertension was not associated with increased CVD risk (HR, 1.03 [95% CI, 0.68–1.57] in contrast to isolated systolic hypertension [HR, 1.57 (95% CI, 1.30–1.90)] and systolic-diastolic hypertension [HR, 1.66 (95% CI, 1.36–2.01)]).

- In an individual participant data meta-analysis of 23 cohorts and 53 172 participants, higher arm compared with lower arm BP reclassified 12% of participants at either 130 or 140 mm Hg SBP thresholds (both $P<0.001$).[99] Higher arm BP models fitted better using Akaike information criteria for all-cause mortality, cardiovascular mortality, and cardiovascular events (all $P<0.001$).
- In an analysis of data from 2 waves of the National Longitudinal Study of Adolescent to Adult Health, including participants who had measured BP at wave IV (2008–09) and a pregnancy that resulted in a singleton live birth between waves IV and V (2016–2018; n=2038), the prevalence of preterm delivery was 12.6%.[100] One-SD increment in SBP (SD, 12.2 mm Hg) and DBP (SD, 9.3 mm Hg) was associated with a 14% (95% CI, 2%–27%) and 20% (95% CI, 4%–37%) higher risk of preterm delivery. Compared with normotension, stage I hypertension (defined as SBP 130–139 mm Hg or DBP 80–89 mm Hg; RR, 1.33 [95% CI, 1.01–1.74]) and stage II (defined as SBP ≥140 mm Hg or DBP ≥ 90 mm Hg; RR, 1.34 [95% CI, 0.89–2.00]) hypertension were also associated with increased subsequent risk of preterm delivery.
- In a meta-analysis of 86 articles with 18 775 387 patients with COVID-19 from 18 countries, hypertension was associated with in-hospital mortality (OR, 1.36 [95% CI, 1.28–1.45]) and other adverse outcomes (OR, 1.32 [95% CI, 1.24–1.41).[101] The analysis by mean age at a study level reported that in-hospital mortality was higher in studies with mean age <49 or >70 years compared with a mean age of 50 to 59 years and 60 to 69 years ($P<0.001$).

## Health Care Use: Hospital Discharges/ Ambulatory Care Visits

## (See Table 8-1)

- Beginning in 2016, a code for hypertensive crisis (*ICD-10-CM* I16) was added to the HCUP inpatient database. For 2016, hypertensive crisis is included in the total number of inpatient hospital stays for HBP. From 2010 to 2020, the number of inpatient discharges from short-stay hospitals with HBP as the principal diagnosis increased from 295 813 to 1 213 745 (Table 8-1). The number of discharges with any listing of HBP increased from 15 445 310 to 16 646 925 in that same time period.
- In 2020, there were 6585 principal diagnosis discharges for essential hypertension (HCUP,[102] unpublished NHLBI tabulation).
- In 2020, there were 8 667 791 all-listed discharges for essential hypertension (HCUP,[102] unpublished NHLBI tabulation).
- In 2019, 56 795 000 of 1 036 484 000 physician office visits had a primary diagnosis of essential hypertension (*ICD-9-CM* 401; NAMCS,[103] unpublished NHLBI tabulation). There were 769 909 ED discharges with a principal diagnosis of essential hypertension in 2020 (HCUP,[102] unpublished NHLBI tabulation).

## Cost

## (See Table 8-1)

- The estimated direct and indirect cost of HBP for 2019 to 2020 (annual average) was $52.4 billion (Table 8-1).
- Estimated US health care expenditures for hypertension in 2016 were $79 billion (95% CI, $72.6–$86.8 billion). Of 154 health conditions, hypertension ranked 10th in health care expenditures.[104]
- In a systematic review of 33 studies reporting cost of care with hypertension from sub-Saharan Africa, only 25% of the countries were represented.[105] The included studies reported costs from the public sector or used a mixed approach including private, nongovernmental, or missionary facilities. Medication costs were accountable for the most part of the monthly expenditures with a range from $1.7 to $97.1 from a patient perspective and $0.1 to $193.6 from a health care professional perspective (per patient per month). Other patient costs reported included transportation, time, and wages lost as a result of hypertension treatment and laboratory costs. At a geographic level, macroeconomic costs ranged from $1.6 million annually for the full population of patients ≥25 years of age living with hypertension on the Seychelles to $397.6 million for direct costs for hypertensive treatment in the sub-Saharan population with SBP pressure ≥115 mm Hg.

## Global Burden

## (See Chart 8-6)

- In 2019, HBP was 1 of the 5 leading risk factors for the burden of disease (YLL and DALYs) in all

regions except Oceania and eastern, central, and western sub-Saharan Africa.[106]

- In a meta-analysis of population-based studies conducted in Africa that included 91 studies from 1989 to 2016, the prevalence of hypertension was 55.2% among adults ≥55 years of age.[107]
- Based on 204 countries and territories in 2021, age-standardized mortality rates attributable to high SBP were highest in central Asia, followed by central sub-Saharan Africa, eastern Europe, and North Africa and the Middle East (Chart 8-6). High SBP was attributed to 11.16 (95% UI, 9.72–12.75) million deaths in 2021.[108] The PAF was 16.16% (95% UI, 13.98%–18.07%).
- In 2015, the prevalence of SBP ≥140 mm Hg was estimated to be 20 526 per 100 000. This represents an increase from 17 307 per 100 000 in 1990.[109] In addition, the prevalence of SBP ≥110 mm Hg increased from 73 119 per 100 000 to 81 373 per 100 000 between 1990 and 2015. There were 3.47 billion adults worldwide with SBP of ≥110 mm Hg in 2015. Of this group, 874 million had SBP ≥140 mm Hg.[109]
- It has been estimated that 7.834 million deaths and 143.037 million DALYs in 2015 could be attributed to SBP ≥140 mm Hg.[109] In addition, 10.7 million deaths and 211 million DALYs in 2015 could be attributed to SBP of ≥110 mm Hg.
- Between 1990 and 2015, the number of deaths related to SBP ≥140 mm Hg did not increase in high-income countries (from 2.197 to 1.956 million deaths) but did increase in high- and middle-income (from 1.288 to 2.176 million deaths), middle-income (from 1.044 to 2.253 million deaths), low- and middle-income (from 0.512 to 1.151 million deaths), and low-income (from 0.146 to 0.293 million deaths) countries.[109]
- In a cross-sectional study of 12 926 individuals from the Bangladesh Demographic and Health Survey conducted over 2017 to 2018, the overall prevalence of hypertension was 27.4%, being higher in females (28.4%) than males (26.2%). Of those with hypertension, 42.4% (n=1508) of people were aware of being hypertensive.[110]
- In a 2021 systematic review of 15 cross-sectional studies from the United Arab Emirates involving 139 907 adults, the pooled prevalence of hypertension was 31% (95% CI, 27%–36%).[111] Among those with hypertension, the level of awareness was 29% (95% CI, 17%–42%). The pooled proportion being treated was 31% (95% CI, 18%–44%); among those taking antihypertensive medications, 38% (95% CI, 19%–57%) had controlled BP (defined as <140/90 mm Hg).
- In an analysis of LASI data from the 2017 to 2019 baseline wave, the estimated hypertension prevalence among adults ≥45 years of age was 45.9% (95% CI, 45.4%–46.5%).[112] Among those with hypertension, 55.7% (95% CI, 54.9%–56.5%) had been diagnosed, 38.9% (95% CI, 38.1%–39.6%) were taking antihypertensive medication, and 31.7% (95% CI, 31.0%–32.4%) achieved BP control.
- In a 2021 systematic review of 64 studies among children <18 years of age in India, the pooled prevalence was 7% (95% CI, 6%–8%) for hypertension, 4% (95% CI, 3%–4.1%) for sustained hypertension, and 10% (95% CI, 8%–13%) for prehypertension.[113] The pooled prevalence was 29% in children with obesity compared with 7% in children with normal weight.
- In an analysis from the CREOLE study, which included 721 Black people from sub-Saharan Africa between 30 and 79 years of age with uncontrolled hypertension and a baseline 24-hour ambulatory BP monitoring, the prevalence of a nondipping pattern was 78%.[114]
- In an analysis of the GBD Study using an age-period-cohort model from 1990 to 2017, the high SBP–attributable stroke mortality rate per 100 000 population declined from 164.7 to 108.7 in males and from 129.1 to 55.5 in females in China.[115] In Japan, the corresponding rates also declined from 63.7 and 24.7 in males and 35.9 and 8.9 in females, respectively.
- In a 2022 meta-analysis of 147 studies involving 1 312 244 general population participants from Middle East and North Africa, the prevalence of hypertension was 26.2% (95% CI, 24.6%–27.9%).[116] The prevalence of hypertension awareness was only 51.3% (95% CI, 47.7%-–54.8%), and the prevalence of hypertension treatment was also low at 47.0% (95% CI, 34.8%–59.2%). The prevalence of BP control among treated patients was 43.1% (95% CI, 38.3%–47.9%). There was a high degree of statistical heterogeneity ($I^2$>99%) in all the analyses. The year of study publication and mean age of patients at the study-level were associated with a higher prevalence and contributed to the heterogeneity in the univariate meta-regression.

**Table 8-1. HBP in the United States**

| Population group | Prevalence, 2017–2020, ≥20 y of age | Mortality,* 2021, all ages | Hospital discharges,† 2020, all ages | Estimated cost, 2019–2020 |
|---|---|---|---|---|
| Both sexes | 122 400 000 (46.7%) (95% CI, 44.2%–49.3%) | 124 508 | 1 213 745 | $52.4 Billion |
| Males | 62 800 000 (50.4%) | 61 079 (49.1%)‡ | | … |
| Females | 59 600 000 (43.0%) | 63 429 (50.9%)‡ | | … |
| NH White males | 48.9% | 41 210 | … | … |
| NH White females | 42.6% | 45 290 | … | … |
| NH Black males | 57.5% | 12 065 | … | … |
| NH Black females | 58.4% | 10 871 | … | … |
| Hispanic males | 50.3% | 4909 | … | … |
| Hispanic females | 35.3% | 4484 | … | … |
| NH Asian males | 50.2% | 1727§ | … | … |
| NH Asian females | 37.6% | 1910§ | … | … |
| NH American Indian/Alaska Native people | … | 884 | … | … |
| NH Native Hawaiian or Pacific Islander people | | 180 | | |

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.[117] Hypertension is defined in terms of NHANES BP measurements and health interviews. A subject was considered to have hypertension if SBP was ≥130 mm Hg or DBP was ≥80 mm Hg, if the subject said "yes" to taking antihypertensive medication, or if the subject was told on 2 occasions that he or she had hypertension. A previous publication that used NHANES 2011 to 2014 data estimated there were 103.3 million noninstitutionalized US adults with hypertension.[118] The number of US adults with hypertension in this table includes both noninstitutionalized and institutionalized US individuals. In addition, the previous study did not include individuals who reported having been told on 2 occasions that they had hypertension as having hypertension unless they met another criterion (SBP was ≥130 mm Hg, DBP was ≥80 mm Hg, or the subject said "yes" to taking antihypertensive medication). CIs have been added for overall prevalence estimates in key chapters. CIs have not been included in this table for all subcategories of prevalence for ease of reading. In March 2020, the COVID-19 pandemic halted NHANES field operations.

BP indicates blood pressure; COVID-19, coronavirus disease 2019; DBP, diastolic blood pressure; ellipses (…), data not available; HBP, high blood pressure; NH, non-Hispanic; NHANES, National Health and Nutrition Examination Survey; and SBP, systolic blood pressure.

*Mortality for Hispanic, American Indian or Alaska Native, and Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting Hispanic origin or race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native, Asian and Pacific Islander, and Hispanic decedents, as well as undercounts of these groups in censuses.

†Beginning in 2016, a code for hypertensive crisis (*International Classification of Diseases, 10th Revision, Clinical Modification* I16) was added to the Healthcare Cost and Utilization Project (HCUP) inpatient database and is included in the total number of hospital discharges for HBP. The large increase in hospital discharges is attributable to *International Classification of Diseases, 10th Revision* coding changes for heart failure using Agency for Healthcare Research and Quality Prevention Quality Indicator 08, heart failure admission rate.

‡These percentages represent the portion of total HBP mortality that is for males versus females.

§Includes Chinese, Filipino, Japanese, and other Asian people.

Sources: Prevalence: Unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using NHANES.[5] Percentages for racial and ethnic groups are age adjusted for Americans ≥20 years of age. Age-specific percentages are extrapolated to the 2020 US population estimates. Mortality (for underlying case of HBP): Unpublished NHLBI tabulation using National Vital Statistics System.[77] These data represent underlying cause of death only. Hospital discharges (with a principal diagnosis of HBP): Unpublished NHLBI tabulation using HCUP.[102] Cost: Unpublished NHLBI tabulation using Medical Expenditure Panel Survey[119]; includes estimated direct costs for 2019 to 2020 (annual average) and indirect costs calculated by NHLBI for 2019 to 2020 (annual average).

**Table 8-2. Hypertension Awareness, Treatment, and Control: NHANES 1999 to 2002, 2007 to 2010, and 2017 to 2020 Age-Adjusted Percent With Hypertension in US Adults, by Sex and Race and Ethnicity**

| | Awareness, % | | | Treatment, % | | | Control, % | | |
|---|---|---|---|---|---|---|---|---|---|
| | 1999–2002 | 2007–2010 | 2017–2020 | 1999–2002 | 2007–2010 | 2017–2020 | 1999–2002 | 2007–2010 | 2017–2020 |
| Overall | 48.9 | 61.2 | 62.0 | 37.7 | 52.5 | 52.6 | 12.0 | 24.1 | 25.7 |
| NH White males | 42.7 | 58.0 | 62.0 | 31.4 | 48.7 | 50.4 | 10.9 | 22.2 | 26.7 |
| NH White females | 56.7 | 66.1 | 62.9 | 45.9 | 59.2 | 56.4 | 14.8 | 28.7 | 27.6 |
| NH Black males | 46.0 | 60.5 | 61.5 | 33.0 | 47.6 | 48.4 | 9.1 | 18.2 | 17.3 |
| NH Black females | 67.7 | 73.5 | 71.2 | 54.9 | 64.3 | 61.0 | 16.4 | 28.2 | 25.6 |
| Mexican American males* | 25.9 | 40.6 | 47.7 | 14.0 | 30.5 | 36.2 | 4.1 | 12.7 | 20.6 |
| Mexican American females* | 50.4 | 55.6 | 60.5 | 35.4 | 49.3 | 49.9 | 10.4 | 21.2 | 23.9 |

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.[117] Hypertension is defined in terms of NHANES BP measurements and health interviews. A subject was considered to have hypertension if SBP was ≥130 mm Hg, DBP was ≥80 mm Hg, or the subject said "yes" to taking antihypertensive medication. Controlled hypertension is considered to be SBP <130 mm Hg or DBP <80 mm Hg. Total includes race and ethnicity groups not shown (other Hispanic, other race, and multiracial).

BP indicates blood pressure; COVID-19, coronavirus disease 2019; DBP, diastolic blood pressure; NH, non-Hispanic; NHANES, National Health and Nutrition Examination Survey; and SBP, systolic blood pressure.

*The category of Mexican American people was consistently collected in all NHANES years, but the combined category of Hispanic people was used only starting in 2007. Consequently, for long-term trend data, the category of Mexican American people is used. Total includes race and ethnicity groups not shown (other Hispanic, other race, and multiracial).

Sources: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.[5]

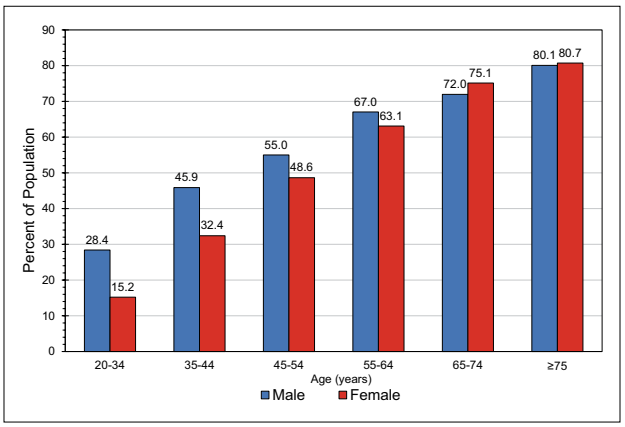



**Chart 8-1. Prevalence of hypertension in US adults ≥20 years of age, by sex and age (NHANES 2017–2020).**
In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.[117] Hypertension is defined in terms of NHANES BP measurements and health interviews. A person was considered to have hypertension if he or she had SBP ≥130 mm Hg or DBP ≥80 mm Hg, if he or she said "yes" to taking antihypertensive medication, or if the person was told on 2 occasions that he or she had hypertension.
BP indicates blood pressure; COVID-19, coronavirus disease 2019; DBP, diastolic blood pressure; NHANES, National Health and Nutrition Examination Survey; and SBP, systolic blood pressure.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.[5]

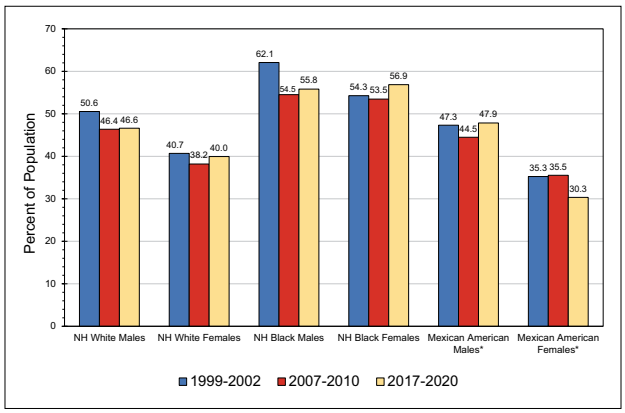



**Chart 8-2. Age-adjusted prevalence trends for hypertension in US adults ≥20 years of age, by race and ethnicity, sex, and survey year (NHANES 1999–2002, 2007–2010, and 2017–2020).**
In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.[117] Hypertension is defined in terms of NHANES BP measurements and health interviews. A person was considered to have hypertension if he or she had SBP ≥130 mm Hg or DBP ≥80 mm Hg or if he or she said "yes" to taking antihypertensive medication.
BP indicates blood pressure; COVID-19, coronavirus disease 2019; DBP, diastolic blood pressure; NH, non-Hispanic; NHANES, National Health and Nutrition Examination Survey; and SBP, systolic blood pressure.
*The category of Mexican American people was consistently collected in all NHANES years, but the combined category of Hispanic people was used only starting in 2007. Consequently, for long-term trend data, the category of Mexican American people is used.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.[5]

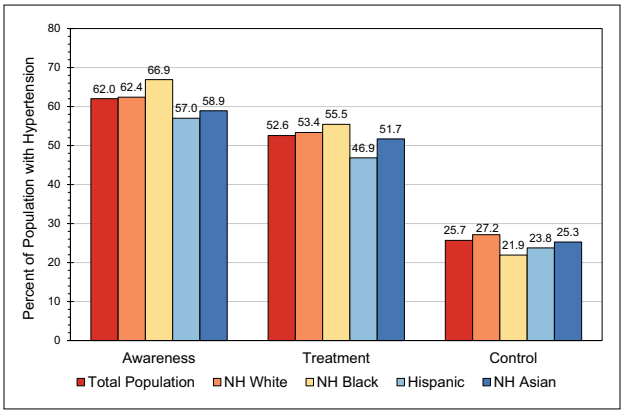



**Chart 8-3. Extent of awareness, treatment, and control of HBP by race and ethnicity, United States (NHANES 2017–2020).**

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.[117] Hypertension is defined in terms of NHANES BP measurements and health interviews. A person was considered to have hypertension if he or she had SBP ≥130 mm Hg or DBP ≥80 mm Hg or if he or she said "yes" to taking antihypertensive medication. BP indicates blood pressure; COVID-19, coronavirus disease 2019; DBP, diastolic blood pressure; HBP, high blood pressure; NH, non-Hispanic; NHANES, National Health and Nutrition Examination Survey; and SBP, systolic blood pressure.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.[5]

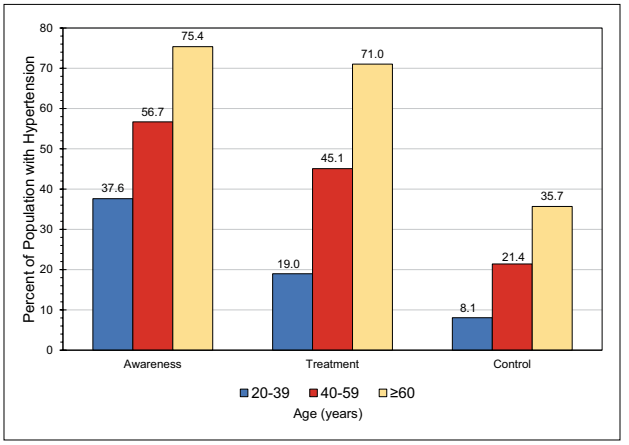



**Chart 8-4. Extent of awareness, treatment, and control of HBP, by age, United States (NHANES 2017–2020).**

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.[117] Hypertension is defined in terms of NHANES BP measurements and health interviews. A person was considered to have hypertension if he or she had SBP ≥130 mm Hg or DBP ≥80 mm Hg or if he or she said "yes" to taking antihypertensive medication. BP indicates blood pressure; COVID-19, coronavirus disease 2019; DBP, diastolic blood pressure; HBP, high blood pressure; NHANES, National Health and Nutrition Examination Survey; and SBP, systolic blood pressure.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.[5]

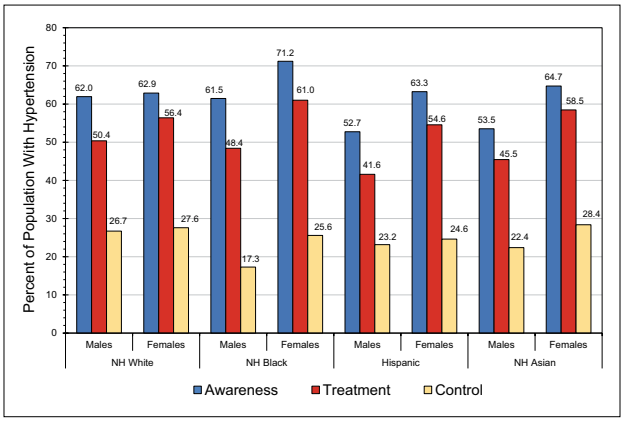



**Chart 8-5. Extent of awareness, treatment, and control of HBP, by race and ethnicity and sex, United States (NHANES, 2017–2020).**

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.[117] Hypertension is defined in terms of NHANES BP measurements and health interviews. A person was considered to have hypertension if he or she had SBP ≥130 mm Hg or DBP ≥80 mm Hg or if he or she said "yes" to taking antihypertensive medication. BP indicates blood pressure; COVID-19, coronavirus disease 2019; DBP, diastolic blood pressure; HBP, high blood pressure; NH, non-Hispanic; NHANES, National Health and Nutrition Examination Survey; and SBP, systolic blood pressure.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.[5]

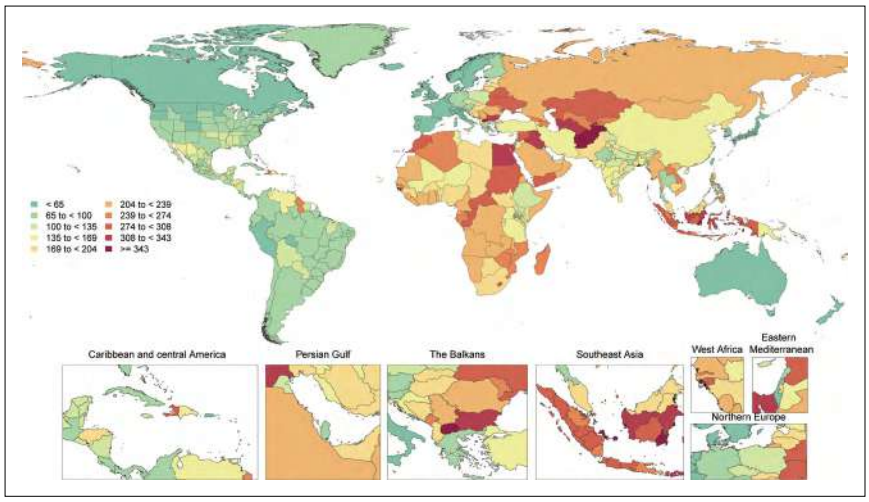



**Chart 8-6. Age-standardized global mortality rates attributable to high SBP per 100 000, both sexes, 2021.** During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles. GBD indicates Global Burden of Disease; and SBP, systolic blood pressure. Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[108]

## REFERENCES


1. Clark D 3rd, Colantonio LD, Min YI, Hall ME, Zhao H, Mentz RJ, Shimbo D, Ogedegbe G, Howard G, Levitan EB, et al. Population-attributable risk for cardiovascular disease associated with hypertension in Black adults. *JAMA Cardiol*. 2019;4:1194–1202. doi: 10.1001/jamacardio.2019.3773
2. Bundy JD, Li C, Stuchlik P, Bu X, Kelly TN, Mills KT, He H, Chen J, Whelton PK, He J. Systolic blood pressure reduction and risk of cardiovascular disease and mortality: a systematic review and network meta-analysis. *JAMA Cardiol*. 2017;2:775–781. doi: 10.1001/jamacardio.2017.1421
3. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, Greenlund K, Daniels S, Nichol G, Tomaselli GF, et al; on behalf of the American Heart Association Strategic Planning Task Force and Statistics Committee. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. *Circulation*. 2010;121:586–613. doi: 10.1161/CIRCULATIONAHA.109.192703
4. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published correction appears in *Hypertension*. 2018;71:e140–e144]. *Hypertension*. 2018;71:e13–e115. doi: 10.1161/HYP.0000000000000065
5. Centers for Disease Control and Prevention and National Center for Health Statistics. National Health and Nutrition Examination Survey (NHANES) public use data files. Accessed April 1, 2023. https://cdc.gov/nchs/nhanes/
6. Centers for Disease Control and Prevention and National Center for Chronic Disease Prevention and Health Promotion. Behavioral Risk Factor Surveillance System (BRFSS): BRFSS prevalence & trends data. Accessed March 27, 2023. https://cdc.gov/brfss/brfssprevalence/
7. Bourque G, Ilin JV, Ruzicka M, Hundemer GL, Shorr R, Hiremath S. Non-adherence is common in patients with apparent resistant hypertension: a systematic review and meta-analysis. *Am J Hypertens*. 2023;36:394–403. doi: 10.1093/ajh/hpad013
8. Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, de Ferranti SD, Dionne JM, Falkner B, Flinn SK, et al; Subcommittee on Screening and Management of High Blood Pressure In Children. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics*. 2017;140:e20171904. doi: 10.1542/peds.2017-1904
9. Overwyk KJ, Zhao L, Zhang Z, Wiltz JL, Dunford EK, Cogswell ME. Trends in blood pressure and usual dietary sodium intake among children and adolescents, National Health and Nutrition Examination Survey 2003 to 2016. *Hypertension*. 2019;74:260–266. doi: 10.1161/HYPERTENSIONAHA.118.12844
10. Cioana M, Deng J, Hou M, Nadarajah A, Qiu Y, Chen SSJ, Rivas A, Banfield L, Chanchlani R, Dart A, et al. Prevalence of hypertension and albuminuria in pediatric type 2 diabetes: a systematic review and meta-analysis. *JAMA Netw Open*. 2021;4:e216069. doi: 10.1001/jamanetworkopen.2021.6069
11. Hamdani G, Mitsnefes MM, Flynn JT, Becker RC, Daniels S, Falkner BE, Ferguson M, Hooper SR, Hanevold CD, Ingelfinger JR, et al. Pediatric and adult ambulatory blood pressure thresholds and blood pressure load as predictors of left ventricular hypertrophy in adolescents. *Hypertension*. 2021;78:30–37. doi: 10.1161/HYPERTENSIONAHA.120.16896
12. Koebnick C, Mohan Y, Li X, Porter AH, Daley MF, Luo G, Kuizon BD. Failure to confirm high blood pressures in pediatric care: quantifying the risks of misclassification. *J Clin Hypertens*. 2018;20:174–182. doi: 10.1111/jch.13159
13. Crouch SH, Soepnel LM, Kolkenbeck-Ruh A, Maposa I, Naidoo S, Davies J, Norris SA, Ware LJ. Paediatric hypertension in Africa: a systematic review and meta-analysis. *EClinicalMedicine*. 2022;43:101229. doi: 10.1016/j.eclinm.2021.101229
14. Nugent JT, Young C, Funaro MC, Jiang K, Saran I, Ghazi L, Wilson FP, Greenberg JH. Prevalence of secondary hypertension in otherwise healthy youths with a new diagnosis of hypertension: a meta-analysis. *J Pediatr*. 2022;244:30–37.e10. doi: 10.1016/j.jpeds.2022.01.047
15. Brown AGM, Houser RF, Mattei J, Mozaffarian D, Lichtenstein AH, Folta SC. Hypertension among US-born and foreign-born non-Hispanic Blacks: National Health and Nutrition Examination Survey 2003-2014 data. *J Hypertens*. 2017;35:2380–2387. doi: 10.1097/HJH.0000000000001489
16. Centers for Disease Control and Prevention and National Center for Health Statistics. Summary health statistics: National Health Interview Survey, 2018, table A-1. Accessed March 22, 2023. https://ftp.cdc.gov/pub/Health_Statistics/NCHS/NHIS/SHS/2018_SHS_Table_A-1.pdf
17. Abdel Magid HS, Milliren CE, Rice K, Molanphy N, Ruiz K, Gooding HC, Richmond TK, Odden MC, Nagata JM. Adolescent individual, school, and neighborhood influences on young adult hypertension risk. *PLoS One*. 2022;17:e0266729. doi: 10.1371/journal.pone.0266729
18. Chen V, Ning H, Allen N, Kershaw K, Khan S, Lloyd-Jones DM, Wilkins JT. Lifetime risks for hypertension by contemporary guidelines in African American and White men and women. *JAMA Cardiol*. 2019;4:455–459. doi: 10.1001/jamacardio.2019.0529
19. Muntner P, Hardy ST, Fine LJ, Jaeger BC, Wozniak G, Levitan EB, Colantonio LD. Trends in blood pressure control among US adults with hypertension, 1999-2000 to 2017-2018. *JAMA*. 2020;324:1190–1200. doi: 10.1001/jama.2020.14545
20. Ananth CV, Duzyj CM, Yadava S, Schwebel M, Tita ATN, Joseph KS. Changes in the prevalence of chronic hypertension in pregnancy, United States, 1970 to 2010. *Hypertension*. 2019;74:1089–1095. doi: 10.1161/HYPERTENSIONAHA.119.12968
21. Egeland GM, Skurtveit S, Staff AC, Eide GE, Daltveit AK, Klungsoyr K, Trogstad L, Magnus PM, Brantsaeter AL, Haugen M. Pregnancy-related risk factors are associated with a significant burden of treated hypertension within 10 years of delivery: findings from a population-based Norwegian cohort. *J Am Heart Assoc*. 2018;7:e008318. doi: 10.1161/JAHA.117.008318
22. Stuart JJ, Tanz LJ, Missmer SA, Rimm EB, Spiegelman D, James-Todd TM, Rich-Edwards JW. Hypertensive disorders of pregnancy and maternal

cardiovascular disease risk factor development: an observational cohort study. *Ann Intern Med*. 2018;169:224–232. doi: 10.7326/M17-2740
23. Joham AE, Kakoly NS, Teede HJ, Earnest A. Incidence and predictors of hypertension in a cohort of Australian women with and without polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2021;106:1585–1593. doi: 10.1210/clinem/dgab134
24. Chen F, Fu W, Shi O, Li D, Jiang Q, Wang T, Zhou X, Lu Z, Cao S. Impact of exposure to noise on the risk of hypertension: a systematic review and meta-analysis of cohort studies. *Environ Res*. 2021;195:110813. doi: 10.1016/j.envres.2021.110813
25. Cheng H, Gu X, He Z, Yang Y. Dose-response relationship between working hours and hypertension: a 22-year follow-up study. *Medicine (Baltimore)*. 2021;100:e25629. doi: 10.1097/MD.0000000000025629
26. Howard G, Cushman M, Moy CS, Oparil S, Muntner P, Lackland DT, Manly JJ, Flaherty ML, Judd SE, Wadley VG, et al. Association of clinical and social factors with excess hypertension risk in black compared with White US adults. *JAMA*. 2018;320:1338–1348. doi: 10.1001/jama.2018.13467
27. Huang L, Trieu K, Yoshimura S, Neal B, Woodward M, Campbell NRC, Li Q, Lackland DT, Leung AA, Anderson CAM, et al. Effect of dose and duration of reduction in dietary sodium on blood pressure levels: systematic review and meta-analysis of randomised trials. *BMJ*. 2020;368:m315. doi: 10.1136/bmj.m315
28. Neal B, Wu Y, Feng X, Zhang R, Zhang Y, Shi J, Zhang J, Tian M, Huang L, Li Z, et al. Effect of salt substitution on cardiovascular events and death. *N Engl J Med*. 2021;385:1067–1077. doi: 10.1056/NEJMoa2105675
29. do Rosario VA, Schoenaker DAJM, Kent K, Weston-Green K, Charlton K. Association between flavonoid intake and risk of hypertension in two cohorts of Australian women: a longitudinal study. *Eur J Nutr*. 2021;60:2507–2519. doi: 10.1007/s00394-020-02424-9
30. Sardana M, Lin H, Zhang Y, Liu C, Trinquart L, Benjamin EJ, Manders ES, Fusco K, Kornej J, Hammond MM, et al. Association of habitual physical activity with home blood pressure in the Electronic Framingham Heart Study (eFHS): cross-sectional study. *J Med Internet Res*. 2021;23:e25591. doi: 10.2196/25591
31. Ramos AR, Weng J, Wallace DM, Petrov MR, Wohlgemuth WK, Sotres-Alvarez D, Loredo JS, Reid KJ, Zee PC, Mossavar-Rahmani Y, et al. Sleep patterns and hypertension using actigraphy in the Hispanic Community Health Study/Study of Latinos. *Chest*. 2018;153:87–93. doi: 10.1016/j.chest.2017.09.028
32. Johnson DA, Thomas SJ, Abdalla M, Guo N, Yano Y, Rueschman M, Tanner RM, Mittleman MA, Calhoun DA, Wilson JG, et al. Association between sleep apnea and blood pressure control among Blacks. *Circulation*. 2019;139:1275–1284. doi: 10.1161/CIRCULATIONAHA.118.036675
33. MacIntyre IM, Turtle EJ, Farrah TE, Graham C, Dear JW, Webb DJ; PATH-BP (Paracetamol in Hypertension–Blood Pressure) Investigators. Regular acetaminophen use and blood pressure in people with hypertension: the PATH-BP trial. *Circulation*. 2022;145:416–423. doi: 10.1161/CIRCULATIONAHA.121.056015
34. Kourieh A, Giorgis-Allemand L, Bouaoun L, Lefèvre M, Champelovier P, Lambert J, Laumon B, Evrard AS. Incident hypertension in relation to aircraft noise exposure: results of the DEBATS longitudinal study in France. *Occup Environ Med*. 2022;79:268–276. doi: 10.1136/oemed-2021-107921
35. Li YD, Ren ZJ, Gao L, Ma JH, Gou YQ, Tan W, Liu C. Association between male infertility and the risk of hypertension: a meta-analysis and literature review. *Andrologia*. 2022;54:e14535. doi: 10.1111/and.14535
36. Sheehy S, Palmer JR, Cozier Y, Bertrand KA, Rosenberg L. Vitamin D and risk of hypertension among Black women. *J Clin Hypertens (Greenwich)*. 2023;25:168–174. doi: 10.1111/jch.14615
37. Forde AT, Sims M, Muntner P, Lewis T, Onwuka A, Moore K, Diez Roux AV. Discrimination and hypertension risk among African Americans in the Jackson Heart Study. *Hypertension*. 2020;76:715–723. doi: 10.1161/HYPERTENSIONAHA.119.14492
38. Glover LM, Cain-Shields LR, Wyatt SB, Gebreab SY, Diez-Roux AV, Sims M. Life course socioeconomic status and hypertension in African American adults: the Jackson Heart Study. *Am J Hypertens*. 2020;33:84–91. doi: 10.1093/ajh/hpz133
39. Mayne SL, Moore KA, Powell-Wiley TM, Evenson KR, Block R, Kershaw KN. Longitudinal associations of neighborhood crime and perceived safety with blood pressure: the Multi-Ethnic Study of Atherosclerosis (MESA). *Am J Hypertens*. 2018;31:1024–1032. doi: 10.1093/ajh/hpy066
40. Trudel X, Brisson C, Gilbert-Ouimet M, Vezina M, Talbot D, Milot A. Long working hours and the prevalence of masked and sustained hypertension. *Hypertension*. 2020;75:532–538. doi: 10.1161/HYPERTENSIONAHA.119.12926
41. Gamboa Madeira S, Fernandes C, Paiva T, Santos Moreira C, Caldeira D. The impact of different types of shift work on blood pressure and hypertension: a systematic review and meta-analysis. *Int J Environ Res Public Health*. 2021;18:6738. doi: 10.3390/ijerph18136738
42. Liu C, Kraja AT, Smith JA, Brody JA, Franceschini N, Bis JC, Rice K, Morrison AC, Lu Y, Weiss S, et al; CHD Exome+ Consortium, ExomeBP Consortium, GoT2DGenes Consortium, T2D-Genes Consortium; Myocardial Infarction Genetics and CARDIoGRAM Exome Consortia; CKDGen Consortium. Meta-analysis identifies common and rare variants influencing blood pressure and overlapping with metabolic trait loci. *Nat Genet*. 2016;48:1162–1170. doi: 10.1038/ng.3660
43. Surendran P, Drenos F, Young R, Warren H, Cook JP, Manning AK, Grarup N, Sim X, Barnes DR, Witkowska K, et al; CHARGE-Heart Failure Consortium; EchoGen Consortium; Metastroke Consortium; Giant Consortium; EPIC-InterAct Consortium; Lifelines Cohort Study; Wellcome Trust Case Control Consortium; Understanding Society Scientific Group; Charge Exome Chip Blood Pressure Consortium; T2D-GENES Consortium; GoT2DGenes Consortium; CHD Exome+ Consortium. Trans-ancestry meta-analyses identify rare and common variants associated with blood pressure and hypertension. *Nat Genet*. 2016;48:1151–1161. doi: 10.1038/ng.3654
44. Ehret GB, Ferreira T, Chasman DI, Jackson AU, Schmidt EM, Johnson T, Thorleifsson G, Luan J, Donnelly LA, Kanoni S, et al; CHARGE-EchoGen Consortium. The genetics of blood pressure regulation and its target organs from association studies in 342,415 individuals. *Nat Genet*. 2016;48:1171–1184. doi: 10.1038/ng.3667
45. Hoffmann TJ, Ehret GB, Nandakumar P, Ranatunga D, Schaefer C, Kwok PY, Iribarren C, Chakravarti A, Risch N. Genome-wide association analyses using electronic health records identify new loci influencing blood pressure variation. *Nat Genet*. 2017;49:54–64. doi: 10.1038/ng.3715
46. Yu B, Pulit SL, Hwang SJ, Brody JA, Amin N, Auer PL, Bis JC, Boerwinkle E, Burke GL, Chakravarti A, et al; CHARGE Consortium and the National Heart, Lung, and Blood Institute GO ESP. Rare exome sequence variants in CLCN6 reduce blood pressure levels and hypertension risk. *Circ Cardiovasc Genet*. 2016;9:64–70. doi: 10.1161/CIRCGENETICS.115.001215
47. Tragante V, Barnes MR, Ganesh SK, Lanktree MB, Guo W, Franceschini N, Smith EN, Johnson T, Holmes MV, Padmanabhan S, et al. Gene-centric meta-analysis in 87,736 individuals of European ancestry identifies multiple blood-pressure-related loci. *Am J Hum Genet*. 2014;94:349–360. doi: 10.1016/j.ajhg.2013.12.016
48. Warren HR, Evangelou E, Cabrera CP, Gao H, Ren M, Mifsud B, Ntalla I, Surendran P, Liu C, Cook JP, et al; International Consortium of Blood Pressure (ICBP) 1000G Analyses, BIOS Consortium, Lifelines Cohort Study, Understanding Society Scientific group, C.H.D. Exome+ Consortium, Exome BP Consortium, T2D GENES Consortium, GoT2DGenes Consortium, Cohorts for Heart and Ageing Research in Genome Epidemiology (CHARGE) BP Exome Consortium, International Genomics of Blood Pressure (iGEN-BP) Consortium, and U. K. Biobank CardioMetabolic Consortium BP working group. Genome-wide association analysis identifies novel blood pressure loci and offers biological insights into cardiovascular risk. *Nat Genet*. 2017;49:403–415. doi: 10.1038/ng.3768
49. He KY, Li X, Kelly TN, Liang J, Cade BE, Assimes TL, Becker LC, Beitelshees AL, Bress AP, Chang YC, et al; NHLBI Trans-Omics for Precision Medicine (TOPMed) Consortium, TOPMed Blood Pressure Working Group. Leveraging linkage evidence to identify low-frequency and rare variants on 16p13 associated with blood pressure using TOPMed whole genome sequencing data. *Hum Genet*. 2019;138:199–210. doi: 10.1007/s00439-019-01975-0
50. Evangelou E, Warren HR, Mosen-Ansorena D, Mifsud B, Pazoki R, Gao H, Ntritsos G, Dimou N, Cabrera CP, Karaman I, et al. Genetic analysis of over 1 million people identifies 535 new loci associated with blood pressure traits. *Nat Genet*. 2018;50:1412–1425. doi: 10.1038/s41588-018-0205-x
51. Giri A, Hellwege JN, Keaton JM, Park J, Qiu C, Warren HR, Torstenson ES, Kovesdy CP, Sun YV, Wilson OD, et al; Understanding Society Scientific Group, International Consortium for Blood Pressure, Blood Pressure-International Consortium of Exome Chip Studies. Trans-ethnic association study of blood pressure determinants in over 750,000 individuals. *Nat Genet*. 2019;51:51–62. doi: 10.1038/s41588-018-0303-9
52. Surendran P, Feofanova EV, Lahrouchi N, Ntalla I, Karthikeyan S, Cook J, Chen L, Mifsud B, Yao C, Kraja AT, et al. Discovery of rare variants associated with blood pressure regulation through meta-analysis of 1.3 million individuals. *Nat Genet*. 2020;52:1314–1332. doi: 10.1038/s41588-020-00713-x
53. Liang J, Le TH, Edwards DRV, Tayo BO, Gaulton KJ, Smith JA, Lu Y, Jensen RA, Chen G, Yanek LR, et al. Single-trait and multi-trait genome-wide association analyses identify novel loci for blood pressure

in African-ancestry populations. *PLoS Genet*. 2017;13:e1006728. doi: 10.1371/journal.pgen.1006728
54. Wan EYF, Fung WT, Schooling CM, Au Yeung SL, Kwok MK, Yu EYT, Wang Y, Chan EWY, Wong ICK, Lam CLK. Blood pressure and risk of cardiovascular disease in UK Biobank: a mendelian randomization study. *Hypertension*. 2021;77:367–375. doi: 10.1161/HYPERTENSIONAHA.120.16138
55. Parcha V, Pampana A, Shetty NS, Irvin MR, Natarajan P, Lin HJ, Guo X, Rich SS, Rotter JI, Li P, et al. Association of a multiancestry genome-wide blood pressure polygenic risk score with adverse cardiovascular events. *Circ Genom Precis Med*. 2022;15:e003946. doi: 10.1161/CIRCGEN.122.003946
56. Gouveia MH, Bentley AR, Leonard H, Meeks KAC, Ekoru K, Chen G, Nalls MA, Simonsick EM, Tarazona-Santos E, Lima-Costa MF, et al. Trans-ethnic meta-analysis identifies new loci associated with longitudinal blood pressure traits. *Sci Rep*. 2021;11:4075. doi: 10.1038/s41598-021-83450-3
57. Jia P, Zhan N, Bat BKK, Feng Q, Tsoi KKF. The genetic architecture of blood pressure variability: a genome-wide association study of 9370 participants from UK Biobank. *J Clin Hypertens (Greenwich)*. 2022;24:1370–1380. doi: 10.1111/jch.14552
58. Kauko A, Aittokallio J, Vaura F, Ji H, Ebinger JE, Niiranen T, Cheng S. Sex differences in genetic risk for hypertension. *Hypertension*. 2021;78:1153–1155. doi: 10.1161/HYPERTENSIONAHA.121.17796
59. Ji H, Kim A, Ebinger JE, Niiranen TJ, Claggett BL, Bairey Merz CN, Cheng S. Sex differences in blood pressure trajectories over the life course. *JAMA Cardiol*. 2020;5:19–26. doi: 10.1001/jamacardio.2019.5306
60. Basson J, Sung YJ, de las Fuentes L, Schwander K, Cupples LA, Rao DC. Influence of smoking status and intensity on discovery of blood pressure loci through gene-smoking interactions. *Genet Epidemiol*. 2015;39:480–488. doi: 10.1002/gepi.21904
61. Sung Y, de Las Fuentes L, Schwander K, Simino J, Rao D. Gene-smoking interactions identify several novel blood pressure loci in the Framingham Heart Study. *Am J Hypertens*. 2015;28:343–354. doi: 10.1093/ajh/hpu149
62. Li C, He J, Chen J, Zhao J, Gu D, Hixson J, Rao D, Jaquish C, Gu C, Chen J, et al. Genome-wide gene-sodium interaction analyses on blood pressure: the Genetic Epidemiology Network of Salt-Sensitivity Study. *Hypertension*. 2016;68:348–355. doi: 10.1161/HYPERTENSIONAHA.115.06765
63. Sung YJ, de Las Fuentes L, Winkler TW, Chasman DI, Bentley AR, Kraja AT, Ntalla I, Warren HR, Guo X, Schwander K, et al; Lifelines Cohort Study. A multi-ancestry genome-wide study incorporating gene-smoking interactions identifies multiple new loci for pulse pressure and mean arterial pressure. *Hum Mol Genet*. 2019;28:2615–2633. doi: 10.1093/hmg/ddz070
64. Cooper-DeHoff RM, Johnson JA. Hypertension pharmacogenomics: in search of personalized treatment approaches. *Nat Rev Nephrol*. 2016;12:110–122. doi: 10.1038/nrneph.2015.176
65. Gill D, Georgakis MK, Koskeridis F, Jiang L, Feng Q, Wei WQ, Theodoratou E, Elliott P, Denny JC, Malik R, et al. Use of genetic variants related to antihypertensive drugs to inform on efficacy and side effects. *Circulation*. 2019;140:270–279. doi: 10.1161/CIRCULATIONAHA.118.038814
66. Wright J Jr, Williamson J, Whelton P, Snyder J, Sink K, Rocco M, Reboussin D, Rahman M, Oparil S, Lewis C; SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control [published correction appears in *N Engl J Med*. 2017;377:2506]. *N Engl J Med*. 2015;373:2103–2116. doi: 10.1056/NEJMoa1511939
67. Bress AP, Tanner RM, Hess R, Colantonio LD, Shimbo D, Muntner P. Generalizability of SPRINT results to the U.S. adult population. *J Am Coll Cardiol*. 2016;67:463–472. doi: 10.1016/j.jacc.2015.10.037
68. Butler MJ, Tanner RM, Muntner P, Shimbo D, Bress AP, Shallcross AJ, Sims M, Ogedegbe G, Spruill TM. Adherence to antihypertensive medications and associations with blood pressure among African Americans with hypertension in the Jackson Heart Study. *J Am Soc Hypertens*. 2017;11:581–588.e5. doi: 10.1016/j.jash.2017.06.011
69. Tapela N, Collister J, Clifton L, Turnbull I, Rahimi K, Hunter DJ. Prevalence and determinants of hypertension control among almost 100 000 treated adults in the UK. *Open Heart*. 2021;8:e001461. doi: 10.1136/openhrt-2020-001461
70. Martin FZ, Fraser A, Zuccolo L. Alcohol intake and hypertensive disorders of pregnancy: a negative control analysis in the ALSPAC cohort. *J Am Heart Assoc*. 2022;11:e025102. doi: 10.1161/JAHA.121.025102
71. Cohen JB, Cohen DL, Herman DS, Leppert JT, Byrd JB, Bhalla V. Testing for primary aldosteronism and mineralocorticoid receptor antagonist use among U.S. veterans: a retrospective cohort study. *Ann Intern Med*. 2021;174:289–297. doi: 10.7326/M20-4873
72. Chang TE, Ritchey MD, Ayala C, Durthaler JM, Loustalot F. Use of strategies to improve antihypertensive medication adherence within United States outpatient health care practices, DocStyles 2015-2016. *J Clin Hypertens (Greenwich)*. 2018;20:225–232. doi: 10.1111/jch.13188
73. Kassavou A, Wang M, Mirzaei V, Shpendi S, Hasan R. The association between smartphone app-based self-monitoring of hypertension-related behaviors and reductions in high blood pressure: systematic review and meta-analysis. *JMIR Mhealth Uhealth*. 2022;10:e34767. doi: 10.2196/34767
74. Feng Y, Zhao Y, Yang X, Li Y, Han M, Qie R, Huang S, Wu X, Zhang Y, Wu Y, et al. Adherence to antihypertensive medication and cardiovascular disease events in hypertensive patients: a dose-response meta-analysis of 2 769 700 participants in cohort study. *QJM*. 2022;115:279–286. doi: 10.1093/qjmed/hcaa349
75. Gnanenthiran SR, Borghi C, Burger D, Caramelli B, Charchar F, Chirinos JA, Cohen JB, Cremer A, Di Tanna GL, Duvignaud A, et al; COVID-METARASI Consortium. Renin-angiotensin system inhibitors in patients with COVID-19: a meta-analysis of randomized controlled trials led by the International Society of Hypertension. *J Am Heart Assoc*. 2022;11:e026143. doi: 10.1161/JAHA.122.026143
76. Mackenzie IS, Rogers A, Poulter NR, Williams B, Brown MJ, Webb DJ, Ford I, Rorie DA, Guthrie G, Grieve JWK, et al; TIME Study Group. Cardiovascular outcomes in adults with hypertension with evening versus morning dosing of usual antihypertensives in the UK (TIME study): a prospective, randomised, open-label, blinded-endpoint clinical trial. *Lancet*. 2022;400:1417–1425. doi: 10.1016/S0140-6736(22)01786-X
77. Centers for Disease Control and Prevention and National Center for Health Statistics. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death micro-data files. Accessed April 8, 2023. https://cdc.gov/nchs/nvss/mortality_public_use_data.htm
78. Centers for Disease Control and Prevention and National Center for Health Statistics. Multiple cause of death, CDC WONDER online database. Accessed April 1, 2023. https://wonder.cdc.gov/mcd-icd10.html
79. Yano Y, Reis JP, Lewis CE, Sidney S, Pletcher MJ, Bibbins-Domingo K, Navar AM, Peterson ED, Bancks MP, Kanegae H, et al. Association of blood pressure patterns in young adulthood with cardiovascular disease and mortality in middle age. *JAMA Cardiol*. 2020;5:382–389. doi: 10.1001/jamacardio.2019.5682
80. Cohen JB, Lotito MJ, Trivedi UK, Denker MG, Cohen DL, Townsend RR. Cardiovascular events and mortality in white coat hypertension: a systematic review and meta-analysis. *Ann Intern Med*. 2019;170:853–862. doi: 10.7326/M19-0223
81. Yano Y, Tanner RM, Sakhuja S, Jaeger BC, Booth JN 3rd, Abdalla M, Pugliese D, Seals SR, Ogedegbe G, Jones DW, et al. Association of daytime and nighttime blood pressure with cardiovascular disease events among African American individuals. *JAMA Cardiol*. 2019;4:910–917. doi: 10.1001/jamacardio.2019.2845
82. Blood Pressure Lowering Treatment Trialists Collaboration. Pharmacological blood pressure lowering for primary and secondary prevention of cardiovascular disease across different levels of blood pressure: an individual participant-level data meta-analysis. *Lancet*. 2021;397:1625–1636. doi: 10.1016/S0140-6736(21)00590-0
83. Yano Y, Reis JP, Colangelo LA, Shimbo D, Viera AJ, Allen NB, Gidding SS, Bress AP, Greenland P, Muntner P, et al. Association of blood pressure classification in young adults using the 2017 American College of Cardiology/American Heart Association blood pressure guideline with cardiovascular events later in life. *JAMA*. 2018;320:1774–1782. doi: 10.1001/jama.2018.13551
84. Kubicki DM, Xu M, Akwo EA, Dixon D, Munoz D, Blot WJ, Wang TJ, Lipworth L, Gupta DK. Race and sex differences in modifiable risk factors and incident heart failure. *JACC Heart Fail*. 2020;8:122–130. doi: 10.1016/j.jchf.2019.11.001
85. Zhang W, Zhang S, Deng Y, Wu S, Ren J, Sun G, Yang J, Jiang Y, Xu X, Wang TD, et al; STEP Study Group. Trial of intensive blood-pressure control in older patients with hypertension. *N Engl J Med*. 2021;385:1268–1279. doi: 10.1056/NEJMoa2111437
86. Soliman EZ, Rahman AF, Zhang ZM, Rodriguez CJ, Chang TI, Bates JT, Ghazi L, Blackshear JL, Chonchol M, Fine LJ, et al. Effect of intensive blood pressure lowering on the risk of atrial fibrillation. *Hypertension*. 2020;75:1491–1496. doi: 10.1161/HYPERTENSIONAHA.120.14766
87. Thomas G, Xie D, Chen HY, Anderson AH, Appel LJ, Bodana S, Brecklin CS, Drawz P, Flack JM, Miller ER 3rd, et al; CRIC Study Investigators. Prevalence and prognostic significance of apparent treatment resistant hypertension in chronic kidney disease: report from the Chronic

Renal Insufficiency Cohort Study. *Hypertension*. 2016;67:387–396. doi: 10.1161/HYPERTENSIONAHA.115.06487
88. Rouabhi M, Durieux J, Al-Kindi S, Cohen JB, Townsend RR, Rahman M. Orthostatic hypertension and hypotension and outcomes in CKD: the CRIC (Chronic Renal Insufficiency Cohort) study. *Kidney Med*. 2021;3:206–215.e1. doi: 10.1016/j.xkme.2020.10.012
89. Rouch L, Cestac P, Sallerin B, Piccoli M, Benattar-Zibi L, Bertin P, Berrut G, Corruble E, Derumeaux G, Falissard B, et al; S.AGES Investigators. Visit-to-visit blood pressure variability is associated with cognitive decline and incident dementia: the S.AGES cohort. *Hypertension*. 2020;76:1280–1288. doi: 10.1161/HYPERTENSIONAHA.119.14553
90. Mahinrad S, Kurian S, Garner CR, Sedaghat S, Nemeth AJ, Moscufo N, Higgins JP, Jacobs DR Jr, Hausdorff JM, Lloyd-Jones DM, et al. Cumulative blood pressure exposure during young adulthood and mobility and cognitive function in midlife. *Circulation*. 2020;141:712–724. doi: 10.1161/CIRCULATIONAHA.119.042502
91. de Heus RAA, Tzourio C, Lee EJL, Opozda M, Vincent AD, Anstey KJ, Hofman A, Kario K, Lattanzi S, Launer LJ, et al; Variable Brain Consortium. Association between blood pressure variability with dementia and cognitive impairment: a systematic review and meta-analysis. *Hypertension*. 2021;78:1478–1489. doi: 10.1161/HYPERTENSIONAHA.121.17797
92. Peters R, Xu Y, Fitzgerald O, Aung HL, Beckett N, Bulpitt C, Chalmers J, Forette F, Gong J, Harris K, et al; Dementia rIsk REduCTion (DIRECT) Collaboration. Blood pressure lowering and prevention of dementia: an individual patient data meta-analysis. *Eur Heart J*. 2022;43:4980–4990. doi: 10.1093/eurheartj/ehac584
93. Schliep KC, McLean H, Yan B, Qeadan F, Theilen LH, de Havenon A, Majersik JJ, Østbye T, Sharma S, Varner MW. Association between hypertensive disorders of pregnancy and dementia: a systematic review and meta-analysis. *Hypertension*. 2023;80:257–267. doi: 10.1161/HYPERTENSIONAHA.122.19399
94. Bohm M, Schumacher H, Teo KK, Lonn EM, Mahfoud F, Emrich I, Mancia G, Redon J, Schmieder RE, Sliwa K, et al. Renal outcomes and blood pressure patterns in diabetic and nondiabetic individuals at high cardiovascular risk. *J Hypertens*. 2021;39:766–774. doi: 10.1097/HJH.0000000000002697
95. Dionne JM, Jiang S, Ng DK, Flynn JT, Mitsnefes MM, Furth SL, Warady BA, Samuels JA; CKiD Study Group. Mean arterial pressure and chronic kidney disease progression in the CKiD cohort. *Hypertension*. 2021;78:65–73. doi: 10.1161/HYPERTENSIONAHA.120.16692
96. Copland E, Canoy D, Nazarzadeh M, Bidel Z, Ramakrishnan R, Woodward M, Chalmers J, Teo KK, Pepine CJ, Davis BR, et al; Blood Pressure Lowering Treatment Trialists' Collaboration. Antihypertensive treatment and risk of cancer: an individual participant data meta-analysis. *Lancet Oncol*. 2021;22:558–570. doi: 10.1016/S1470-2045(21)00033-4
97. Borrelli S, Garofalo C, Gabbai FB, Chiodini P, Signoriello S, Paoletti E, Ravera M, Bussalino E, Bellizzi V, Liberti ME, et al. Dipping status, ambulatory blood pressure control, cardiovascular disease, and kidney disease progression: a multicenter cohort study of CKD. *Am J Kidney Dis*. 2023;81:15–24.e1. doi: 10.1053/j.ajkd.2022.04.010
98. Bourdillon MT, Song RJ, Musa Yola I, Xanthakis V, Vasan RS. Prevalence, predictors, progression, and prognosis of hypertension subtypes in the Framingham Heart Study. *J Am Heart Assoc*. 2022;11:e024202. doi: 10.1161/JAHA.121.024202
99. Clark CE, Warren FC, Boddy K, McDonagh STJ, Moore SF, Teresa Alzamora M, Ramos Blanes R, Chuang SY, Criqui MH, Dahl M, et al. Higher arm versus lower arm systolic blood pressure and cardiovascular outcomes: a meta-analysis of individual participant data from the INTERPRESS-IPD Collaboration. *Hypertension*. 2022;79:2328–2335. doi: 10.1161/HYPERTENSIONAHA.121.18921
100. Delker E, Bandoli G, LaCoursiere Y, Ferran K, Gallo L, Oren E, Gahagan S, Ramos GA, Allison M. Chronic hypertension and risk of preterm delivery: National Longitudinal Study of Adolescents to Adult Health. *Paediatr Perinat Epidemiol*. 2022;36:370–379. doi: 10.1111/ppe.12858
101. Kabia AU, Li P, Jin Z, Tan X, Liu Y, Feng Y, Yu K, Hu M, Jiang D, Cao G. The effects of hypertension on the prognosis of coronavirus disease 2019: a systematic review and meta-analysis on the interactions with age and antihypertensive treatment. *J Hypertens*. 2022;40:2323–2336. doi: 10.1097/HJH.0000000000003266
102. Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project (HCUP). Accessed April 1, 2023. http://hcupnet.ahrq.gov/
103. Centers for Disease Control and Prevention and National Center for Health Statistics. National Ambulatory Medical Care Survey (NAMCS) public use data files. Accessed April 1, 2023. https://cdc.gov/nchs/ahcd/datasets_documentation_related.htm#data
104. Dieleman JL, Cao J, Chapin A, Chen C, Li Z, Liu A, Horst C, Kaldjian A, Matyasz T, Scott KW, et al. US health care spending by payer and health condition, 1996-2016. *JAMA*. 2020;323:863–884. doi: 10.1001/jama.2020.0734
105. Gnugesser E, Chwila C, Brenner S, Deckert A, Dambach P, Steinert JI, Bärnighausen T, Horstick O, Antia K, Louis VR. The economic burden of treating uncomplicated hypertension in sub-Saharan Africa: a systematic literature review. *BMC Public Health*. 2022;22:1507. doi: 10.1186/s12889-022-13877-4
106. GBD Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. 2020;396:1223–1249. doi: 10.1016/S0140-6736(20)30752-2
107. Kaze AD, Schutte AE, Erqou S, Kengne AP, Echouffo-Tcheugui JB. Prevalence of hypertension in older people in Africa: a systematic review and meta-analysis. *J Hypertens*. 2017;35:1345–1352. doi: 10.1097/HJH.0000000000001345
108. Global Burden of Disease Study and Institute for Health Metrics and Evaluation. University of Washington. Accessed August 2, 2023. http://ghdx.healthdata.org/
109. Forouzanfar MH, Liu P, Roth GA, Ng M, Biryukov S, Marczak L, Alexander L, Estep K, Hassen Abate K, Akinyemiju TF, et al. Global burden of hypertension and systolic blood pressure of at least 110 to 115 mm Hg, 1990-2015. *JAMA*. 2017;317:165–182. doi: 10.1001/jama.2016.19043
110. Al Kibria GM, Gupta RD, Nayeem J. Prevalence, awareness, and control of hypertension among Bangladeshi adults: an analysis of demographic and health survey 2017-18. *Clin Hypertens*. 2021;27:17. doi: 10.1186/s40885-021-00174-2
111. Bhagavathula AS, Shah SM, Aburawi EH. Prevalence, awareness, treatment, and control of hypertension in the United Arab Emirates: a systematic review and meta-analysis. *Int J Environ Res Public Health*. 2021;18:12693. doi: 10.3390/ijerph182312693
112. Lee J, Wilkens J, Meijer E, Sekher TV, Bloom DE, Hu P. Hypertension awareness, treatment, and control and their association with healthcare access in the middle-aged and older Indian population: a nationwide cohort study. *PLoS Med*. 2022;19:e1003855. doi: 10.1371/journal.pmed.1003855
113. Meena J, Singh M, Agarwal A, Chauhan A, Jaiswal N. Prevalence of hypertension among children and adolescents in India: a systematic review and meta-analysis. *Indian J Pediatr*. 2021;88:1107–1114. doi: 10.1007/s12098-021-03686-9
114. Ingabire PM, Ojji DB, Rayner B, Ogola E, Damasceno A, Jones E, Dzudie A, Ogah OS, Poulter N, Sani MU, et al; CREOLE Study Investigators. High prevalence of non-dipping patterns among Black Africans with uncontrolled hypertension: a secondary analysis of the CREOLE trial. *BMC Cardiovasc Disord*. 2021;21:254. doi: 10.1186/s12872-021-02074-7
115. Cao J, Eshak ES, Liu K, Arafa A, Sheerah HA, Yu C. Age-period-cohort analysis of stroke mortality attributable to high systolic blood pressure in China and Japan. *Sci Rep*. 2021;11:19083. doi: 10.1038/s41598-021-98072-y
116. Balouchi A, Rafsanjani M, Al-Mutawaa K, Naderifar M, Rafiemanesh H, Ebadi A, Ghezeljeh TN, Shahraki-Mohammadi A, Al-Mawali A. Hypertension and pre-hypertension in Middle East and North Africa (MENA): a meta-analysis of prevalence, awareness, treatment, and control. *Curr Probl Cardiol*. 2022;47:101069. doi: 10.1016/j.cpcardiol.2021.101069
117. Stierman B, Afful J, Carroll M, Chen T, Davy O, Fink S, Fryar C, Gu Q, Hales C, Hughes J, et al. National Health and Nutrition Examination Survey 2017-March 2020 prepandemic data files: development of files and prevalence estmates for selected health outcomes. *Natl Health Stat Rep*. 2021. Accessed October 25, 2023. https://stacks.cdc.gov/view/cdc/106273
118. Muntner P, Carey RM, Gidding S, Jones DW, Taler SJ, Wright JT Jr, Whelton PK. Potential US population impact of the 2017 ACC/AHA high blood pressure guideline. *Circulation*. 2018;137:109–118. doi: 10.1161/CIRCULATIONAHA.117.032582
119. Agency for Healthcare Research and Quality. Medical Expenditure Panel Survey (MEPS): household component summary tables: medical conditions, United States. Accessed April 2, 2023. https://meps.ahrq.gov/mepsweb/

# 9. DIABETES

***ICD-9 250; ICD-10 E10 to E11. See Tables 9-1 and 9-2 and Charts 9-1 through 9-10***

Click here to return to the Table of Contents

Click here to return to the Abbreviations

Diabetes is a heterogeneous condition characterized by glucose dysregulation. In the United States, the most common forms are type 2 diabetes, which affects 90% to 95% of those with diabetes, and type 1 diabetes, which constitutes 5% to 10% of cases of diabetes.[1] For this chapter, diabetes type (ie, type 1 diabetes or type 2 diabetes) is used when reported as such in the original data source; otherwise, the broader term diabetes is used and may include different diabetes types, of which the vast majority will be type 2 diabetes. Diabetes is defined on the basis of FPG ≥126 mg/dL, 2-hour postchallenge glucose ≥200 mg/dL during an oral glucose tolerance test, random glucose ≥200 mg/dL with presentation of hyperglycemia symptoms, or HbA1c ≥6.5%[2] and may be classified as diagnosed by a health care professional or undiagnosed (ie, meeting glucose or HbA1c criterion but without a clinical diagnosis). Prediabetes increases the risk of diabetes and is defined as an FPG of 100 to 125 mg/dL, 2-hour postchallenge glucose of 140 to 199 mg/dL during an oral glucose tolerance test, or HbA1c of 5.7% to 6.4%. Diabetes is a major risk factor for CVD, including CHD, HF, PAD, and stroke.[3] The AHA has identified untreated FPG levels of <100 mg/dL for children and adults as 1 of the 8 components of ideal CVH.[4]

## Prevalence

### Youth

- In 2019, 283 000 children and adolescents <20 years of age, or 35 per 10 000 US youths, had diagnosed diabetes. This includes 244 000 with type 1 diabetes.[1]
- Among US adolescents 12 to 18 years of age in 2005 to 2016, the prevalence of prediabetes was 18.0% (95% CI, 16.0%–20.1%). Adolescent males were more likely to have prediabetes than adolescent females (22.5% [95% CI, 19.8%–25.4%] versus 13.4% [95% CI, 10.8%–16.5%]).[5]
- A mathematical prediction model from the SEARCH for Diabetes in Youth study suggests that the number of youths with diabetes will increase from 213 000 (type 1 diabetes, 185 000; type 2 diabetes, 28 000) in 2017 to 239 000 (type 1 diabetes, 191 000; type 2 diabetes, 48 000) in 2060 if the incidence remains constant as observed in 2017, which corresponds to relative increases of 3% for type 1 diabetes and 69% for type 2 diabetes.[6] But if one bases this estimate on increasing trends in incidence observed between 2002 and 2017, the projected number of youths with diabetes will be 526 000 (type 1 diabetes, 306 000; type 2 diabetes, 220 000), corresponding to relative increases of 65% for type 1 diabetes and 673% for type 2 diabetes.

### Adults

***(See Table 9-1 and Charts 9-1 through 9-3)***

- On the basis of NHANES 2017 to 2020 data,[7] 29.3 million adults (10.6%) had diagnosed diabetes, 9.7 million adults (3.5%) had undiagnosed diabetes, and 115.9 million adults (46.4%) had prediabetes (Table 9-1).
- After adjustment for population age differences, NHANES 2017 to 2020[7] data for people ≥20 years of age indicate that the prevalence of diagnosed diabetes varied by race and sex and was lowest in NH Asian and NH White females and highest in NH Asian and Hispanic males (Table 9-1 and Chart 9-1).
- On the basis of US Indian Health Service data from 2018 to 2019, the age-adjusted prevalence of diagnosed diabetes among American Indian/Alaska Native people was 14.4% for males and 14.7% for females.[1]
- On the basis of NHANES 2017 to 2020 data,[7] the age-adjusted prevalence of diagnosed diabetes in adults ≥20 years of age varied by race and ethnicity and years of education. NH White adults with more than a high school education had the lowest prevalence (7.9%), and Hispanic adults with less than a high school education had the highest prevalence (16.2%; Chart 9-2).
- Geographic variations in diabetes prevalence have been reported in US adults:
  - From state-level data from BRFSS[8] 2021, Puerto Rico (14.4%) and Mississippi (13.7%) had the highest age-adjusted prevalence of diagnosed diabetes, and Colorado (6.5%) had the lowest prevalence (Chart 9-3).

The 2024 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2024. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

## Incidence

### Youth

- During 2014 to 2015, an estimated 18 291 people <20 years of age in the United States were diagnosed with incident type 1 diabetes, and 5758 individuals 10 to 19 years of age were newly diagnosed with type 2 diabetes annually.[1]
- On the basis of SEARCH 2014 to 2015 data, a population-based registry of 69 457 475 youths <20 years of age from Arizona, California, Colorado, New Mexico, Ohio, South Carolina, and Washington, the incidence rate (per 100 000) of type 1 and type 2 diabetes was 22.3 (95% CI, 21.0–23.6) and 13.8 (95% CI, 12.4–15.3), respectively.[9]
  - For type 1 diabetes, the incidence rate (per 100 000) was 6.2 (95% CI, 3.0–12.9) for American Indian youths, 9.4 (95% CI, 6.6–13.3) for Asian or Pacific Islander youths, 20.8 (95% CI, 17.7–24.4) for Black youths, 16.3 (95% CI, 14.1–18.8) for Hispanic youths, and 27.3 (95% CI, 25.5–29.3) for White youths.[9]
  - For type 2 diabetes, the incidence rate (per 100 000) was 32.8 (95% CI, 20.8–51.6) for American Indian youths, 11.9 (95% CI, 7.8–18.3) for Asian or Pacific Islander youths, 37.8 (95% CI, 31.9–44.7) for Black youths, 20.9 (95% CI, 17.4–24.9) for Hispanic youths, and 4.5 (95% CI, 3.5–5.7) for White youths.[9]

### Adults

*(See Table 9-1)*

- Approximately 1.4 million US adults ≥18 years of age were diagnosed with incident diabetes in 2019 (Table 9-1). This included ≈723 000 males and 675 000 females, 71 000 NH Asian individuals, 181 000 NH Black individuals, 261 000 Hispanic individuals, and 860 000 NH White individuals.[1]
- During 2018 to 2019, adults with less than a high school education had a higher age-adjusted incidence rate for diagnosed diabetes (8.2 per 1000 [95% CI, 5.8–11.6]) than adults with more than a high school education (5.2 per 1000 [95% CI, 4.5–6.2]).[1]
- Data from a large UK primary care database of 94 870 South Asian individuals matched with 189 740 White individuals showed that South Asian individuals were at a greater risk of developing type 2 diabetes (aHR, 3.1 [95% CI, 2.97–3.23]), hypertension (1.34 [95% CI, 1.29–1.39]), IHD (1.81, [95% CI, 1.68–1.93]), and HF (1.11 [95% CI, 1.003–1.24]).[10]

## Secular Trends

## (See Charts 9-4 and 9-5)

- Among adults ≥18 years of age, there was a similar age-adjusted incidence of diagnosed diabetes in 2000 (6.2 per 1000 adults) and 2019 (5.7 per 1000 adults), with a decreasing trend noted since 2008 (8.4 per 1000 adults).[1]
- In the SEARCH study, the incidence rate of type 1 diabetes increased by 1.9% annually and the incidence of type 2 diabetes increased by 4.8% annually from 2002 to 2015.[9]
  - The annual increase in diabetes varied by race and ethnicity. For type 1 diabetes, the annual percent increase was 2.7% for Black youths, 4.0% for Hispanic youths, 4.4% for Asian or Pacific Islander youths, and 0.7% for White youths. For type 2 diabetes, the annual percent increase was 6.0% for Black youths, 6.5% for Hispanic youths, 3.7% for American Indian youths, 7.7% for Asian or Pacific Islander youths, and 0.8% for White youths (Chart 9-4).[9]
- The prevalence of diagnosed diabetes in adults was higher for both males and females in the NHANES 2017 to 2020 data than in the NHANES 1988 to 1994 data. Males had a higher prevalence of both types of diagnosed diabetes than females in 2017 to 2020 (Chart 9-5).

## Risk Factors

- In a meta-analysis of 76 513 individuals from 16 studies, progression from prediabetes to diabetes was 23.7 per 1000 person-years for FPG 100 to 125 mg/dL, 43.8 per 1000 person-years for 2-hour postchallenge glucose 140 to 199 mg/dL, and 45.2 per 1000 person-years for HbA1c 5.7% to 6.4%.[11]
- In the WHI, the risk of diabetes in females varied by metabolic status. Compared with females who were metabolically healthy and normal weight, the risk of diabetes was increased among those who were metabolically unhealthy and obese (HR, 4.51 [95% CI, 3.82–5.35]), those who were metabolically unhealthy and normal weight (HR, 2.24 [95% CI, 1.74–2.88]), and those who were metabolically healthy and obese (HR, 1.68 [95% CI, 1.40–2.00]).[12]
- In JHS, the risk of diabetes was increased for adults with obesity who were insulin resistant (IRR, 2.35 [95% CI, 1.53–3.60]), for adults without obesity who were insulin resistant (IRR, 1.59 [95% CI, 1.02–2.46]), and for adults with obesity who were insulin sensitive (IRR, 1.70 [95% CI, 0.97–2.99]) compared with those without obesity who were insulin sensitive.[13]
- In a meta-analysis, each 1-SD higher BMI in childhood was associated with an increased risk for developing diabetes as an adult (pooled OR, 1.23 [95% CI, 1.10–1.37] for children ≤6 years of age, 1.78 [95% CI, 1.51–2.10] for children 7–11 years of age, and 1.70 [95% CI, 1.30–2.22] for those 12–18 years of age).[14]

- Lifestyle factors (higher alcohol consumption, lower PA, higher sedentary time, and unhealthy diet) were independently associated with diabetes risk over a median 3.8 years of follow-up. Adults with the least favorable lifestyle profile had an increased risk for diabetes compared with those with the most favorable lifestyle profile, with excess alcohol intake (RR, 1.12 [95% CI, 1.03–1.22]), physical inactivity (RR, 1.14 [95% CI, 1.07–1.22]), sedentary behavior (RR, 1.10 [95% CI, 1.04–1.16]), and unhealthy diet (RR, 1.26 [95% CI, 1.18–1.35]) contributing to higher risks for diabetes.[15]
- In a meta-analysis of 14 studies, adults with the most favorable combined lifestyle factors had a lower diabetes risk than those with the least favorable combined lifestyle factors (HR, 0.25 [95% CI, 0.18–0.35]).[16]
- In analyses adjusted for PA, total sedentary behavior (RR, 1.01 [95% CI, 1.00–1.01]) and television viewing (RR, 1.09 [95% CI, 1.07–1.12]) were associated with diabetes risk in a systematic review and meta-analysis.[17]
- In a meta-analysis of prospective cohort studies, SSB intake was associated with an increased risk of diabetes (RR per 250 mL/d, 1.19 [95% CI, 1.13–1.25]). ASB intake was also associated with diabetes risk (RR per 250 mL/d, 1.15 [95% CI, 1.05–1.26]).[18]
- In NHANES 2007 to 2014, the prevalence of gestational diabetes was 7.6%, with 19.7% of females with gestational diabetes having a subsequent diagnosis of type 2 diabetes. Age-standardized prevalence of gestational diabetes was highest among Hispanic females (9.3%) and lower among NH White females (7.0%) and NH Black females (6.9%).[19]
- In the NHS II, the risk of diabetes was also increased for females with a history of gestational hypertension (HR, 1.65 [95% CI, 1.42–1.91]) or preeclampsia (HR, 1.75 [95% CI, 1.58–1.93]) during first pregnancy compared with females with normotension.[20]
- Among 1 956 452 individuals with type 2 diabetes in the Korean National Health Insurance Service database, those in the highest quartile of remnant cholesterol level had a 28% significantly higher risk of MI and a 22% significantly higher risk of stroke.[21]
- An analysis of 11 prospective studies of 355 230 individuals recently showed highest dietary cholesterol intake to be associated with a 15% greater risk of developing type 2 diabetes, with relationships strongest in Western countries (United States, France, and Finland) compared with Eastern countries (China, Japan, and Korea).[22] In a meta-analysis of 9 observational studies, the risk of developing gestational diabetes was 49% greater comparing the highest and lowest categories of dietary cholesterol intake, with a 32% increase per 100–mg/d cholesterol intake.[23]
- In a systematic review and meta-analysis of 24 prospective cohort studies, olive oil consumption was associated with a 22% lower risk for developing type 2 diabetes.[24]
- Among 18 908 Japanese participants with prediabetes in an observational cohort study of claims data, nonideal BMI, BP, and TC and the number of nonideal CVH metrics were associated with an increased risk of developing diabetes.[25]
- Among participants in the FHS and HCHS/SOL, the risk of incident diabetes increased by ≈50% for each 10-year increment in age or 5-unit increment in BMI and was 50% to 70% higher in those with hypertension compared with those without hypertension. [26]

## Social Determinants of Health/Health Equity

- In NHIS 2013 to 2017, adults with diabetes who were <65 years of age were more likely to report overall financial hardship from medical bills (41.1%) than adults with diabetes ≥65 years of age (20.7%). Among adults with diabetes <65 years of age, the prevalence of cost-related medication nonadherence was 34.7%, and the prevalence of delayed medical care was 55.5%.[27]
- In NHANES 2011 to 2016, 83.4% of adults with diabetes had an HbA1c test in the past year. Testing rates were higher for individuals with health insurance (86.6%) than for those without health insurance (55.9%).[28]
- According to BRFSS 2013, individuals with private health insurance were more likely than those without health insurance to have had HbA1c testing (OR, 2.60 [95% CI, 2.02–3.35]), a foot examination (OR, 1.72 [95% CI, 1.32–2.25]), or an eye examination (OR, 2.01 [95% CI, 1.56–2.58]) in the past year.[29]
- In the SEARCH study (Washington and South Carolina sites), the prevalence of food insecurity among individuals with type 1 diabetes was 19.5%. Youth and young adults from food-insecure households were more likely to have an HbA1c >9.0% (OR, 2.37 [95% CI, 1.10–5.09]).[30]
- Data from the NHIS 2013 to 2018 for >170 000 adults demonstrate low versus high social cohesion to be associated with a higher adjusted prevalence of type 2 diabetes (PR, 1.17 [95% CI, 1.11–1.22]) after adjustment, with even stronger associations in those 31 to 49 years of age (PR, 1.36 [95% CI, 1.20–1.54]) and in Hispanic/Latino women 18 to 30 years (PR, 3.70 [95% CI, 1.40–9.80]).[31]

- In a case-control study using Geisinger electronic health records (2008–2016), compared with people living in rural affordable residence tracts, higher odds of new-onset type 2 diabetes were found in those categorized as living in extreme poverty (OR, 1.11 [95% CI, 1.02–1.21]) or those categorized as multilingual working (OR, 1.07 [95% CI, 1.03–1.23]).[31]

## Risk Prediction: Risk Scores, Risk-Enhancing Factors, and Coronary Calcium

- Diabetes is associated with great heterogeneity in risk of CVD, and in many individuals with diabetes, their risk is not equivalent to those with preexisting CVD, with only 19% of those with diabetes without CVD recently estimated to be a CVD risk equivalent.[32] This emphasizes the importance of risk stratification in individuals with diabetes. Currently, the US PCE includes a diabetes factor and can be used in individuals with diabetes to predict the 10-year risk of ASCVD (for those 40–79 years of age) and lifetime risk of ASCVD (for those 20–59 years of age).[33] However, this equation does not include diabetes-specific risk enhancers that can be used to inform the treatment decision, including (1) long duration (≥10 years for type 2 diabetes or ≥20 years for type 1 diabetes), (2) albuminuria (≥30 µg albumin/mg creatinine), and (3) eGFR (<60 $mL{\cdot}min^{-1}{\cdot}1.73\ m^{-2}$, retinopathy, neuropathy, and an ABI <0.9 if uncertain).[34] There is currently no available US-based pooled cohort risk score developed specifically in individuals with diabetes.
- In a recent analysis of 27 730 subjects with diabetes from 4 major US cohorts (ARIC, JHS, MESA, FHS Offspring), diabetes was identified as a CVD risk equivalent in only one-fifth of CVD-free adults with diabetes. A high HbA1c, long diabetes duration, and diabetes medication use were predictors of being a CVD risk equivalent. Moreover, diabetes was a CVD risk equivalent for women, White people, those of younger age, people with higher triglycerides or CRP, or people with reduced kidney function.[32]
- CAC is also an effective risk stratifier for individuals with diabetes. In MESA, annual CHD event rates ranged from 0.4%/y in those with CAC scores of 0 to 4%/y for CAC scores of ≥400, and CAC provided significant improvements in the C statistic beyond risk factors.[35] A subsequent report noted that a duration of diabetes of at least 10 years further stratified risk, especially at higher CAC scores.[36] Moreover, incidence and progression of CAC and the relation of progression of CAC with subsequent CHD events also are greater for those with MetS or diabetes compared with individuals without these conditions.[37] More recently, in the Coronary Calcium Consortium, among 4503 adults with diabetes (32.5% women) 21 to 93 years of age, higher levels of CAC were more strongly related to CVD and total mortality in women compared with men.[38] For CVD mortality, HRs for CAC scores of 101 to 400 and >400 were 3.67 and 6.27, respectively, for women and 1.63 and 3.48, respectively, for men ($P_{interaction}$=0.04). For total mortality, HRs were 2.56 (CAC scores 101–400) and 4.05 (CAC scores >400) for women, and 1.88 (CAC scores 101–400) and 2.66 for men (CAC scores >400; $P_{interaction}$=0.01).
- A recent report from the CLARIFY registry of 6462 patients with diabetes showed higher levels of CAC (>400 versus CAC=0) to be associated with greater statin and high-intensity statin initiation and CAC scores of >400 versus lower levels to be associated with reductions in SBP, TC, LDL-C, and triglycerides.[39]
- From a recent systematic review of 15 observational studies reporting 7 risk models with >1 validation cohort, the Risk Equations for Complications of Type 2 Diabetes had the best calibration in primary studies with the greatest discrimination measures for all-cause mortality (C statistics, 0.75 [95% CI, 0.70–0.80]; high certainty), cardiovascular mortality (0.79 [95% CI, 0.75–0.84]; low certainty), ESRD (0.73 [95% CI, 0.52–0.94]; low certainty), MI (0.72 [95% CI, 0.69–0.74]; moderate certainty), and stroke (0.71 [95% CI, 0.68–0.74]; moderate certainty).[40]
- The updated version of the QDiabetes risk prediction algorithm had C statistics between 0.81 and 0.89.[41]
- Risk prediction algorithms for CVD among individuals with diabetes have also been developed.[42–44] A meta-analysis found an overall pooled C statistic of 0.67 for 15 algorithms developed in populations with diabetes and 0.64 for 11 algorithms originally developed in a general population.[43]
- The TIMI risk score for CVD events performed moderately well among adults with type 2 diabetes and high CVD risk. The C statistic was 0.71 (95% CI, 0.69–0.73) for CVD death and 0.66 (95% CI, 0.64–0.67) for a composite end point of CVD death, MI, or stroke.[45]
- A diabetic kidney disease risk prediction model including age, BMI, smoking, diabetic retinopathy, HbA1c, SBP, HDL-C, triglycerides, and ACR performed well in a validation cohort (C statistic, 0.77 [95% CI, 0.71–0.82]).[46]

## Family History and Genetics

- Diabetes is heritable. Twin or family studies have demonstrated a range of heritability estimates from

30% to 70%, depending on age at onset.[47,48] In the FHS, having a parent or sibling with diabetes conferred a 3.4-fold increased risk of diabetes, which increased to 6.1 if both parents were affected.[49] On the basis of data from NHANES 2009 to 2014, individuals with diabetes had an adjusted PR for family history of diabetes of 4.27 (95% CI, 3.57–5.12) compared with individuals without diabetes or prediabetes.[50]

- There are monogenic forms of diabetes such as maturity-onset diabetes of the young (caused by variants in *GCK* [glucokinase] and other genes) and latent autoimmune diabetes in adults. In the TODAY study of overweight and obese children and adolescents with type 2 diabetes, 4.5% of individuals were found to have monogenic diabetes.[51] Genetic testing can be considered if maturity-onset diabetes is suspected and can guide the management and screening of family members.
- Diabetes is most often a complex disease characterized by multiple genetic variants with gene-gene and gene-environment interactions. Genome-wide genetic studies of common diabetes conducted in large sample sizes of adult populations have identified >500 genetic variants associated with diabetes,[52] with ORs in a GWAS of 74 124 cases with type 2 diabetes and 824 006 controls ranging from 1.04 to 8.05.[53]
- A common intronic variant in the *TCF7L2* (transcription factor 7 like 2) gene is the most consistently identified diabetes variant.[54–57] Together, common variants account for 18% of type 2 diabetes risk.[53] Several of these variants have also been associated with gestational diabetes (see Chapter 11 [Adverse Pregnancy Outcomes]).[58]
- Few GWASs have examined type 2 diabetes in youths. Using data from n=3006 youth type 2 diabetes cases and n=6061 controls, the multiethnic ProDiGY Consortium identified 7 genome-wide significant loci, including a novel locus in *PHF2*.[59] *PHF2* may influence adipogenesis and fat storage through CEBPα and peroxisome proliferator–activated receptor γ transcriptional regulation in adipose tissue.[60] The 6 known loci previously identified in adult populations that generalized to youths at genome-wide significant levels were *TCF7L2*, *MC4R*, *CDC123*, *KCNQ1*, *IGF2BP2*, and *SLC16A11*.
- Genetic studies in non-European ancestral populations have also identified significant risk loci for diabetes. For example, the DIAMANTE Consortium of n=180 834 cases and n=1 159 055 controls (48.9% European ancestry) identified 338 independent variants at 237 loci.[61] Population diversity was particularly valuable for fine mapping, in which 54.4% of associations were localized to a single variant with high posterior probability, enabling assessment of causal genes and molecular mechanisms.
- GWASs of quantitative glycemic traits (eg, fasting glucose, fasting insulin, and HbA1c) also have been published. These GWASs have identified >600 loci in genes and pathways related to glucose metabolism, regulation of circadian rhythms, and cell proliferation.[62] These loci include common and low-frequency variants, some of which may be population specific.[63]
- A diabetes GRS composed of >6 million diabetes-associated variants was associated with incident diabetes in >130 000 individuals in the FINRISK study (HR, 1.74 [95% CI, 1.72–1.77]; $P<1\times10^{-300}$), with the GRS showing improved reclassification over a clinical model (net reclassification index, 4.5% [95% CI, 3.0%–6.1%]).[64] However, a GRS composed in European ancestral populations may not transfer to other ancestral populations, potentially requiring population-specific optimization.[65]
- A transancestry diabetes GRS developed in populations of European, African, and East Asian ancestry significant predicted type 2 diabetes in external European, African, and Hispanic populations.[66] However, prediction accuracy remained highest for European populations (AUC, 0.66) and lowest for African populations (AUC, 0.58).
- Several studies have examined whether genetic risk modifies the effect of a poor lifestyle on diabetes incidence. In a study of the UK Biobank, high genetic risk and poor lifestyle together were associated with an HR of 15.5 (95% CI, 10.8-22.1) for diabetes compared with participants with an ideal lifestyle and in the group at low genetic risk.[67] However, no evidence of interaction between genetic risk and lifestyle factors was detected ($P>0.3$). A second study in the UK Biobank assessed the interaction between diet quality and a type 2 diabetes GRS with n=5663 incident type 2 diabetes cases (N=357 419 participants of European ancestry at study baseline). The authors reported an antagonistic interaction in which a simultaneous 1-SD increment in both the diet quality score and GRS was associated with a 3% lower type 2 diabetes risk, indicating that adherence to a healthy diet was associated with a reduced type 2 diabetes risk among individuals with higher genetic risk.[68]
- Genetic variants associated with traits that are risk factors for diabetes have themselves been shown to be associated with diabetes. For example, in a genome-wide study in the UK Biobank, a waist-specific polygenic score was associated with a higher risk of diabetes (OR, 1.57 [95% CI, 1.34–1.83]; absolute risk increase per 1000 participant-years, 4.4 [95% CI, 2.7–6.5]; $P<0.001$).[69] Providing additional evidence are studies examining

coheritability or evidence of a shared genetic architecture between type 2 diabetes and cardiometabolic diseases. For example, a prior study examined coheritability by estimating genetic correlation. The authors reported significant positive genetic correlation between type 2 diabetes and BMI (*rg*=0.36), extreme BMI (*rg*=0.34), overweight (*rg*=0.38), obesity (*rg*=0.34), hip circumference (*rg*=0.27), WC (*rg*=0.40), glycemic traits (*rg*=0.58), triglycerides (*rg*=0.31), and CAD (*rg*=0.38).[70] Conversely, inverse genetic correlations for type 2 diabetes were observed with HDL-C (*rg*=−0.45) and birth weight (−0.37).

- In the ACCORD trial, 2 genetic markers were identified with excess CVD mortality in the intensive treatment arm. A GRS including these genetic markers was found to be associated with the effect of intensive glycemic treatment of cardiovascular outcomes: Those with a GRS of 0 had a substantial reduction in risk in response to intensive treatment (HR, 0.24 [95% CI, 0.07–0.86]); those with a GRS of 1 experienced no difference (HR, 0.92 [95% CI, 0.54–1.56]); and those with a GRS ≥2 experienced a 3-fold increase in risk (HR, 3.08 [95% CI, 1.82–5.21]).[71]
- In a mendelian randomization analysis, prediabetes (determined by SNPs for glycemic traits) was not associated with diabetes (OR, 0.91 [95% CI, 0.73–1.14]).[72]

### *Type 1 Diabetes*

- Type 1 diabetes is also heritable. Early genetic studies identified the role of the *MHC* (major histocompatibility complex) gene in this disease, with the greatest contributor being the human leukocyte antigen region, estimated to contribute to ≈50% of the genetic risk.[73] Other studies have identified additional genes associated with type 1 diabetes risk, including rare variants at *STK39* and *LRP1B*.[74]
- A GRS composed of 9 type 1 diabetes–associated risk variants has been shown to be able to discriminate type 1 diabetes from type 2 diabetes (AUC, 0.87).[75] In a study of 7798 high-risk children, a risk score combining type 1 diabetes genetic variants, autoantibodies, and clinical factors improved the prediction of incident type 1 diabetes (AUC ≥0.9).[76]

### *Genetic Factors and Diabetes Complications*

- The risk of complications from diabetes is also heritable:
  - Diabetic kidney disease shows familial clustering, with diabetic siblings of patients with diabetic kidney disease having a 2-fold increased risk of also developing diabetic kidney disease.[77]
  - Genetic variants have also been identified that increase the risk of CAD or dyslipidemia in patients with diabetes[78,79] and that are associated with end-organ complications in diabetes (retinopathy,[80] nephropathy,[81] and neuropathy[82]).
  - A GRS of type 2 diabetes variants was associated with diabetes-related retinopathy (OR of the highest GRS decile compared with the lowest GRS decile, 1.59 [95% CI, 1.44–1.77]), CKD (OR, 1.16 [95% CI, 1.07–1.26]), PAD (OR, 1.20 [95% CI, 1.11–1.29]), and neuropathy (OR, 1.21 [95% CI, 1.12–1.30]).[52]

### *Role of Nongenetic Factors*

- Metabolomic profiling has identified several strong type 2 diabetes markers that appear to have causal effects on diabetes:
  - Branched chain amino acids are associated with insulin resistance[83] and incident type 2 diabetes risk. For example, a meta-analysis reported that every 1-SD increase in isoleucine, leucine, and valine was associated with type 2 diabetes ORs of 1.54 (95% CI, 1.36–1.74), 1.40 (95% CI, 1.29–1.52), and 1.40 (95% CI, 1.25–1.57), respectively.[84] Branched chain amino acids also respond to weight loss interventions.[85] Circulating glycine levels are associated with lower diabetes risk (meta-analysis RR, 0.89 [95% CI, 0.81–0.96]).[86] Other metabolites associated with type 2 diabetes include complex lipid species such as triacylglycerols[87] and alpha amino-adipic acid.[88]

## Prevention

- Among adults without diabetes in NHANES 2007 to 2012, 37.8% met the moderate-intensity PA goal of ≥150 min/wk, and 58.6% met the weight loss or maintenance goal for diabetes prevention. Adults with prediabetes were less likely to meet the PA and weight goals than adults with normal glucose levels.[89]
- In NHANES 2011 to 2014 data, among adults with prediabetes, 36.6% had hypertension, 51.2% had dyslipidemia, 24.3% smoked, 7.7% had albuminuria, and 4.6% had reduced eGFR.[90]
- In the DPP of adults with prediabetes (defined as 2-hour postchallenge glucose of 140–199 mg/dL), the absolute risk reduction for diabetes was 20% for those adherent to the lifestyle modification intervention and 9% for those adherent to the metformin intervention compared with those receiving placebo over a median 3-year follow-up. Metformin was effective among those with higher predicted risk at baseline, whereas lifestyle intervention was effective regardless of baseline predicted risk.[91]
- Acarbose was associated with a lower diabetes risk (RR, 0.82 [95% CI, 0.71–0.94]) compared with placebo among adults with impaired glucose tolerance and CHD over a median 5 years of follow-up.[92]

## Awareness, Treatment, and Control

Although lifestyle management through diet and exercise is the foundation for treatment of diabetes, metformin has for many years been recommended as first-line pharmacological treatment. However, more recently, SGLT-2 inhibitors and GLP-1Ra have been shown to reduce cardiovascular outcomes[93] and are now currently recommended as first-line therapy in higher-risk individuals with diabetes with preexisting CVD or multiple risk factors. In particular, SGLT-2 inhibitors have a dramatic benefit on reducing the risk of subsequent HF hospitalizations both in those with diabetes and in those with HF, as well as reducing the progression of CKD.[94] Furthermore, aspirin therapy is recommended for those with both diabetes and ASCVD to reduce future ASCVD risk. Control of diabetes in most individuals includes a reduction of HbA1c to <7% (<8% may be appropriate for those with limited life expectancy or when harms outweigh benefits), BP reduction to <130/80 mm Hg, and control of LDL-C with statin therapy. For those at highest risk, high-intensity statin is recommended with additional non-statin therapy if LDL-C remains ≥55 mg/dL in those with ASCVD or LDL-C ≥70 mg/dL among those with additional risk factors after maximally tolerated statin therapy.[94] It has been estimated that aggressive control of lipids, BP, and glucose in individuals with diabetes could prevent up to 51% of CHD events in males and 61% of CHD events in females.[95]

### *Awareness*

- Of 37.1 million adults ≥18 years of age with diabetes in 2019, 8.5 million were not aware of or did not report having diabetes (undiagnosed diabetes), representing 23.0% of all US adults with diabetes.[96]
- A recent NHANES study of trends in awareness of prediabetes shows that the age-adjusted prevalence of prediabetes based on FPG/HbA1c definition increased from 32.1% in 2005 to 2006 to 39.6% in 2007 to 2008 and then plateaued to 38.6% in 2017 to March 2020 without a significant trend for improvement.[97]

### *Treatment*

#### *(See Chart 9-6)*

- Among data from 324 706 patients with diabetes and established ASCVD in the National Patient-Centered Research Network studied during 2018, 58.6% were prescribed a statin, but only 26.8% were prescribed a high-intensity statin.[99] Only 3.9% were prescribed a GLP-1Ra and 2.8% an SGLT-2 inhibitor. Only 4.6% were prescribed all 3 classes of therapies, and 42.6% were prescribed none. Patients who were prescribed a high-intensity statin were more likely to be male or to have ASCVD.
- Among 321 304 patients with type 2 diabetes and ASCVD in 88 US health care systems, from January 2018 to March 2021, the use of SGLT-2 inhibitors increased from 5.8% to 12.9% and the use of GLP1-RAs from 6.9% to 13.8% (and either agent from 11.4% to 23.2%).[100] Those taking either of these agents were younger, less likely to have been hospitalized in the past year, and more likely to be taking other secondary prevention medications.
- In the US Precision Medicine Initiative *All of Us* Research Program including >80 000 patients with diabetes studied during 2018 to 2022, among those with both diabetes and ASCVD, only 8.6% were on an SGLT-2 inhibitor and 11.9% were on a GLP1-RA, with <10% of those with HF or CKD on an SGLT-2 inhibitor.[101] Moreover, only 18.2% were on high-intensity statins, and use of ezetimibe and PCSK9 inhibitors was also low (5.1% and 0.6%, respectively). Among those with triglycerides >150 mg/dL, only 1.9% were taking icosapent ethyl.[102]
- A large meta-analysis of glucose-lowering agents showed GLP1-RAs and SGLT-2 inhibitors to be associated with significant reductions in all-cause mortality (OR, 0.88 [95% CI, 0.83–0.95] and 0.85 [95% CI, 0.79–0.91], respectively) and MACEs (OR, 0.89 [95% CI, 0.84–0.94] and 0.90 [95% CI, 0.84–0.96], respectively), with SGLT-2 inhibitors additionally associated with a reduced risk of HF hospitalizations (OR, 0.68 [95% CI, 0.62–0.85]).[103] Metformin and pioglitazone were also associated with a lower risk of MACEs (OR, 0.60 [95% CI, 0.47–0.80] and 0.85 [95% CI, 0.74–0.97], respectively), but pioglitazone was associated with a higher risk of HF hospitalizations (OR, 1.30 [95% CI, 1.04–1.62]), and insulin secretagogues were associated with higher risks of both all-cause mortality (OR, 1.12 [95% CI, 1.01–1.24]) and MACEs (OR, 1.19 [95% CI, 1.02–1.39]).
- In the long-term 21-year follow-up of the DPP among 3234 participants with impaired glucose tolerance, neither lifestyle intervention nor metformin (versus placebo) was associated with a reduction in the incidence of major cardiovascular events, despite the long-term prevention of diabetes.[104]
- In a recent analysis of 2 large US health insurance databases (Clinformatics and Medicare) examining adult patients with type 2 diabetes who initiated diabetes treatment from 2013 through 2019, metformin was the most frequently initiated medication, used by 80.6% of Medicare beneficiaries and 83.1% of commercially insured patients, followed by sulfonylureas at 8.7% and 4.7%, respectively.[105] However, use of newer cardioprotective diabetes agents was low: SGLT-2 inhibitor in 0.8% (Medicare) and 1.7% (commercial) and GLP-1Ra in 1.0% (Medicare) and 3.5% (commercial), although with trends of greater

use over time ($P<0.01$). Those using an SGLT-2 inhibitor and GLP-1Ra were more likely to be younger or to have prevalent CVD and higher SES compared with those initiating metformin.

- From an analysis of NHANES 2017 to 2018 data, among individuals with type 2 diabetes representing 33.2 million adults nationally, 52.6% had an indication for SGLT-2 inhibitors, 32.8% for GLP-1RAs, and 26.6% for both medications.[106] However, only 4.5% were treated with SGLT-2 inhibitors and 1.5% with GLP-1RAs. ASCVD, HF, or CKD was associated with their use.
- Among 1 202 596 adults with type 2 diabetes in a large US administrative claims database of whom 45.2% had established ASCVD, the use of GLP-1RAs and SGLT-2 inhibitors was low overall (<12%) and even lower in the ASCVD group (<9%), and use of either was ≤5% in the subgroup ≥65 years of age, regardless of ASCVD status.[107]
- In a secondary analysis examining the association of race and ethnicity with the initiation of newer diabetes medications (GLP-1RAs, dipeptidyl peptidase-4 inhibitors, SGLT-2 inhibitors) in the Look AHEAD trial, initiation was lower among Black (HR, 0.81 [95% CI, 0.70–0.94]) and American Indian/Alaska Native (HR, 0.51 [95% CI, 0.26–0.99]) participants, and yearly family income was inversely associated with initiation of newer diabetes medications (HR, 0.78 [95% CI, 0.62–0.98]) when the lowest and highest income groups were compared, findings that were influenced mostly by GLP-1RAs.[108]
- According to NHANES 2017 to 2020 data for adults with diabetes, 20.7% had their diabetes treated and controlled with a fasting glucose <126 mg/dL; however, 48% still had uncontrolled diabetes despite being treated, and 22% were not treated and not diagnosed (unpublished NHLBI tabulation; Chart 9-6).
- In NHANES, the percentage of adults 40 to 75 years of age with diabetes who were taking a statin was 48.5% in 2011 through 2014 and 53% in 2015 through 2018 ($P=0.133$).[109]
- In NHANES 2011 to 2016, 50.4% of adults with diabetes who were taking antihypertensive medications did not meet BP treatment goals according to both the 2017 Hypertension Clinical Practice Guidelines and the American Diabetes Association standards of medical care.[110]
- Continuous glucose monitoring allows more granular monitoring of glucose levels compared with a single glucose measurement.[110a] In a meta-analysis of 22 studies of 2188 people with type 1 diabetes, continuous glucose monitoring was associated with a 2.46–mmol/mol mean decrease in HbA1c levels compared with single glucose monitoring (–0.23%).[110a]

### Control

- In a pooled analysis of ARIC, MESA, and JHS, 41.8%, 32.1%, and 41.9% of participants were at target levels for BP, LDL-C, and HbA1c, respectively; 41.1%, 26.5%, and 7.2% were at target levels for any 1, 2, or all 3 factors, respectively. Having 1, 2, and 3 factors at goal was associated with 36%, 52%, and 62%, respectively, lower risk of CVD events compared with having no risk factors at goal.[111] This study showed multivariable-adjusted risk reductions of 62% for CVD events and 60% for CHD events.
- Recent data from the *All of Us* Research Program (2018–2022) show that 73% of US adults with diabetes have an HbA1c <7%, with control slightly better in women (73.6%) than in men (69.8%) and in NH White individuals (78.3) and Asian individuals (76.3%) compared with NH Black (65.1%) or Hispanic/Latino (60.8%) individuals.[101] Overall, 50.6% of the participants had LDL-C levels <100 mg/dL, although only 16.0% had levels <70 mg/dL, and among those with diabetes and ASCVD, only 21.1% had LDL-C <70 mg/dL. Overall, 64.4% had triglyceride levels <150 mg/dL, and 31.6% had levels <100 mg/dL.[102]
- Data from the US Diabetes Collaborative Registry of 74 393 adults with diabetes show 74% at HbA1c <7%, 40% at BP <130/80 mm Hg, and 49% at LDL-C <100 mg/dL (<70 mg/dL if with ASCVD) but only 15% at target for all 3 factors.[112]
- In a study of 1179 adults with type 2 diabetes (representing 19.7 million in the US population in 2013–2016) with diabetes, 56% of adults were at target control of HbA1c (<7% or <8% if with CVD), 51% for BP (<130/80 mm Hg), and 49% for LDL-C (<100 mg/dL or <70 mg/dL if with CVD); 84% were nonsmokers.[113] Only 9% had BMI <25 kg/m$^2$. Only 17% were at all targets for HbA1c, BP, and LDL-C.
- According to data from NHANES 1988 through 2018, among adults with newly diagnosed type 2 diabetes, there were a significant increase in the proportion of individuals with HbA1c <7% (59.8% for 1998–1994 versus 73.7% for 2009–2018) and decreases in mean HbA1c (7.0% versus 6.7%), mean BP (130.1/77.5 versus 126.0/72.1 mm Hg), and mean TC (219.4 and 182.4 mg/dL). The proportion with HbA1c <7.0%, BP <140/90 mmHg, and TC <240 mg/dL improved from 31.6% to 56.2%.[114]
- Among HCHS/SOL study participants with diabetes in 2008 to 2011, 43.0% had HbA1c <7.0%, 48.7% had BP <130/80 mmHg, and 36.6% had LDL-C <100 mg/dL; 8.4% had reached all 3 treatment targets.[115]
- In a national cohort of 1 140 634 veterans with diabetes, in adjusted models, higher levels of HbA1c

(≥8% versus <7%) were more likely in NH Black and Hispanic than in White people (OR, 1.11 [95% CI, 1.09–1.14] for NH Black and 1.36 [95% CI, 1.32–1.41] for Hispanic people).[116]
- In MEPS, US adults with diabetes who received appropriate diabetes care (HbA1c measurement, foot examination, and an eye examination) varied from 70% (95% CI, 68%–71%) in 2002 to 67% (95% CI, 66%–69%) in 2007 and 68% (95% CI, 66%–70%) in 2013.[117]
- Among those with type 1 diabetes in the SEARCH study, 60% reported having ≥3 HbA1c measurements in the past year. Other screening tests reported were as follows: 93% for BP, 81% for eye examination, 71% for lipid levels, 64% for foot examination, and 63% for albuminuria screening.[118]
- In a decision analytical model, the BRAVO diabetes microsimulation model applied to adults with type 2 diabetes from NHANES (2015–2016) with linked short-term mortality data showed that improvements in BMI, SBP, LDL-C, and HbA1c were estimated to be associated with up to 3.9, 1.9, 0.9, and 3.8 years of gain in life expectancy, respectively.[119]

## Mortality

## (See Table 9-1)

- Diabetes was listed as the underlying cause of mortality for 103 294 people (58 628 males and 44 666 females) in the United States in 2021 (Table 9-1).[120]
- The 2021 overall age-adjusted death rate attributable to diabetes was 25.4 per 100 000. For males, the age-adjusted death rates per 100 000 population were 28.6 for NH White people, 55.9 for NH Black people, 35.8 for Hispanic people, 22.4 for NH Asian people, 62.8 for NH Native Hawaiian or other Pacific Islander people, and 57.9 for NH American Indian/Alaska Native people. For females, the age-adjusted death rates per 100 000 population were 17.0 for NH White people, 38.9 for NH Black people, 24.0 for Hispanic people, 14.7 for NH Asian people, 46.8 for Native Hawaiian or other Pacific Islander people, and 44.4 for NH American Indian/Alaska Native people (unpublished NHLBI tabulation using CDC WONDER[121]). In 2021, diabetes was the eighth leading cause of death in the United States.[122]
- In the NHIS from 1985 to 2014, there was a decrease in major CVD deaths, with 25% greater 10-year percentage reduction among adults with diabetes than among adults without diabetes.[123]
- In the NHIS from 1985 to 1994 and 2010 to 2015, among adults with diabetes, there was a decline in all-cause mortality from 23.1 (95% CI, 20.1–26.0) to 15.2 (95% CI, 14.6–15.8) per 1000 person-years. This represents a 20% decline every 10 years. Over this same time period, death attributable to vascular causes decreased from 11.0 (95% CI, 9.2–12.2) to 5.2 (95% CI, 4.8–5.6) per 1000 person-years, a 32% decline every 10 years.[124]
- In NIS 2017, the mortality rate for diabetic ketoacidosis was higher among males (40.5 per 10 000 admissions) compared with females (35.3 per 10 000 admissions) and higher for NH Black people (39.1 per 10 000 admissions) compared with NH White people (36.2 per 10 000 admissions) and Hispanic people (36.3 per 10 000 admissions).[125]
- From a systematic review and meta-analysis including 20 studies among individuals after MI, in adjusted analyses, diabetes was associated with increased short-term (males: RR, 1.16 [95% CI, 1.12–1.20]; females: RR, 1.29 [95% CI, 1.15–1.46]), mid-term (males: RR, 1.39 [95% CI, 1.31–1.46]; females: RR, 1.38 [95% CI, 1.20–1.58]), and long-term (males: RR, 1.58 [95% CI, 1.22–2.05]; females: RR, 1.76 [95% CI, 1.25–2.47]) mortality.[126]

## Complications

### *Peripheral Artery Disease*

### *(See Chart 9-7)*

- In a cohort study of patients in Denmark undergoing coronary angiography, those with diabetes but not CAD had an increased risk of PAD (HR, 1.73 [95% CI, 1.51–1.97]) and lower-limb revascularization (HR, 1.73 [95% CI, 1.51–1.97]) compared with those with neither diabetes nor CAD.[127] Patients with both diabetes and CAD also had an increased risk of PAD (HR, 3.90 [95% CI, 3.55–4.28]) and lower-limb revascularization (HR, 4.61 [95% CI, 3.85–5.52]).[127]
- In the Freemantle Diabetes Study of adults with type 2 diabetes, the rate of incident hospitalization for diabetic foot ulcers increased between the 2 study phases (1993–1996 and 2008–2011) from 1.9 (95% CI, 0.9–3.3) per 1000 person-years to 4.5 (95% CI, 3.0–6.4) per 1000 person-years.[128]
- On the basis of analyses of data from the NIS and NHIS between 2000 and 2016 (Chart 9-7), declines in hospitalization for lower-extremity amputations were observed between 2000 and 2010, with subsequent increases from 2010 to 2016.[129]
- In the Swedish National Diabetes Register using data from 1998 to 2013, type 1 diabetes was associated with an HR for amputation of 40.1 (95% CI, 32.8–49.1) compared with no diabetes. The incidence has been decreasing and was 3.09 per 1000 person-years in 1998 to 2001 compared with 2.64 per 1000 person-years in 2011 to 2013.[130]

- According to data from Medicare fee-for-service claims from 2000 to 2017, among beneficiaries with diabetes, the rate of nontraumatic lower-extremity amputation decreased from 8.5 in 2000 to 4.4 in 2009 but then increased to 4.8 in 2017.[131]
- From data from NIS and NHIS 2000 through 2015, the age-adjusted rate of nontraumatic lower-extremity amputation among individuals with diabetes decreased from 5.38 (95% CI, 4.93–5.84) per 1000 adults with diabetes in 2000 to 3.07 (95% CI, 2.79–3.34) per 1000 adults in 2009 and then increased to 4.62 (95% CI, 4.25–5.00) per 1000 adults in 2015. The increase was greatest among individuals 18 to 44 and 45 to 64 years of age.[132]
- Reasons for stagnation or even slight increases in recent years in lower-extremity amputation rates could be explained by more comorbidities in patients with diabetes in recent years; shortcomings in prevention practices; reduced mortality resulting in longer duration of diabetes, affecting the risk of complications; and increasing costs of insulin and other therapies, which may result in patients cutting back on some therapies, leading them to greater risks of complications.[129]

### *Retinopathy*

- Among those ≤21 years of age with newly diagnosed diabetes in a US managed care network, 20.1% of youths with type 1 diabetes and 7.2% of youths with type 2 diabetes developed diabetic retinopathy over a median follow-up of 3 years.[133]
- In DCCT/EDIC, over >30 years of follow-up, the rates of ocular events per 1000 person-years were 12 for proliferative diabetic retinopathy, 14.5 for clinically significant macular edema, and 7.6 for ocular surgeries.[134]
- Among adults ≥18 years of age with diagnosed diabetes in 2019, the prevalence of a severe vision disability or blindness was 11.8% (95% CI, 11.1%–12.4%).[1]
- Among American Indian and Alaska Native individuals with diabetes using primary care clinics of the US Indian Health Service, tribal, and urban Indian health care facilities, 17.7% had nonproliferative diabetic retinopathy, 2.3% had proliferative diabetic retinopathy, and 2.3% had diabetic macular edema.[135]
- According to NHIS 2016 and 2017, among individuals with young-onset diabetes (diagnosed <40 years of age), individuals with type 1 diabetes had a higher prevalence of retinopathy (24.7% [95% CI, 17.1%–32.2%]) compared with those with type 2 diabetes (11.4% [95% CI, 8.9%–13.9%]) but similar rates of kidney disease, CHD, MI, and stroke.[136]
- Among patients with type 1 diabetes diagnosed before 35 years of age, after 32 years since diagnosis, the prevalence of proliferative diabetic retinopathy and macroalbuminuria increased with increasing HbA1c levels, being highest (74% and 44%, respectively) in those who had HbA1c >9.5%.[137]

### *Chronic Kidney Disease*

- Among adults ≥18 years of age (37.4% were ≥65 years of age) with type 2 diabetes in NHANES 2007 to 2014, the prevalence of stage 3a CKD (mildly to moderately decreased kidney function) was 10.4% (95% CI, 9.1%–11.7%), stage 3b CKD (moderately to severely decreased) was 5.4% (95% CI, 4.5%–6.4%), stage 4 CKD (severely decreased) was 1.8% (95% CI, 1.3%–2.4%), and stage 5 CKD (kidney failure) was 0.4% (95% CI, 0.2%–0.7%).[138]
- According to data from NHANES 1988 through 2014, the prevalence of any diabetic kidney disease, defined as persistent albuminuria, persistent reduced eGFR, or both, did not change significantly from 1988 to 1994 (28.4% [95% CI, 23.8%–32.9%]) to 2009 to 2014 (26.2% [95% CI, 22.6%–29.9%]). Comparing the 2 times periods shows that the prevalence of albuminuria decreased from 20.8% (95% CI, 16.3%–25.3%) to 15.9% (95% CI, 12.7%–19.0%), whereas the prevalence of reduced eGFR increased from 9.2% (95% CI, 6.2%–12.2%) to 14.1% (95% CI, 11.3%–17.0%).[139]
- According to data from NHANES 1988 through 2018, among adults with newly diagnosed diabetes, there was a significant decrease in the prevalence of any CKD (40.4% for 1988–1994 and 25.5% for 2009–2018). This was driven by a decrease in albuminuria (38.9% to 18.7%). There was no significant change in the prevalence of reduced eGFR (7.5%–9.9%).[114]
- According to data from 142 countries representing 97.3% of the world population, the global annual incidence of ESRD increased from 375.8 to 1016.0 per million with diabetes from 2000 to 2015. The percentage of individuals with ESRD with diabetes increased from 19.0% to 29.7% over this same period.[140]
- Among 4217 patients with type 1 diabetes from the FinnDiane Study, eGFR categories grade 3, 4, and 5 were associated with 3-, 27-, 3.62-, and 4.03-fold greater risks for cardiovascular and diabetes-related mortality.[141]
- In a systematic review of 15 studies globally (most in North America and Europe) examining CKD outcomes in individuals diagnosed with type 2 diabetes before 20 years of age, incidence rates per 1000 person years varied from 12.4 to 114.8 for albuminuria, 10 to 35.0 for macroalbuminuria, 0.4 to 25.0 for end-stage kidney disease, and 1.0 to 18.6 for total mortality, being greatest in Australian Aboriginal and Pima Indian populations.[142]

### Neuropathy

- In the T1D Exchange Clinic Registry, from 2016 to 2018, the prevalence of self-reported diabetic peripheral neuropathy was 11%.[143]

### CVD Complications

#### (Chart 9-7)

- From the UK Clinical Practice Research Datalink for 734 543 adults with and without type 2 diabetes diagnosed in 2000 to 2006 with follow-up for first CVD events over 11 years, type 2 diabetes was associated with a small increase in CVD events (aHR, 1.06 [95% CI, 1.02–1.09]) in White individuals, but a greater increase was seen in individuals of South Asian ethnicity (1.28 [95% CI, 1.09–1.51]), attributable primarily to an increased risk of MI (1.53 [95% CI, 1.08–2.18]).[144]
- Data from a large clinical trial of youths with early-onset type 2 diabetes followed up for >13 years since diagnosis of diabetes showed a cumulative incidence of 67.5% for hypertension, 51.6% for dyslipidemia, 54.8% for diabetic kidney disease, and 32.4% for nerve disease.[145] At least 1 complication occurred in 60.1% of the participants, and at least 2 complications occurred in 28.4%. Risk factors for the development of complications included underrepresented racial or ethnic group, hyperglycemia, hypertension, and dyslipidemia.
- Data among 1.9 million individuals with diabetes from the CALIBER UK cohort show the most common initial CVD complications for those with diabetes to be PAD (16.2%) and HF (14.1%), followed by stable angina (11.9%), nonfatal MI (11.5%), and stroke (10.3%).[146]
- In the Look AHEAD study of 4095 participants with type 2 diabetes, microvascular disease in adults free of HF was associated with a 2.5-fold higher risk of incident HF than no microvascular disease (HR, 2.54 [95% CI, 1.73–3.75]).[147] The HRs for HF by type of microvascular disease were 2.22 (95% CI, 1.51–3.27), 1.30 (95% CI, 0.72–2.36), and 1.33 (95% CI, 0.86–2.07) for nephropathy, retinopathy, and neuropathy, respectively.
- A systematic review and meta-analysis of 26 observational studies among 1 325 493 individuals across 30 countries showed age at diabetes diagnosis to be inversely associated with all-cause mortality and macrovascular and microvascular disease risk (all $P<0.001$).[148] Each 1-year increase in age at diabetes diagnosis was associated with a 4%, 3%, and 5% decreased risk of all-cause mortality, macrovascular disease, and microvascular disease, respectively, adjusted for age.
- A systematic review and meta-analysis of 5 eligible prospective studies of 22 591 participants with an average follow-up of 9.8 years showed reduced cardiovascular outcomes from replacement analyses of saturated fat with polyunsaturated fat (RR for 2% energy replacement, 0.87 [95% CI, 0.77–0.99]) or carbohydrate (RR for 5% energy replacement, 0.82 [95% CI, 0.67–1.00]).[149]
- Among male NHIS participants enrolled in 2000 to 2009 and followed up through 2011, diabetes was associated with increased risk for HD mortality (HR, 1.72 [95% CI, 1.53–1.93]), cerebrovascular mortality (HR, 1.48 [95% CI, 1.18–1.85]), and CVD mortality (HR, 1.67 [95% CI, 1.51–1.86]). Among female participants, diabetes was also associated with increased risk for HD mortality (HR, 2.02 [95% CI, 1.81–2.25]), cerebrovascular mortality (HR, 1.43 [95% CI, 1.15–1.77]), and CVD mortality (HR, 1.85 [95% CI, 1.69–1.96]).[150]
- In the TECOS trial of adults with type 2 diabetes and ASCVD, females with diabetes had a lower risk of MI (HR, 0.70 [95% CI, 0.55–0.90]) and stroke (HR, 0.52 [95% CI, 0.38–0.71]) than males with diabetes.[151]
- In the UK Biobank, the association between previously diagnosed diabetes and MI was stronger in females (HR, 2.33 [95% CI, 1.96–2.78]) than in males (HR, 1.81 [95% CI, 1.63–2.02]).[152]
- Based on analyses of data from the NIS and NHIS between 2000 and 2016 (Chart 9-7), substantial declines were observed in the age-standardized rates of hospitalizations for IHD and HF among those with diagnosed diabetes. Declines in hospitalization for stroke were observed between 2000 and 2010, with subsequent increases from 2010 to 2016.[129]
- In the REGARDS study, the HRs of CHD events comparing participants with diabetes only, diabetes and prevalent CHD, and neither diabetes nor prevalent CHD with those with prevalent CHD were 0.65 (95% CI, 0.54–0.77), 1.54 (95% CI, 1.30–1.83), and 0.41 (95% CI, 0.35–0.47), respectively, after adjustment for demographics and risk factors.[153] Compared with participants who had prevalent CHD, the HR of CHD events for participants with severe diabetes (defined as insulin use or presence of albuminuria) was 0.88 (95% CI, 0.72–1.09).
- In data from the Cardiovascular Disease Lifetime Risk Pooling Project, the 30-year risk of CVD was positively associated with fasting glucose at midlife, even within the range of nondiabetic values.[154]
  - Among females, the absolute risk of CVD was 15.3% (95% CI, 12.3%–18.3%) for fasting glucose <5.0 mmol/L and 18.6% (95% CI, 13.1%–24.1%) for fasting glucose 6.3 to 6.9 mmol/L.
  - Among males, the absolute risk of CVD was 23.5% (95% CI, 19.7%–27.3%) for fasting glucose <5.0 mmol/L and 31.0% (95% CI, 25.6%–36.3%) for fasting glucose 6.3 to 6.9 mmol/L.
- In the Freemantle Diabetes Study of adults with type 2 diabetes, the rate of first hospitalizations for MI, stroke, and HF improved between the 2 study

phases (1993–1996 and 2008–2011), with IRRs of 0.61 (95% CI, 0.47–0.78), 0.55 (95% CI, 0.35–0.85), and 0.62 (95% CI, 0.50–0.77), respectively.[155]
- In MESA, 63% of participants with diabetes had a CAC score >0 compared with 48% of those without diabetes.[156] A longer duration of diabetes was associated with CAC presence (per 5-year-longer duration: HR, 1.15 [95% CI, 1.06–1.25]) and worse cardiac function, including early diastolic relaxation and higher diastolic filling pressure, in the CARDIA study.[157]
- In the Swedish National Diabetes Register from 2001 to 2013, the IRR for AF compared with diabetes and matched control subjects was 1.35 (95% CI, 1.33–1.36).[158]
- From a 29-year follow-up of patients with type 1 diabetes among the combined DCCT and EDIC studies at 27 clinical centers in the United States and Canada, although females achieved BP <130/80 mm Hg (90% versus 77%; $P<0.001$) and triglycerides <150 mg/dL (97% versus 91%; $P<0.001$) targets more often than males, their use of cardioprotective medications (ACE inhibitors/ARBs [30% versus 40%; $P=0.001$] and lipid-lowering medication [25% versus 40%; $P<0.001$]) was less, and they did not have a lower burden of cardiovascular events.[159]

### *Hypoglycemia*

- In the Veterans Affairs Diabetes Trial, severe hypoglycemia within the prior 3 months was associated with an increased risk of a CVD event (HR, 1.9 [95% CI, 1.06–3.52]), CVD mortality (HR, 3.7 [95% CI, 1.3–10.4]), and all-cause mortality (HR, 2.4 [95% CI, 1.1–5.1]).[160]
- In the LEADER trial, patients with type 2 diabetes who experienced a severe hypoglycemic event had an increased risk of MACEs, defined as cardiovascular death, nonfatal MI, or nonfatal stroke (HR, 2.2 [95% CI, 1.6–3.0]), and CVD death (HR, 3.7 [95% CI, 2.6–5.4]).[161] Similarly, in the EXAMINE trial, severe hypoglycemia was associated with an increased risk of MACEs (HR, 2.42 [95% CI, 1.27–4.60]).[162]
- In ARIC data from 1996 through 2013, severe hypoglycemia was associated with an increased risk of CHD (HR, 2.02 [95% CI, 1.27–3.20]), all-cause mortality (HR, 1.73 [95% CI, 1.38–2.17]), cardiovascular mortality (HR, 1.64 [95% CI, 1.15–2.34]), and cancer mortality (HR, 2.49 [95% CI, 1.46–4.24]).[163] In a similar ARIC analysis using individuals with diabetes who attended the 2011 to 2013 visit and had follow-up data through 2018, severe hypoglycemia was associated with incident or recurrent CVD (IRR, 2.19 [95% CI, 1.24–3.88]).[164]
- In a cohort of adults with diabetes receiving care at a large integrated health care system, severe hypoglycemia was associated with ASCVD events, with an unadjusted HR of 3.2 (95% CI, 2.9–3.6) and an aHR of 1.3 (95% CI, 1.2–1.5).[165]
- With the use of data from the Optum Labs Data Warehouse, 6419 index hospitalizations for hypoglycemia were identified among individuals with diabetes from 2009 to 2014. The 30-day readmission rate was 10%, with most of these readmissions being for other primary causes and only 12% for recurrent hypoglycemia.[166]
- Among patients in the ACCORD study, severe hypoglycemia was noted in 4% (n=365) of the 9208 participants; severe hypoglycemia requiring medical assistance was associated with a 38% higher risk of incident HF.[167]

## Coronavirus Disease 2019

Individuals with diabetes are at increased risk of severe disease, hospitalization, and death resulting from COVID-19.

- Studies from Northern California and New York reported a prevalence of diabetes among individuals hospitalized with COVID-19 of 31% to 36%.[168–171]
- From an internet survey that included 760 adults with diabetes during February to March 2021, younger adults (18–29 years of age) with diabetes were more likely to report having missed medical care during the past 3 months (87%) than were those 30 to 59 years of age (63%) or ≥60 years of age (26%), with 44% of younger adults reporting difficulty accessing diabetes medications and a lower intention to receive COVID-19 vaccination (66%) compared with adults ≥60 years of age (85%; $P<0.001$).[172]
- In a meta-analysis of 158 observational studies of 270 212 of participants, patients with diabetes had a higher risk of COVID-19–related mortality (OR, 1.87 [95% CI, 1.61–2.17]), ventilator use (OR, 1.44 [95% CI, 1.20–1.73]), and severe or critical presentation (OR, 2.88 [95% CI, 2.29–3.63]).[173] Patients with diabetes had increased odds of ICU admissions (OR, 1.59 [95% CI, 1.15–2.18]); however, this was driven by studies from East Asia (OR, 1.94 [95% CI, 1.51–2.49]).
- According to data from the Vanderbilt University Medical Center data warehouse of 6451 individuals with COVID-19, compared with individuals without diabetes, individuals with diabetes had a higher rate of hospitalization (OR, 3.90 [95% CI, 1.75–8.69] for type 1 diabetes and 3.36 [95% CI, 2.49–4.55] for type 2 diabetes) and greater illness severity (OR, 3.35 [95% CI, 1.53–7.33] for type 1 diabetes and 3.42 [95% CI, 2.55–4.58] for type 2 diabetes).[174]
- Among 450 patients with COVID-19 at Massachusetts General Hospital, 178 (39.6%) had diabetes. In adjusted models, diabetes was associated with greater odds of ICU admission (OR, 1.59 [95% CI, 1.01–2.52]), mechanical ventilation (OR, 1.97 [95% CI, 1.21–3.20]), and death (OR, 2.02 [95% CI, 1.01–4.03]) within 14 days of presentation to care.[175]

- In a nationwide retrospective study in England, the adjusted ORs for in-hospital COVID-19–related death were 2.86 (95% CI, 2.58–3.18) for individuals with type 1 diabetes and 1.80 (95% CI, 1.76–1.86) for individuals with type 2 diabetes.[176] Among individuals hospitalized with COVID-19, patients with type 2 diabetes were at increased risk of death (HR, 1.23 [95% CI, 1.14–1.32]).[177]

## Health Care Use

## (See Table 9-1)

- According to the 2016 US Nationwide Emergency Department Sample, the rate of ED visits was 69.1 per 1000 people with diabetes for diabetes as any listed diagnosis (16.0 million visits), 10.2 per 1000 people with diabetes for hypoglycemia (235 000 visits), and 9.7 per 1000 people with diabetes for hyperglycemia (224 000 visits).[1]
- According to the US Nationwide Emergency Department Sample and NIS 2014, there were 185 255 ED visits or inpatient admissions among adults for diabetic ketoacidosis and 27 532 for hyperglycemic hyperosmolar state. Most encounters for diabetic ketoacidosis were for individuals with type 1 diabetes (70.6%), and most encounters for hyperglycemic hyperosmolar state were for individuals with type 2 diabetes (88.1%). Rates of diabetic ketoacidosis and hyperglycemic hyperosmolar state increased from 2009 to 2015 in all age groups and among both males and females.[178]
- In 2020, there were 659 135 principal diagnosis discharges for diabetes (HCUP,[179] unpublished NHLBI tabulation; Table 9-1).
- According to the 2016 NHIS, the rate of hospitalization among adults with diabetes was 339.0 per 1000 people with diabetes for any cause (7.8 million discharges), 75.3 per 1000 people with diabetes for major CVD (1.7 million discharges), 5.6 per 1000 people with diabetes for lower-extremity amputation (130 000 discharges), 9.1 per 1000 people with diabetes for hyperglycemic crisis (209 000 discharges), and 2.5 per 1000 people with diabetes for hypoglycemia (57 000 discharges).[1]
- Among Medicare beneficiaries with type 2 diabetes enrolled in Medicare Advantage prescription drug plans hospitalized between 2012 and 2014, there was a 17.1% 30-day readmission rate.[180] According to data from the Optum Labs Data Warehouse, adults with diabetes hospitalized between 2009 and 2014 had a 10.8% 30-day readmission rate.[181] Thirty-day readmission rates were 10.2% among White people, 12.2% among NH Black people, 10.9% among Hispanic people, and 9.9% among Asian people.[182]

## Cost

- According to data from MEPS, spending in the United States on glucose-lowering medications increased by $40.6 billion between 2005 through 2007 and 2015 through 2017, an increase of 240%.[183] From 2007 to 2018, list prices of branded insulins increased by 262% and of branded noninsulin antidiabetic agents by 165%.[184] In the Optum Labs Data Warehouse data from 2016 to 2019, there were higher rates of initiation of newer diabetes agents among individuals with commercial health plans compared with Medicare Advantage plans.[185]
- In 2016, of 154 health conditions evaluated, diabetes had the third highest health care spending ($111.2 billion), the highest public insurance spending ($55.4 billion), the fifth highest private insurance spending ($49.1 billion), and the eighth highest out-of-pocket payments ($6.7 billion).[186]
- In 2017, the cost of diabetes was estimated at $327 billion, up 26% from 2012, accounting for 1 in 4 health care dollars.[187] Of these costs, $237 billion was direct medical costs and $90 billion resulted from reduced productivity. Medical costs for patients with diabetes were 2.3 times higher than for people without diabetes, with an average per capita medical expenditure of $16 752/y for people with diabetes, of which $9601 was attributed to diabetes.[187]
- Informal care is estimated to cost $1192 to $1321 annually per person with diabetes.[188]
- According to 2001 to 2013 MarketScan data, the per capita total excess medical expenditure for individuals with diabetes in the first 10 years after diagnosis is $50 445.[189]
- In 2014, the cost for diabetes-related preventable hospitalizations was $5.9 billion. Between 2001 and 2014, this cost increased annually by 1.6%, of which 25% was attributable to an increase in the cost per hospitalization and 75% was attributable to an increase in the number of hospitalizations.[190] The diabetes-related preventable hospitalization rate has decreased slightly[190] or stayed stable.[191]
- A systematic review estimated that CVD costs account for 20% to 49% of the total direct costs of diabetes care.[192]

## Global Burden of Diabetes

## (See Table 9-2 and Charts 9-8 through 9-10)

- Based on 204 countries and territories in 2021, high FPG caused an estimated 5.40 (95% UI, 4.62-6.15) million deaths, a change of 150.10% (95% UI, 139.15%–161.16%) since 1990.[193] The number of prevalent cases of diabetes increased by 285.77% (95% UI, 276.36%–293.89%) for males and 269.67% (95% UI, 262.20%–275.72%) for

females between 1990 and 2021. Overall, 270.82 (95% UI, 255.80–288.65) million males and 254.81 (95% UI, 240.66–270.97) million females worldwide had diabetes. In 2021, there were 1.70 (95% UI, 1.57–1.80) million deaths attributable to diabetes (Table 9-2).
  - In 2021, the age-standardized prevalence of diabetes was estimated to be highest in Oceania, North Africa and the Middle East, the Caribbean, and high-income North America (Chart 9-8).
  - In 2021, age-standardized mortality rates attributable to high FPG were highest in Oceania, followed by southern and central sub-Saharan Africa and North Africa and the Middle East (Chart 9-9).
  - In 2021, age-standardized mortality estimated for diabetes was highest in Oceania, followed by southern and central sub-Saharan Africa and central Latin America (Chart 9-10).
- The global diabetes prevalence in those 20 to 79 years of age was estimated to be 10.5% (536.6 million people) in 2021 and expected to increase to 12.2% (783.2 million) by 2045 with a similar prevalence in males and females.[194] A higher prevalence in 2021 was seen in urban (12.1%) compared with rural (8.3%) areas and among higher-income (11.1%) compared with lower-income (5.5%) countries. Through 2045, a greater relative increase in the prevalence of diabetes is projected to be seen in middle-income countries (21.1%) than in high- (12.2%) and low- (11.9%) income countries. Global health care costs attributable to diabetes were estimated at US $966 billion in 2021, projected to reach US $1054 billion by 2045. Approximately 4.2 million deaths (11.1% of deaths) worldwide among individuals 20 to 79 years of age are attributable to diabetes according to 2019 estimates.[195] The IDF atlas global prevalence estimate did not include all ages and used a different methodology from the GBD prevalence estimate reported here.
- The global economic burden of diabetes was $1.3 trillion in 2015. It is estimated to increase to $2.1 to $2.5 trillion by 2030.[196]

**Table 9-1. Diabetes in the United States**

| Population group | Prevalence of diagnosed diabetes, 2017–2020: ≥20 y of age | Prevalence of undiagnosed diabetes, 2017–2020: ≥20 y of age | Prevalence of prediabetes, 2017–2020: ≥20 y of age | Incidence of diagnosed diabetes, 2019: ≥18 y of age | Mortality, 2021: all ages* | Hospital discharges, 2020: all ages | Cost, 2017 |
|---|---|---|---|---|---|---|---|
| Both sexes | 29 300 000 (10.6%) | 9 700 000 (3.5%) | 115 900 000 (46.4%) | 1 398 000 | 103 294 | 659 135 | $327 Billion |
| Males | 16 400 000 (12.2%) | 4 600 000 (3.5%) | 63 500 000 (52.9%) | 723 000 | 58 628 (56.8%)† | | … |
| Females | 12 900 000 (9.1%) | 5 100 000 (3.5%) | 52 400 000 (40.0%) | 675 000 | 44 666 (43.2%)† | | … |
| NH White males | 11.5% | 2.6% | 57.2% | … | 38 428 | … | … |
| NH White females | 7.7% | 2.8% | 38.8% | … | 27 361 | … | … |
| NH Black males | 11.8% | 5.6% | 35.3% | … | 9843 | … | … |
| NH Black females | 13.3% | 3.2% | 35.7% | … | 9125 | … | … |
| Hispanic males | 14.5% | 5.3% | 50.7% | … | 7029 | … | … |
| Hispanic females | 12.3% | 4.5% | 41.3% | … | 5460 | … | … |
| NH Asian males | 14.4% | 5.4% | 51.6% | … | 1963‡ | … | … |
| NH Asian females | 9.9% | 5.2% | 40.2% | … | 1676‡ | … | … |
| NH American Indian or Alaska Native | … | … | … | … | 1269 | … | … |
| NH Native Hawaiian or Pacific Islander | | | | | 314 | | |

Undiagnosed diabetes is defined as those whose fasting glucose is ≥126 mg/dL but who did not report being told by a health care professional that they had diabetes. Prediabetes is a fasting blood glucose of 100 to <126 mg/dL (impaired fasting glucose); prediabetes includes impaired glucose tolerance. In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.[197]

COVID-19 indicates coronavirus disease 2019; ellipses (…), data not available; NH, non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

*Mortality for Hispanic, American Indian or Alaska Native, Asian, and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting Hispanic origin or race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native, Asian and Pacific Islander, and Hispanic decedents, as well as undercounts of these groups in censuses.

†These percentages represent the portion of total diabetes mortality that is for males versus females.

‡Includes Chinese, Filipino, Japanese, and other Asian people.

Sources: Prevalence: Prevalence of diagnosed and undiagnosed diabetes: unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using NHANES.[7] Percentages for sex and racial and ethnic groups are age adjusted for Americans ≥20 years of age. Incidence: Centers for Disease Control and Prevention, National Diabetes Statistics Report.[1] Mortality (for underlying cause of diabetes): Unpublished NHLBI tabulation using National Vital Statistics System.[120] These data represent diabetes as the underlying cause of death only. Hospital discharges (with a principal diagnosis of diabetes): Healthcare Cost and Utilization Project.[179] Cost: American Diabetes Association.[187]

**Table 9-2. Global Prevalence and Mortality of Diabetes, 2021**

| | Both sexes | | Male | | Female | |
|---|---|---|---|---|---|---|
| | Deaths (95% UI) | Prevalence (95% UI) | Deaths (95% UI) | Prevalence (95% UI) | Deaths (95% UI) | Prevalence (95% UI) |
| Total number (millions), 2021 | 1.70 (1.57 to 1.80) | 525.62 (496.13 to 560.20) | 0.81 (0.75 to 0.87) | 270.82 (255.80 to 288.65) | 0.89 (0.82 to 0.95) | 254.81 (240.66 to 270.97) |
| Percent change in total number, 1990–2021 | 153.12 (135.76 to 168.54) | 277.80 (269.20 to 284.11) | 167.25 (140.02 to 192.35) | 285.77 (276.36 to 293.89) | 141.39 (121.41 to 157.18) | 269.67 (262.20 to 275.72) |
| Percent change in total number, 2010–2021 | 44.88 (36.90 to 51.99) | 61.20 (59.90 to 62.90) | 44.83 (32.60 to 55.73) | 61.37 (60.07 to 62.92) | 44.94 (37.33 to 51.98) | 61.03 (59.37 to 63.17) |
| Rate per 100 000, age-standardized, 2021 | 19.93 (18.39 to 21.10) | 6137.79 (5799.71 to 6536.41) | 21.03 (19.51 to 22.41) | 6,545.98 (6193.64 to 6968.42) | 19.00 (17.55 to 20.35) | 5756.64 (5441.03 to 6123.63) |
| Percent change in rate, age standardized, 1990 to 2021 | 8.76 (1.36 to 14.96) | 90.39 (85.80 to 93.59) | 11.78 (0.69 to 22.55) | 93.15 (88.40 to 97.21) | 5.77 (−2.26 to 12.46) | 87.08 (82.56 to 90.94) |
| Percent change in rate, age standardized, 2010 to 2021 | 3.57 (−2.00 to 8.69) | 26.45 (25.31 to 27.94) | 2.88 (−5.69 to 10.55) | 26.61 (25.49 to 27.95) | 4.08 (−1.31 to 9.08) | 26.16 (24.83 to 28.05) |

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Disease; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[193]

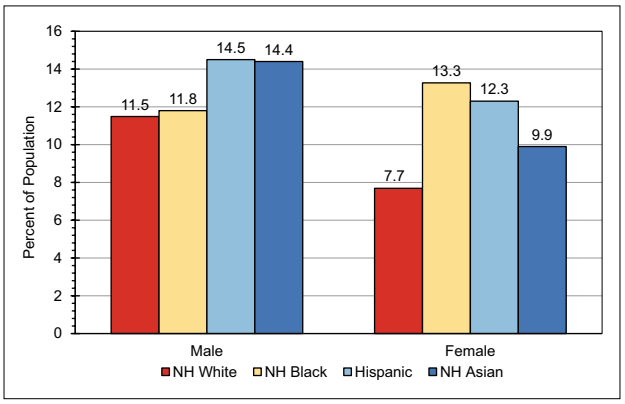



**Chart 9-1. Age-adjusted prevalence of diagnosed diabetes in US adults ≥20 years of age, by race and ethnicity and sex (NHANES 2017–2020).**

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.[197]

COVID-19 indicates coronavirus disease 2019; NH, non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.[7]

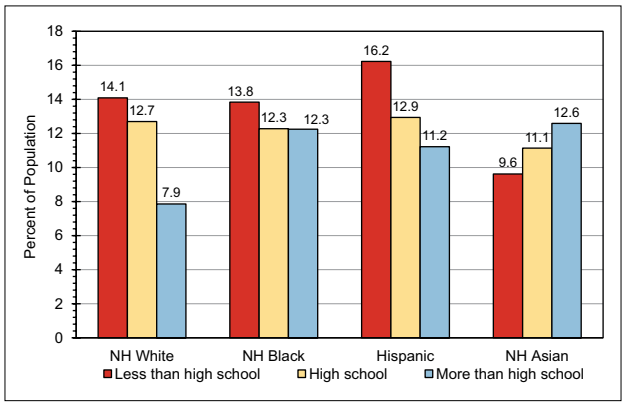



**Chart 9-2. Age-adjusted prevalence of diagnosed diabetes in US adults ≥20 years of age, by race and ethnicity and years of education (NHANES 2017–2020).**

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.[197]

COVID-19 indicates coronavirus disease 2019; NH, non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.[7]

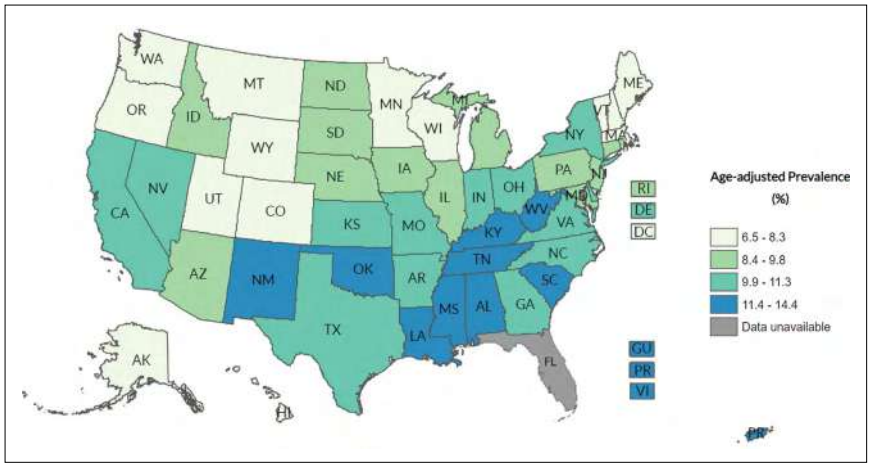



**Chart 9-3. Age-adjusted percentage of adults with diagnosed diabetes, US states and territories, 2021.**
Reprinted image has been altered to remove background colors, white space, and page headers and footers.
Source: Reprinted from Behavioral Risk Factor Surveillance System prevalence and trends data.[8]

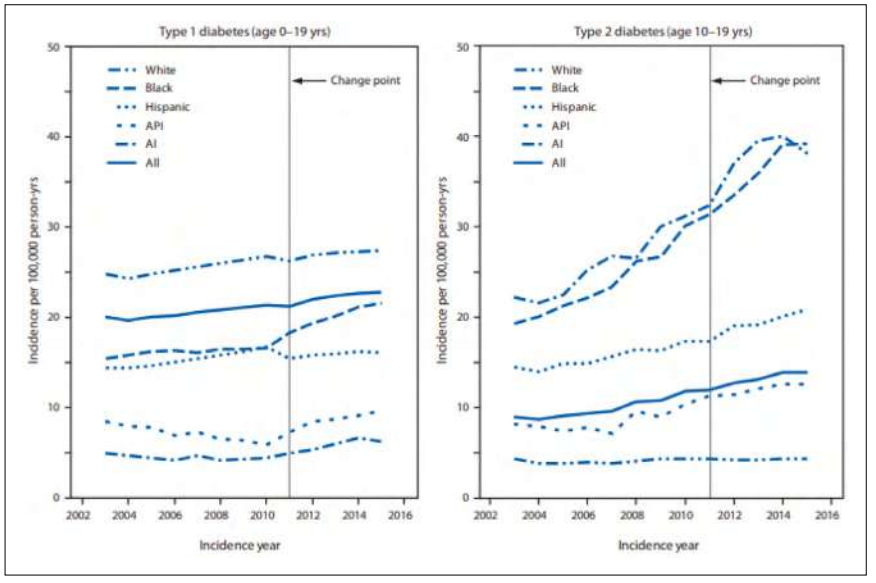



**Chart 9-4. Incidence of type 1 and type 2 diabetes, overall and by race and ethnicity, among US youths ≤19 years of age (SEARCH study, 2002–2015).**
Models included a change point at the year 2011 to compare trends in incidence rates between 2002 to 2010 and 2011 to 2015. People who were AI were from primarily 1 southwestern tribe. SEARCH includes data on youths (<20 years of age) in Colorado (all 64 counties plus selected Indian reservations in Arizona and New Mexico under the direction of Colorado), Ohio (8 counties), South Carolina (all 46 counties), and Washington (5 counties) and in California for Kaiser Permanente Southern California health plan enrollees in 7 counties.
AI indicates American Indian; API, Asian/Pacific Islander; and SEARCH, Search for Diabetes in Youth.
Source: Reprinted from Divers et al.[9]

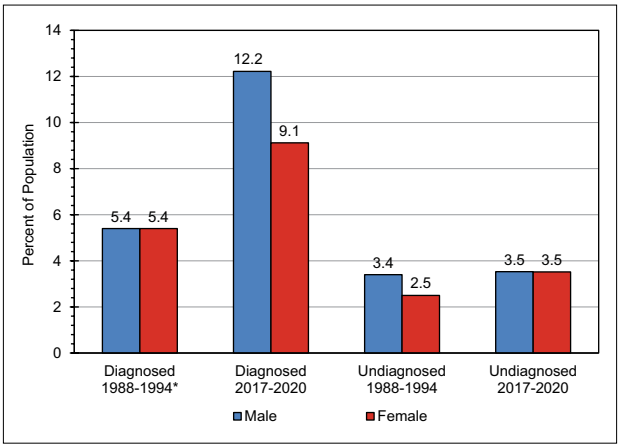



**Chart 9-5. Prevalence of diagnosed and undiagnosed diabetes in US adults ≥20 years of age by sex (NHANES 1988–1994 and 2017-2020).**

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.[197]

COVID-19 indicates coronavirus disease 2019; and NHANES, National Health and Nutrition Examination Survey.

*The definition of diabetes changed in 1997 (from glucose ≥140 to ≥126 mg/dL).

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.[7]

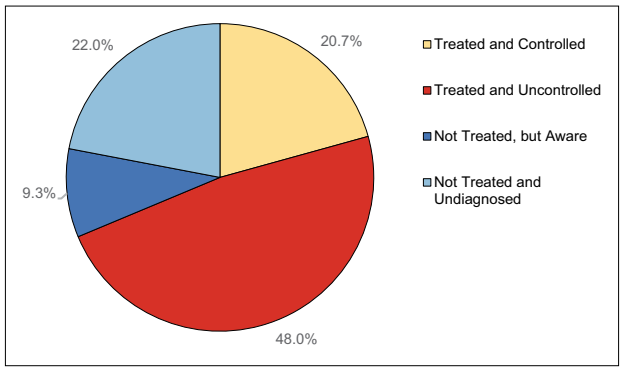



**Chart 9-6. Awareness, treatment, and control of diabetes in US adults ≥20 years of age (NHANES 2017–2020).**

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.[197] Controlled is defined as currently treated (taking insulin or diabetic pills to lower blood sugar) and fasting glucose <126 mg/dL. Uncontrolled is defined as currently treated (taking insulin or diabetic pills to lower blood sugar) and fasting glucose ≥126 mg/dL.

COVID-19 indicates coronavirus disease 2019; and NHANES, National Health and Nutrition Examination Survey.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.[7]

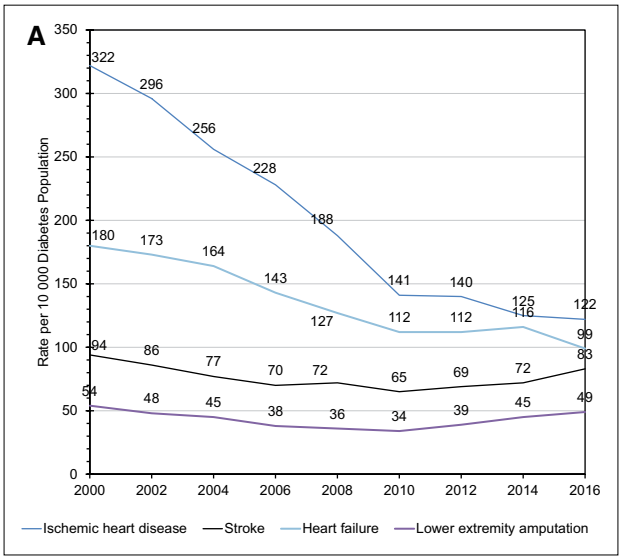



**Chart 9-7. Trends in age-standardized hospitalization rates for diabetes-related complications among US adults ≥18 years of age from 2000 to 2016.**

**A**, Data include the population with diabetes. **B**, Data include the general population (with or without diabetes). Age adjustment is to the 2000 US standard population using age groups <45, 45 to 64, 65 to 74, and ≥75 years of age.

Source: Centers for Disease Control and Prevention Diabetes Atlas[129] using data from Healthcare Cost and Utilization Project[179] and National Health Interview Survey.[198]

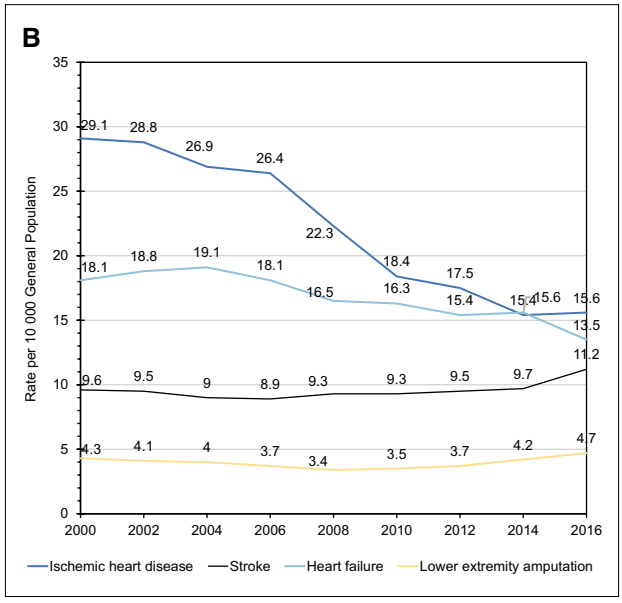



**Chart 9-7 Continued.**

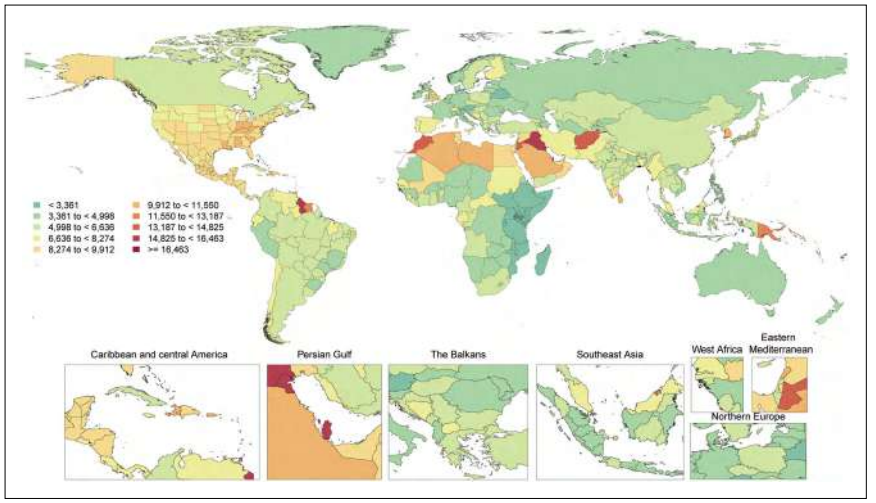



**Chart 9-8. Age-standardized global prevalence rates of diabetes per 100 000, both sexes, 2021.**
During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.
GBD indicates Global Burden of Disease.
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[193]

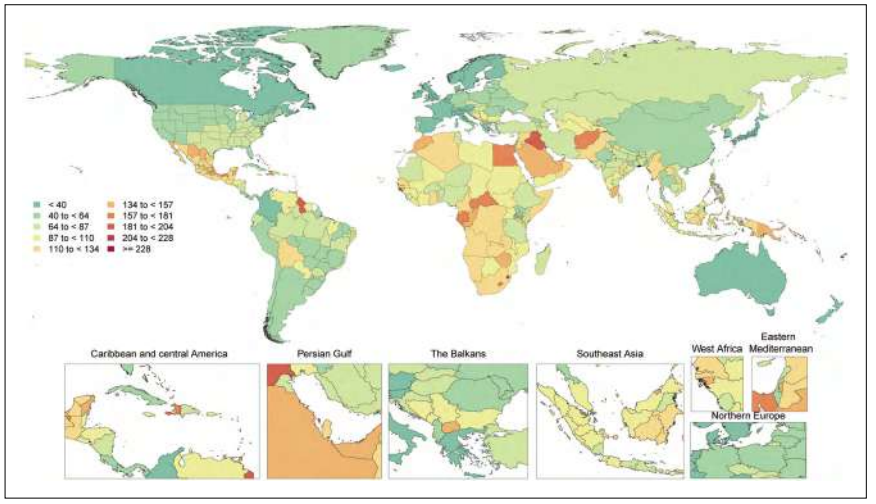



**Chart 9-9. Age-standardized global mortality rates attributable to high FPG per 100 000, both sexes, 2021.**
During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles. High FPG is defined as serum fasting plasma glucose of >4.8 to 5.4 mmol/L.
FPG indicates fasting plasma glucose; and GBD, Global Burden of Disease.
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[193]

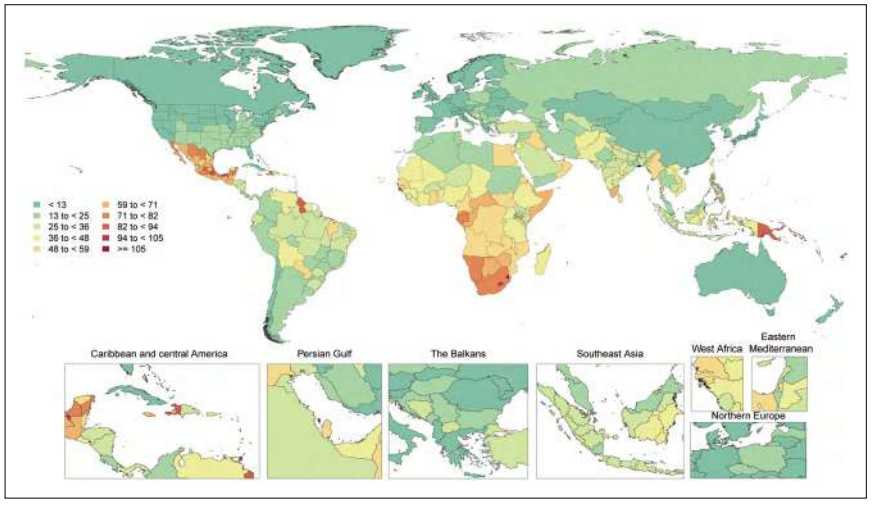



**Chart 9-10. Age-standardized global mortality rates of diabetes per 100 000, both sexes, 2021.**
During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.
GBD indicates Global Burden of Disease.
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[193]



 *Circulation*. 2024;149:e347–e913. DOI: 10.1161/CIR.0000000000001209

## REFERENCES


1. Centers for Disease Control and Prevention. National Diabetes Statistics Report website. Accessed April 4, 2023. https://cdc.gov/diabetes/data/statistics-report/index.html
2. American Diabetes Association. Classification and diagnosis of diabetes: standards of medical care in Diabetes–2020. *Diabetes Care*. 2020;43(suppl 1):S14–S31. doi: 10.2337/dc20-S002
3. Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, Ingelsson E, Lawlor DA, Selvin E, Stampfer M, et al; Emerging Risk Factors Collaboration. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet*. 2010;375:2215–2222. doi: 10.1016/S0140-6736(10)60484-9
4. Lloyd-Jones DM, Allen NB, Anderson CAM, Black T, Brewer LC, Foraker RE, Grandner MA, Lavretsky H, Perak AM, Sharma G, et al; on behalf of the American Heart Association. Life's Essential 8: updating and enhancing the American Heart Association's construct of cardiovascular health: a presidential advisory from the American Heart Association. *Circulation*. 2022;146:e18–e43. doi: 10.1161/CIR.0000000000001078
5. Andes LJ, Cheng YJ, Rolka DB, Gregg EW, Imperatore G. Prevalence of prediabetes among adolescents and young adults in the United States, 2005-2016. *JAMA Pediatr*. 2019;174:e194498. doi: 10.1001/jamapediatrics.2019.4498
6. Tonnies T, Brinks R, Isom S, Dabelea D, Divers J, Mayer-Davis EJ, Lawrence JM, Pihoker C, Dolan L, Liese AD, et al. Projections of type 1 and type 2 diabetes burden in the U.S. population aged <20 years through 2060: the SEARCH for Diabetes in Youth Study. *Diabetes Care*. 2023;46:313–320. doi: 10.2337/dc22-0945
7. Centers for Disease Control and Prevention and National Center for Health Statistics. National Health and Nutrition Examination Survey (NHANES) public use data files. Accessed April 1, 2023. https://cdc.gov/nchs/nhanes/
8. Centers for Disease Control and Prevention and National Center for Chronic Disease Prevention and Health Promotion. Behavioral Risk Factor Surveillance System (BRFSS): BRFSS prevalence & trends data. Accessed March 27, 2023. https://cdc.gov/brfss/brfssprevalence/
9. Divers J, Mayer-Davis EJ, Lawrence JM, Isom S, Dabelea D, Dolan L, Imperatore G, Marcovina S, Pettitt DJ, Pihoker C, et al. Trends in incidence of type 1 and type 2 diabetes among youths: selected counties and Indian reservations, United States, 2002-2015. *MMWR Morb Mortal Wkly Rep*. 2020;69:161–165. doi: 10.15585/mmwr.mm6906a3
10. Almulhem M, Chandan JS, Gokhale K, Adderley NJ, Thayakaran R, Khunti K, Tahrani AA, Hanif W, Nirantharakumar K. Cardio-metabolic outcomes in South Asians compared to White Europeans in the United Kingdom: a matched controlled population-based cohort study. *BMC Cardiovasc Disord*. 2021;21:320. doi: 10.1186/s12872-021-02133-z
11. Lee CMY, Colagiuri S, Woodward M, Gregg EW, Adams R, Azizi F, Gabriel R, Gill TK, Gonzalez C, Hodge A, et al. Comparing different definitions of prediabetes with subsequent risk of diabetes: an individual participant data meta-analysis involving 76 513 individuals and 8208 cases of incident diabetes. *BMJ Open Diabetes Res Care*. 2019;7:e000794. doi: 10.1136/bmjdrc-2019-000794
12. Cordola Hsu AR, Ames SL, Xie B, Peterson DV, Garcia L, Going SB, Phillips LS, Manson JE, Anton-Culver H, Wong ND. Incidence of diabetes according to metabolically healthy or unhealthy normal weight or overweight/obesity in postmenopausal women: the Women's Health Initiative. *Menopause*. 2020;27:640–647. doi: 10.1097/GME.0000000000001512
13. Lee S, Lacy ME, Jankowich M, Correa A, Wu WC. Association between obesity phenotypes of insulin resistance and risk of type 2 diabetes in African Americans: the Jackson Heart Study. *J Clin Transl Endocrinol*. 2020;19:100210. doi: 10.1016/j.jcte.2019.100210
14. Llewellyn A, Simmonds M, Owen CG, Woolacott N. Childhood obesity as a predictor of morbidity in adulthood: a systematic review and meta-analysis. *Obes Rev*. 2016;17:56–67. doi: 10.1111/obr.12316
15. Li M, Xu Y, Wan Q, Shen F, Xu M, Zhao Z, Lu J, Gao Z, Chen G, Wang T, et al. Individual and combined associations of modifiable lifestyle and metabolic health status with new-onset diabetes and major cardiovascular events: the China Cardiometabolic Disease and Cancer Cohort (4C) Study. *Diabetes Care*. 2020;43:1929–1936. doi: 10.2337/dc20-0256
16. Zhang Y, Pan XF, Chen J, Xia L, Cao A, Zhang Y, Wang J, Li H, Yang K, Guo K, et al. Combined lifestyle factors and risk of incident type 2 diabetes and prognosis among individuals with type 2 diabetes: a systematic review and meta-analysis of prospective cohort studies. *Diabetologia*. 2020;63:21–33. doi: 10.1007/s00125-019-04985-9
17. Patterson R, McNamara E, Tainio M, de Sa TH, Smith AD, Sharp SJ, Edwards P, Woodcock J, Brage S, Wijndaele K. Sedentary behaviour and risk of all-cause, cardiovascular and cancer mortality, and incident type 2 diabetes: a systematic review and dose response meta-analysis. *Eur J Epidemiol*. 2018;33:811–829. doi: 10.1007/s10654-018-0380-1
18. Qin P, Li Q, Zhao Y, Chen Q, Sun X, Liu Y, Li H, Wang T, Chen X, Zhou Q, et al. Sugar and artificially sweetened beverages and risk of obesity, type 2 diabetes mellitus, hypertension, and all-cause mortality: a dose-response meta-analysis of prospective cohort studies. *Eur J Epidemiol*. 2020;35:655–671. doi: 10.1007/s10654-020-00655-y
19. Casagrande SS, Linder B, Cowie CC. Prevalence of gestational diabetes and subsequent type 2 diabetes among U.S. women. *Diabetes Res Clin Pract*. 2018;141:200–208. doi: 10.1016/j.diabres.2018.05.010
20. Stuart JJ, Tanz LJ, Missmer SA, Rimm EB, Spiegelman D, James-Todd TM, Rich-Edwards JW. Hypertensive disorders of pregnancy and maternal cardiovascular disease risk factor development: an observational cohort study. *Ann Intern Med*. 2018;169:224–232. doi: 10.7326/M17-2740
21. Huh JH, Han KD, Cho YK, Roh E, Kang JG, Lee SJ, Ihm SH. Remnant cholesterol and the risk of cardiovascular disease in type 2 diabetes: a nationwide longitudinal cohort study. *Cardiovasc Diabetol*. 2022;21:228. doi: 10.1186/s12933-022-01667-6
22. Li Y, Pei H, Zhou C, Lou Y. Dietary cholesterol consumption and incidence of type 2 diabetes mellitus: a dose-response meta-analysis of prospective cohort studies. *Nutr Metab Cardiovasc Dis*. 2023;33:2–10. doi: 10.1016/j.numecd.2022.07.016
23. Gao F, Cui CY. Dietary cholesterol intake and risk of gestational diabetes mellitus: a meta-analysis of observational studies. *J Am Nutr Assoc*. 2022;41:107–115. doi: 10.1080/07315724.2020.1844605
24. Martínez-González MA, Sayón-Orea C, Bullón-Vela V, Bes-Rastrollo M, Rodríguez-Artalejo F, Yusta-Boyo MJ, García-Solano M. Effect of olive oil consumption on cardiovascular disease, cancer, type 2 diabetes, and all-cause mortality: a systematic review and meta-analysis. *Clin Nutr*. 2022;41:2659–2682. doi: 10.1016/j.clnu.2022.10.001
25. Suzuki Y, Kaneko H, Okada A, Matsuoka S, Itoh H, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, et al. Prediabetes in young adults and its association with cardiovascular health metrics in the progression to diabetes. *J Clin Endocrinol Metab*. 2022;107:1843–1853. doi: 10.1210/clinem/dgac247
26. Kaplan RC, Song RJ, Lin J, Xanthakis V, Hua S, Chernofsky A, Evenson KR, Walker ME, Cuthbertson C, Murabito JM, et al. Predictors of incident diabetes in two populations: Framingham Heart Study and Hispanic Community Health Study/ Study of Latinos. *BMC Public Health*. 2022;22:1053. doi: 10.1186/s12889-022-13463-8
27. Caraballo C, Valero-Elizondo J, Khera R, Mahajan S, Grandhi GR, Virani SS, Mszar R, Krumholz HM, Nasir K. Burden and consequences of financial hardship from medical bills among nonelderly adults with diabetes mellitus in the United States. *Circ Cardiovasc Qual Outcomes*. 2020;13:e006139. doi: 10.1161/CIRCOUTCOMES.119.006139
28. Twarog JP, Charyalu AM, Subhani MR, Shrestha P, Peraj E. Differences in HbA1C% screening among U.S. adults diagnosed with diabetes: findings from the National Health and Nutrition Examination Survey (NHANES). *Prim Care Diabetes*. 2018;12:533–536. doi: 10.1016/j.pcd.2018.07.006
29. Doucette ED, Salas J, Wang J, Scherrer JF. Insurance coverage and diabetes quality indicators among patients with diabetes in the US general population. *Prim Care Diabetes*. 2017;11:515–521. doi: 10.1016/j.pcd.2017.05.007
30. Mendoza JA, Haaland W, D'Agostino RB, Martini L, Pihoker C, Frongillo EA, Mayer-Davis EJ, Liu LL, Dabelea D, Lawrence JM, et al. Food insecurity is associated with high risk glycemic control and higher health care utilization among youth and young adults with type 1 diabetes. *Diabetes Res Clin Pract*. 2018;138:128–137. doi: 10.1016/j.diabres.2018.01.035
31. Williams PC, Alhasan DM, Gaston SA, Henderson KL, Braxton Jackson W 2nd, Jackson CL. Neighborhood social cohesion and type 2 diabetes mellitus by age, gender, and race/ethnicity in the United States. *Prev Med*. 2023;170:107477. doi: 10.1016/j.ypmed.2023.107477
32. Zhao Y, Malik S, Budoff MJ, Correa A, Ashley KE, Selvin E, Watson KE, Wong ND. Identification and predictors for cardiovascular disease risk equivalents among adults with diabetes mellitus. *Diabetes Care*. 2021:dc210431. doi: 10.2337/dc21-0431
33. Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [published correction appears in *Circulation*. 2014;129(suppl 2):S74–S75]. *Circulation*. 2014;129(suppl 2):S49–S73. doi: 10.1161/01.cir.0000437741.48606.98

34. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol [published corrections appear in *Circulation*. 2019;139:e1182–e1186 and *Circulation*. 2023;148:e5]. *Circulation*. 2019;139:e1082–e1143. doi: 10.1161/CIR.0000000000000625
35. Malik S, Budoff MJ, Katz R, Blumenthal RS, Bertoni AG, Nasir K, Szklo M, Barr RG, Wong ND. Impact of subclinical atherosclerosis on cardiovascular disease events in individuals with metabolic syndrome and diabetes: the Multi-Ethnic Study of Atherosclerosis. *Diabetes Care*. 2011;34:2285–2290. doi: 10.2337/dc11-0816
36. Malik S, Zhao Y, Budoff M, Nasir K, Blumenthal RS, Bertoni AG, Wong ND. Coronary artery calcium score for long-term risk classification in individuals with type 2 diabetes and metabolic syndrome from the Multi-Ethnic Study of Atherosclerosis. *JAMA Cardiol*. 2017;2:1332–1340. doi: 10.1001/jamacardio.2017.4191
37. Wong ND, Nelson JC, Granston T, Bertoni AG, Blumenthal RS, Carr JJ, Guerci A, Jacobs DR Jr, Kronmal R, Liu K, et al. Metabolic syndrome, diabetes, and incidence and progression of coronary calcium: the Multiethnic Study of Atherosclerosis study. *JACC Cardiovasc Imaging*. 2012;5:358–366. doi: 10.1016/j.jcmg.2011.12.015
38. Wong ND, Cordola Hsu AR, Rozanski A, Shaw LJ, Whelton SP, Budoff MJ, Nasir K, Miedema MD, Rumberger J, Blaha MJ, et al. Sex differences in coronary artery calcium and mortality from coronary heart disease, cardiovascular disease, and all causes in adults with diabetes: the Coronary Calcium Consortium. *Diabetes Care*. 2020;43:2597–2606. doi: 10.2337/dc20-0166
39. Al-Kindi S, Dong T, Chen W, Tashtish N, Neeland IJ, Nasir K, Rajagopalan S. Relation of coronary calcium scoring with cardiovascular events in patients with diabetes: the CLARIFY Registry. *J Diabetes Complications*. 2022;36:108269. doi: 10.1016/j.jdiacomp.2022.108269
40. Buchan TA, Malik A, Chan C, Chambers J, Suk Y, Zhu JW, Ge FZ, Huang LM, Vargas LA, Hao Q, et al. Predictive models for cardiovascular and kidney outcomes in patients with type 2 diabetes: systematic review and meta-analyses. *Heart*. 2021;107:1962–1973. doi: 10.1136/heartjnl-2021-319243
41. Hippisley-Cox J, Coupland C. Development and validation of QDiabetes-2018 risk prediction algorithm to estimate future risk of type 2 diabetes: cohort study. *BMJ*. 2017;359:j5019. doi: 10.1136/bmj.j5019
42. Read SH, van Diepen M, Colhoun HM, Halbesma N, Lindsay RS, McKnight JA, McAllister DA, Pearson ER, Petrie JR, Philip S, et al; Scottish Diabetes Research Network Epidemiology Group. Performance of cardiovascular disease risk scores in people diagnosed with type 2 diabetes: external validation using data from the National Scottish Diabetes Register. *Diabetes Care*. 2018;41:2010–2018. doi: 10.2337/dc18-0578
43. Chowdhury MZI, Yeasmin F, Rabi DM, Ronksley PE, Turin TC. Prognostic tools for cardiovascular disease in patients with type 2 diabetes: A systematic review and meta-analysis of C-statistics. *J Diabetes Complications*. 2019;33:98–111. doi: 10.1016/j.jdiacomp.2018.10.010
44. Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. *BMJ*. 2017;357:j2099. doi: 10.1136/bmj.j2099
45. Bergmark BA, Bhatt DL, Braunwald E, Morrow DA, Steg PG, Gurmu Y, Cahn A, Mosenzon O, Raz I, Bohula E, et al. Risk assessment in patients with diabetes with the timi risk score for atherothrombotic disease. *Diabetes Care*. 2018;41:577–585. doi: 10.2337/dc17-1736
46. Jiang W, Wang J, Shen X, Lu W, Wang Y, Li W, Gao Z, Xu J, Li X, Liu R, et al. Establishment and validation of a risk prediction model for early diabetic kidney disease based on a systematic review and meta-analysis of 20 cohorts. *Diabetes Care*. 2020;43:925–933. doi: 10.2337/dc19-1897
47. Almgren P, Lehtovirta M, Isomaa B, Sarelin L, Taskinen MR, Lyssenko V, Tuomi T, Groop L; Botnia Study Group. Heritability and familiality of type 2 diabetes and related quantitative traits in the Botnia Study. *Diabetologia*. 2011;54:2811–2819. doi: 10.1007/s00125-011-2267-5
48. Poulsen P, Kyvik KO, Vaag A, Beck-Nielsen H. Heritability of type II (non-insulin-dependent) diabetes mellitus and abnormal glucose tolerance: a population-based twin study. *Diabetologia*. 1999;42:139–145. doi: 10.1007/s001250051131
49. Meigs JB, Cupples LA, Wilson PW. Parental transmission of type 2 diabetes: the Framingham Offspring Study. *Diabetes*. 2000;49:2201–2207. doi: 10.2337/diabetes.49.12.2201
50. Moonesinghe R, Beckles GLA, Liu T, Khoury MJ. The contribution of family history to the burden of diagnosed diabetes, undiagnosed diabetes, and prediabetes in the United States: analysis of the National Health and Nutrition Examination Survey, 2009-2014. *Genet Med*. 2018;20:1159–1166. doi: 10.1038/gim.2017.238
51. Kleinberger JW, Copeland KC, Gandica RG, Haymond MW, Levitsky LL, Linder B, Shuldiner AR, Tollefsen S, White NH, Pollin TI. Monogenic diabetes in overweight and obese youth diagnosed with type 2 diabetes: the TODAY clinical trial. *Genet Med*. 2018;20:583–590. doi: 10.1038/gim.2017.150
52. Vujkovic M, Keaton JM, Lynch JA, Miller DR, Zhou J, Tcheandjieu C, Huffman JE, Assimes TL, Lorenz K, Zhu X, et al; HPAP Consortium. Discovery of 318 new risk loci for type 2 diabetes and related vascular outcomes among 1.4 million participants in a multi-ancestry meta-analysis. *Nat Genet*. 2020;52:680–691. doi: 10.1038/s41588-020-0637-y
53. Mahajan A, Taliun D, Thurner M, Robertson NR, Torres JM, Rayner NW, Payne AJ, Steinthorsdottir V, Scott RA, Grarup N, et al. Fine-mapping type 2 diabetes loci to single-variant resolution using high-density imputation and islet-specific epigenome maps. *Nat Genet*. 2018;50:1505–1513. doi: 10.1038/s41588-018-0241-6
54. Morris AP, Voight BF, Teslovich TM, Ferreira T, Segre AV, Steinthorsdottir V, Strawbridge RJ, Khan H, Grallert H, Mahajan A, et al; Wellcome Trust Case Control Consortium. Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes. *Nat Genet*. 2012;44:981–990. doi: 10.1038/ng.2383
55. Diabetes Genetics Replication and Meta-Analysis (DIAGRAM) Consortium, Asian Genetic Epidemiology Network Type 2 Diabetes (AGEN-T2D) Consortium, South Asian Type 2 Diabetes (SAT2D) Consortium, Mexican American Type 2 Diabetes (MAT2D) Consortium, and Type 2 Diabetes Genetic Exploration by Next-Generation Sequencing in Multi-Ethnic Samples (T2D-GENES) Consortium. Genome-wide trans-ancestry meta-analysis provides insight into the genetic architecture of type 2 diabetes susceptibility. *Nat Genet*. 2014;46:234–244. doi: 10.1038/ng.2897
56. Sladek R, Rocheleau G, Rung J, Dina C, Shen L, Serre D, Boutin P, Vincent D, Belisle A, Hadjadj S, et al. A genome-wide association study identifies novel risk loci for type 2 diabetes. *Nature*. 2007;445:881–885. doi: 10.1038/nature05616
57. Woo HJ, Reifman J. Genetic interaction effects reveal lipid-metabolic and inflammatory pathways underlying common metabolic disease risks. *BMC Med Genomics*. 2018;11:54. doi: 10.1186/s12920-018-0373-7
58. Rosta K, Al-Aissa Z, Hadarits O, Harreiter J, Nadasdi A, Kelemen F, Bancher-Todesca D, Komlosi Z, Nemeth L, Rigo J Jr, et al. Association study with 77 SNPs confirms the robust role for the rs10830963/G of MTNR1B variant and identifies two novel associations in gestational diabetes mellitus development. *PLoS One*. 2017;12:e0169781. doi: 10.1371/journal.pone.0169781
59. Srinivasan S, Chen L, Todd J, Divers J, Gidding S, Chernausek S, Gubitosi-Klug RA, Kelsey MM, Shah R, Black MH, et al. The first genome-wide association study for type 2 diabetes in youth: the Progress in Diabetes Genetics in Youth (ProDiGY) Consortium. *Diabetes*. 2021;70:996–1005. doi: 10.2337/db20-0443
60. Lee KH, Ju UI, Song JY, Chun YS. The histone demethylase PHF2 promotes fat cell differentiation as an epigenetic activator of both C/EBPalpha and C/EBPdelta. *Mol Cells*. 2014;37:734–741. doi: 10.14348/molcells.2014.0180
61. Mahajan A, Spracklen CN, Zhang W, Ng MCY, Petty LE, Kitajima H, Yu GZ, Rueger S, Speidel L, Kim YJ, et al. Multi-ancestry genetic study of type 2 diabetes highlights the power of diverse populations for discovery and translation. *Nat Genet*. 2022;54:560–572.
62. Chen J, Spracklen CN, Marenne G, Varshney A, Corbin LJ, Luan J, Willems SM, Wu Y, Zhang X, Horikoshi M, et al. The trans-ancestral genomic architecture of glycemic traits. *Nat Genet*. 2021;53:840–860. doi: 10.1038/s41588-021-00852-9
63. Downie CG, Dimos SF, Bien SA, Hu Y, Darst BF, Polfus LM, Wang Y, Wojcik GL, Tao R, Raffield LM, et al. Multi-ethnic GWAS and fine-mapping of glycaemic traits identify novel loci in the PAGE study. *Diabetologia*. 2022;65:477–489. doi: 10.1007/s00125-021-05635-9
64. Mars N, Koskela JT, Ripatti P, Kiiskinen TTJ, Havulinna AS, Lindbohm JV, Ahola-Olli A, Kurki M, Karjalainen J, Palta P, et al. Polygenic and clinical risk scores and their impact on age at onset and prediction of cardiometabolic diseases and common cancers. *Nat Med*. 2020;26:549–557. doi: 10.1038/s41591-020-0800-0
65. Hodgson S, Huang QQ, Sallah N, Griffiths CJ, Newman WG, Trembath RC, Wright J, Lumbers RT, Kuchenbaecker K, van Heel DA, et al; Genes and Health Research Team. Integrating polygenic risk scores in the prediction of type 2 diabetes risk and subtypes in British Pakistanis and Bangladeshis: a population-based cohort study. *PLoS Med*. 2022;19:e1003981. doi: 10.1371/journal.pmed.1003981

66. Ge T, Irvin MR, Patki A, Srinivasasainagendra V, Lin YF, Tiwari HK, Armstrong ND, Benoit B, Chen CY, Choi KW, et al. Development and validation of a trans-ancestry polygenic risk score for type 2 diabetes in diverse populations. *Genome Med*. 2022;14:70. doi: 10.1186/s13073-022-01074-2
67. Said MA VN, van der Harst P. Associations of combined genetic and lifestyle risks with incident cardiovascular disease and diabetes in the UK Biobank study. *JAMA Cardiol*. 2018;3:693–702. doi: 10.1001/jamacardio.2018.1717
68. Zhuang P, Liu X, Li Y, Wan X, Wu Y, Wu F, Zhang Y, Jiao J. Effect of diet quality and genetic predisposition on hemoglobin A1c and type 2 diabetes risk: gene-diet interaction analysis of 357,419 individuals. *Diabetes Care*. 2021;44:2470–2479. doi: 10.2337/dc21-1051
69. Lotta LA, Wittemans LBL, Zuber V, Stewart ID, Sharp SJ, Luan J, Day FR, Li C, Bowker N, Cai L, et al. Association of genetic variants related to gluteofemoral vs abdominal fat distribution with type 2 diabetes, coronary disease, and cardiovascular risk factors. *JAMA*. 2018;320:2553–2563. doi: 10.1001/jama.2018.19329
70. Bulik-Sullivan B, Finucane HK, Anttila V, Gusev A, Day FR, Loh PR, Duncan L, Perry JR, Patterson N, Robinson EB, et al; ReproGen Consortium. An atlas of genetic correlations across human diseases and traits. *Nat Genet*. 2015;47:1236–1241. doi: 10.1038/ng.3406
71. Shah HS, Gao H, Morieri ML, Skupien J, Marvel S, Pare G, Mannino GC, Buranasupkajorn P, Mendonca C, Hastings T, et al. genetic predictors of cardiovascular mortality during intensive glycemic control in type 2 diabetes: findings from the ACCORD clinical trial. *Diabetes Care*. 2016;39:1915–1924. doi: 10.2337/dc16-0285
72. Mutie PM, Pomares-Millan H, Atabaki-Pasdar N, Jordan N, Adams R, Daly NL, Tajes JF, Giordano GN, Franks PW. An investigation of causal relationships between prediabetes and vascular complications. *Nat Commun*. 2020;11:4592. doi: 10.1038/s41467-020-18386-9
73. Pociot F, Lernmark A. Genetic risk factors for type 1 diabetes. *Lancet*. 2016;387:2331–2339. doi: 10.1016/S0140-6736(16)30582-7
74. Forgetta V, Manousaki D, Istomine R, Ross S, Tessier MC, Marchand L, Li M, Qu HQ, Bradfield JP, Grant SFA, et al; DCCT/EDIC Research Group. Rare genetic variants of large effect influence risk of type 1 diabetes. *Diabetes*. 2020;69:784–795. doi: 10.2337/db19-0831
75. Oram RA, Patel K, Hill A, Shields B, McDonald TJ, Jones A, Hattersley AT, Weedon MN. A type 1 diabetes genetic risk score can aid discrimination between type 1 and type 2 diabetes in young adults. *Diabetes Care*. 2016;39:337–344. doi: 10.2337/dc15-1111
76. Ferrat LA, Vehik K, Sharp SA, Lernmark A, Rewers MJ, She JX, Ziegler AG, Toppari J, Akolkar B, Krischer JP, et al; TEDDY Study Group. A combined risk score enhances prediction of type 1 diabetes among susceptible children. *Nat Med*. 2020;26:1247–1255. doi: 10.1038/s41591-020-0930-4
77. Langefeld CD, Beck SR, Bowden DW, Rich SS, Wagenknecht LE, Freedman BI. Heritability of GFR and albuminuria in Caucasians with type 2 diabetes mellitus. *Am J Kidney Dis*. 2004;43:796–800. doi: 10.1053/j.ajkd.2003.12.043
78. Qi L, Qi Q, Prudente S, Mendonca C, Andreozzi F, di Pietro N, Sturma M, Novelli V, Mannino GC, Formoso G, et al. Association between a genetic variant related to glutamic acid metabolism and coronary heart disease in individuals with type 2 diabetes. *JAMA*. 2013;310:821–828. doi: 10.1001/jama.2013.276305
79. Słomiński B, Ławrynowicz U, Ryba-Stanisławowska M, Skrzypkowska M, Myśliwska J, Myśliwiec M. CCR5- Δ 32 polymorphism is a genetic risk factor associated with dyslipidemia in patients with type 1 diabetes. *Cytokine*. 2018;114:81–85. doi: 10.1016/j.cyto.2018.11.005
80. Cao M, Tian Z, Zhang L, Liu R, Guan Q, Jiang J. Genetic association of AKR1B1 gene polymorphism rs759853 with diabetic retinopathy risk: a meta-analysis. *Gene*. 2018;676:73–78. doi: 10.1016/j.gene.2018.07.014
81. Guan M, Keaton JM, Dimitrov L, Hicks PJ, Xu J, Palmer ND, Ma L, Das SK, Chen YI, Coresh J, et al; FIND Consortium. Genome-wide association study identifies novel loci for type 2 diabetes-attributed end-stage kidney disease in African Americans. *Hum Genomics*. 2019;13:21. doi: 10.1186/s40246-019-0205-7
82. Tang Y, Lenzini PA, Pop-Busui R, Ray PR, Campbell H, Perkins BA, Callaghan B, Wagner MJ, Motsinger-Reif AA, Buse JB, et al. A genetic locus on chromosome 2q24 predicting peripheral neuropathy risk in type 2 diabetes: results from the ACCORD and BARI 2D Studies. *Diabetes*. 2019;68:1649–1662. doi: 10.2337/db19-0109
83. Newgard CB, An J, Bain JR, Muehlbauer MJ, Stevens RD, Lien LF, Haqq AM, Shah SH, Arlotto M, Slentz CA, et al. A branched-chain amino acid-related metabolic signature that differentiates obese and lean humans and contributes to insulin resistance. *Cell Metab*. 2009;9:311–326. doi: 10.1016/j.cmet.2009.02.002
84. Morze J, Wittenbecher C, Schwingshackl L, Danielewicz A, Rynkiewicz A, Hu FB, Guasch-Ferre M. Metabolomics and type 2 diabetes risk: an updated systematic review and meta-analysis of prospective cohort studies. *Diabetes Care*. 2022;45:1013–1024. doi: 10.2337/dc21-1705
85. Yu D, Richardson NE, Green CL, Spicer AB, Murphy ME, Flores V, Jang C, Kasza I, Nikodemova M, Wakai MH, et al. The adverse metabolic effects of branched-chain amino acids are mediated by isoleucine and valine. *Cell Metab*. 2021;33:905–922.e6. doi: 10.1016/j.cmet.2021.03.025
86. Guasch-Ferre M, Hruby A, Toledo E, Clish CB, Martinez-Gonzalez MA, Salas-Salvado J, Hu FB. Metabolomics in prediabetes and diabetes: a systematic review and meta-analysis. *Diabetes Care*. 2016;39:833–846. doi: 10.2337/dc15-2251
87. Rhee EP, Cheng S, Larson MG, Walford GA, Lewis GD, McCabe E, Yang E, Farrell L, Fox CS, O'Donnell CJ, et al. Lipid profiling identifies a triacylglycerol signature of insulin resistance and improves diabetes prediction in humans. *J Clin Invest*. 2011;121:1402–1411. doi: 10.1172/JCI44442
88. Wang TJ, Ngo D, Psychogios N, Dejam A, Larson MG, Vasan RS, Ghorbani A, O'Sullivan J, Cheng S, Rhee EP, et al. 2-Aminoadipic acid is a biomarker for diabetes risk. *J Clin Invest*. 2013;123:4309–4317. doi: 10.1172/JCI64801
89. Siegel KR, Bullard KM, Imperatore G, Ali MK, Albright A, Mercado CI, Li R, Gregg EW. Prevalence of major behavioral risk factors for type 2 diabetes. *Diabetes Care*. 2018;41:1032–1039. doi: 10.2337/dc17-1775
90. Ali MK, Bullard KM, Saydah S, Imperatore G, Gregg EW. Cardiovascular and renal burdens of prediabetes in the USA: analysis of data from serial cross-sectional surveys, 1988-2014. *Lancet Diabetes Endocrinol*. 2018;6:392–403. doi: 10.1016/S2213-8587(18)30027-5
91. Herman WH, Pan Q, Edelstein SL, Mather KJ, Perreault L, Barrett-Connor E, Dabelea DM, Horton E, Kahn SE, Knowler WC, et al; Diabetes Prevention Program Research Group. Impact of lifestyle and metformin interventions on the risk of progression to diabetes and regression to normal glucose regulation in overweight or obese people with impaired glucose regulation. *Diabetes Care*. 2017;40:1668–1677. doi: 10.2337/dc17-1116
92. Gerstein HC, Coleman RL, Scott CAB, Xu S, Tuomilehto J, Ryden L, Holman RR; ACE Study Group. Impact of acarbose on incident diabetes and regression to normoglycemia in people with coronary heart disease and impaired glucose tolerance: insights from the ACE trial. *Diabetes Care*. 2020;43:2242–2247. doi: 10.2337/dc19-2046
93. Das SR, Everett BM, Birtcher KK, Brown JM, Januzzi JL Jr, Kalyani RR, Kosiborod M, Magwire M, Morris PB, Neumiller JJ, et al. 2020 Expert consensus decision pathway on novel therapies for cardiovascular risk reduction in patients with type 2 diabetes: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2020;76:1117–1145. doi: 10.1016/j.jacc.2020.05.037
94. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, Collins BS, Das SR, Hilliard ME, Isaacs D, et al; American Diabetes Association. 10. Cardiovascular disease and risk management: Standards of Care in Diabetes–2023. *Diabetes Care*. 2023;46:S158–S190. doi: 10.2337/dc23-S010
95. Wong ND, Patao C, Malik S, Iloeje U. Preventable coronary heart disease events from control of cardiovascular risk factors in US adults with diabetes (projections from utilizing the UKPDS risk engine). *Am J Cardiol*. 2014;113:1356–1361. doi: 10.1016/j.amjcard.2013.12.042
96. Centers for Disease Control and Prevention. Prevalence of both diagnosed and undiagnosed diabetes from the National Diabetes Statistics Report. Accessed April 4, 2023. https://cdc.gov/diabetes/data/statistics-report/diagnosed-undiagnosed-diabetes.html
97. Xia PF, Tian YX, Geng TT, Li Y, Tu ZZ, Zhang YB, Guo K, Yang K, Liu G, Pan A. Trends in prevalence and awareness of prediabetes among adults in the U.S., 2005-2020. *Diabetes Care*. 2022;45:e21–e23. doi: 10.2337/dc21-2100
98. Deleted in proof.
99. Nelson AJ, O'Brien EC, Kaltenbach LA, Green JB, Lopes RD, Morse CG, Al-Khalidi HR, Aroda VR, Cavender MA, Gaynor T, et al. Use of lipid-, blood pressure-, and glucose-lowering pharmacotherapy in patients with type 2 diabetes and atherosclerotic cardiovascular disease. *JAMA Netw Open*. 2022;5:e2148030. doi: 10.1001/jamanetworkopen.2021.48030
100. Nanna MG, Kolkailah AA, Page C, Peterson ED, Navar AM. Use of sodium-glucose cotransporter 2 inhibitors and glucagonlike peptide-1 receptor agonists in patients with diabetes and cardiovascular disease in community practice. *JAMA Cardiol*. 2023;8:89–95. doi: 10.1001/jamacardio.2022.3839
101. Devineni D, Akbarpour M, Gong Y, Wong ND. Inadequate use of newer treatments and glycemic control by cardiovascular risk and sociodemographic groups in US adults with diabetes in the NIH Precision Medicine

Initiative *All of Us* Research Program [published online November 15, 2022]. *Cardiovasc Drugs Ther*. doi: 10.1007/s10557-022-07403-2. https://link.springer.com/article/10.1007/s10557-022-07403-2
102. Akbarpour M, Devineni D, Gong Y, Wong ND. Dyslipidemia treatment and lipid control in US adults with diabetes by sociodemographic and cardiovascular risk groups in the NIH Precision Medicine Initiative *All of Us* Research Program. *J Clin Med*. 2023;12:1668. doi: 10.3390/jcm12041668
103. Mannucci E, Gallo M, Giaccari A, Candido R, Pintaudi B, Targher G, Monami M; SID-AMD Joint Panel for Italian Guidelines on Treatment of Type 2 Diabetes. Effects of glucose-lowering agents on cardiovascular and renal outcomes in subjects with type 2 diabetes: an updated meta-analysis of randomized controlled trials with external adjudication of events. *Diabetes Obes Metab*. 2023;25:444–453. doi: 10.1111/dom.14888
104. Goldberg RB, Orchard TJ, Crandall JP, Boyko EJ, Budoff M, Dabelea D, Gadde KM, Knowler WC, Lee CG, Nathan DM, et al; Diabetes Prevention Program Research Group. Effects of long-term metformin and lifestyle interventions on cardiovascular events in the Diabetes Prevention Program and Its Outcome Study. *Circulation*. 2022;145:1632–1641. doi: 10.1161/CIRCULATIONAHA.121.056756
105. Shin H, Schneeweiss S, Glynn RJ, Patorno E. Trends in first-line glucose-lowering drug use in adults with type 2 diabetes in light of emerging evidence for SGLT-2i and GLP-1RA. *Diabetes Care*. 2021;44:1774–1782. doi: 10.2337/dc20-2926
106. Nargesi AA, Jeyashanmugaraja GP, Desai N, Lipska K, Krumholz H, Khera R. Contemporary national patterns of eligibility and use of novel cardioprotective antihyperglycemic agents in type 2 diabetes mellitus. *J Am Heart Assoc*. 2021;10:e021084. doi: 10.1161/JAHA.121.021084
107. Weng W, Tian Y, Kong SX, Ganguly R, Hersloev M, Brett J, Hobbs T. The prevalence of cardiovascular disease and antidiabetes treatment characteristics among a large type 2 diabetes population in the United States. *Endocrinol Diabetes Metab*. 2019;2:e00076. doi: 10.1002/edm2.76
108. Elhussein A, Anderson A, Bancks MP, Coday M, Knowler WC, Peters A, Vaughan EM, Maruthur NM, Clark JM, Pilla S, et al. Racial/ethnic and socioeconomic disparities in the use of newer diabetes medications in the Look AHEAD study. *Lancet Reg Health Am*. 2022;6:100111. doi: 10.1016/j.lana.2021.100111
109. Leino AD, Dorsch MP, Lester CA. Changes in statin use among U.S. adults with diabetes: a population-based analysis of NHANES 2011-2018. *Diabetes Care*. 2020;43:3110–3112. doi: 10.2337/dc20-1481
110. Muntner P, Whelton PK, Woodward M, Carey RM. A comparison of the 2017 American College of Cardiology/American Heart Association blood pressure guideline and the 2017 American Diabetes Association diabetes and hypertension position statement for U.S. adults with diabetes. *Diabetes Care*. 2018;41:2322–2329. doi: 10.2337/dc18-1307
110a. Teo E, Hassan N, Tam W, Koh S. Effectiveness of continuous glucose monitoring in maintaining glycaemic control among people with type 1 diabetes mellitus: a systematic review of randomised controlled trials and meta-analysis. *Diabetologia*. 2022;65:604–619. doi: 10.1007/s00125-021-05648-4
111. Wong ND, Zhao Y, Patel R, Patao C, Malik S, Bertoni AG, Correa A, Folsom AR, Kachroo S, Mukherjee J, et al. Cardiovascular risk factor targets and cardiovascular disease event risk in diabetes: a pooling project of the Atherosclerosis Risk in Communities Study, Multi-Ethnic Study of Atherosclerosis, and Jackson Heart Study. *Diabetes Care*. 2016;39:668–676. doi: 10.2337/dc15-2439
112. Fan W, Song Y, Inzucchi SE, Sperling L, Cannon CP, Arnold SV, Kosiborod M, Wong ND. Composite cardiovascular risk factor target achievement and its predictors in US adults with diabetes: the Diabetes Collaborative Registry. *Diabetes Obes Metab*. 2019;21:1121–1127. doi: 10.1111/dom.13625
113. Andary R, Fan W, Wong ND. Control of cardiovascular risk factors among US adults with type 2 diabetes with and without cardiovascular disease. *Am J Cardiol*. 2019;124:522–527. doi: 10.1016/j.amjcard.2019.05.035
114. Fang M, Selvin E. Thirty-year trends in complications in U.S. adults with newly diagnosed type 2 diabetes. *Diabetes Care*. 2021;44:699–706. doi: 10.2337/dc20-2304
115. Casagrande SS, Aviles-Santa L, Corsino L, Daviglus ML, Gallo LC, Espinoza Giacinto RA, Llabre MM, Reina SA, Savage PJ, Schneiderman N, et al. Hemoglobin A1C, blood pressure, and LDL-cholesterol control among Hispanic/Latino adults with diabetes: results from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). *Endocr Pract*. 2017;23:1232–1253. doi: 10.4158/EP171765.OR
116. Hunt KJ, Davis M, Pearce J, Bian J, Guagliardo MF, Moy E, Axon RN, Neelon B. Geographic and racial/ethnic variation in glycemic control and treatment in a national sample of veterans with diabetes. *Diabetes Care*. 2020;43:2460–2468. doi: 10.2337/dc20-0514
117. Levine DM, Linder JA, Landon BE. The quality of outpatient care delivered to adults in the United States, 2002 to 2013. *JAMA Intern Med*. 2016;176:1778–1790. doi: 10.1001/jamainternmed.2016.6217
118. Malik FS, Stafford JM, Reboussin BA, Klingensmith GJ, Dabelea D, Lawrence JM, Mayer-Davis E, Saydah S, Corathers S, Pihoker C; SEARCH for Diabetes in Youth Study. Receipt of recommended complications and comorbidities screening in youth and young adults with type 1 diabetes: associations with metabolic status and satisfaction with care. *Pediatr Diabetes*. 2020;21:349–357. doi: 10.1111/pedi.12948
119. Kianmehr H, Zhang P, Luo J, Guo J, Pavkov ME, Bullard KM, Gregg EW, Ospina NS, Fonseca V, Shi L, et al. Potential gains in life expectancy associated with achieving treatment goals in US adults with type 2 diabetes. *JAMA Netw Open*. 2022;5:e227705. doi: 10.1001/jamanetworkopen.2022.7705
120. Centers for Disease Control and Prevention and National Center for Health Statistics. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death micro-data files. Accessed April 8, 2023. https://cdc.gov/nchs/nvss/mortality_public_use_data.htm
121. Centers for Disease Control and Prevention and National Center for Health Statistics. Multiple cause of death, CDC WONDER online database. Accessed April 1, 2023. https://wonder.cdc.gov/mcd-icd10.html
122. Xu J, Murphy SL, Kochanek KD, Arias E. Mortality in the United States, 2021. *NCHS Data Brief*. 2022;456:1–8.
123. Cheng YJ, Imperatore G, Geiss LS, Saydah SH, Albright AL, Ali MK, Gregg EW. Trends and disparities in cardiovascular mortality among U.S. adults with and without self-reported diabetes, 1988-2015. *Diabetes Care*. 2018;41:2306–2315. doi: 10.2337/dc18-0831
124. Gregg EW, Cheng YJ, Srinivasan M, Lin J, Geiss LS, Albright AL, Imperatore G. Trends in cause-specific mortality among adults with and without diagnosed diabetes in the USA: an epidemiological analysis of linked national survey and vital statistics data. *Lancet*. 2018;391:2430–2440. doi: 10.1016/S0140-6736(18)30314-3
125. Ramphul K, Joynauth J. An update on the incidence and burden of diabetic ketoacidosis in the U.S. *Diabetes Care*. 2020;43:e196–e197. doi: 10.2337/dc20-1258
126. Ding Q, Funk M, Spatz ES, Lin H, Batten J, Wu E, Whittemore R. Sex-specific impact of diabetes on all-cause mortality among adults with acute myocardial infarction: an updated systematic review and meta-analysis, 1988-2021. *Front Endocrinol (Lausanne)*. 2022;13:918095. doi: 10.3389/fendo.2022.918095
127. Olesen KKW, Gyldenkerne C, Thim T, Thomsen RW, Maeng M. Peripheral artery disease, lower limb revascularization, and amputation in diabetes patients with and without coronary artery disease: a cohort study from the Western Denmark Heart Registry. *BMJ Open Diabetes Res Care*. 2021;9:e001803. doi: 10.1136/bmjdrc-2020-001803
128. Hamilton EJ, Davis WA, Siru R, Baba M, Norman PE, Davis TME. Temporal trends in incident hospitalization for diabetes-related foot ulcer in type 2 diabetes: the Fremantle Diabetes Study. *Diabetes Care*. 2021;44:722–730. doi: 10.2337/dc20-1743
129. Centers for Disease Control and Prevention. United States Diabetes Surveillance System Diabetes Atlas. Accessed March 31, 2023. https://gis.cdc.gov/grasp/diabetes/DiabetesAtlas.html
130. Olafsdottir AF, Svensson AM, Pivodic A, Gudbjornsdottir S, Nystrom T, Wedel H, Rosengren A, Lind M. Excess risk of lower extremity amputations in people with type 1 diabetes compared with the general population: amputations and type 1 diabetes. *BMJ Open Diabetes Res Care*. 2019;7:e000602. doi: 10.1136/bmjdrc-2018-000602
131. Harding JL, Andes LJ, Rolka DB, Imperatore G, Gregg EW, Li Y, Albright A. National and state-level trends in nontraumatic lower-extremity amputation among U.S. Medicare beneficiaries with diabetes, 2000-2017. *Diabetes Care*. 2020;43:2453–2459. doi: 10.2337/dc20-0586
132. Geiss LS, Li Y, Hora I, Albright A, Rolka D, Gregg EW. Resurgence of diabetes-related nontraumatic lower-extremity amputation in the young and middle-aged adult U.S. population. *Diabetes Care*. 2019;42:50–54. doi: 10.2337/dc18-1380
133. Wang SY, Andrews CA, Herman WH, Gardner TW, Stein JD. Incidence and risk factors for developing diabetic retinopathy among youths with type 1 or type 2 diabetes throughout the United States. *Ophthalmology*. 2017;124:424–430. doi: 10.1016/j.ophtha.2016.10.031
134. Hainsworth DP, Bebu I, Aiello LP, Sivitz W, Gubitosi-Klug R, Malone J, White NH, Danis R, Wallia A, Gao X, et al; Complications Trial/Epidemiology of Diabetes I and Complications Research Group. Risk factors for retinopathy in type 1 diabetes: the DCCT/EDIC study. *Diabetes Care*. 2019;42:875–882. doi: 10.2337/dc18-2308
135. Bursell SE, Fonda SJ, Lewis DG, Horton MB. Prevalence of diabetic retinopathy and diabetic macular edema in a primary care-based

teleophthalmology program for American Indians and Alaskan Natives. *PLoS One*. 2018;13:e0198551. doi: 10.1371/journal.pone.0198551
136. Fang M, Echouffo-Tcheugui JB, Selvin E. Burden of complications in U.S. adults with young-onset type 2 or type 1 diabetes. *Diabetes Care*. 2020;43:e47–e49. doi: 10.2337/dc19-2394
137. Arnqvist HJ, Westerlund MC, Fredrikson M, Ludvigsson J, Nordwall M. Impact of HbA1c followed 32 years from diagnosis of type 1 diabetes on development of severe retinopathy and nephropathy: the VISS study. *Diabetes Care*. 2022;45:2675–2682. doi: 10.2337/dc22-0239
138. Wang T, Xi Y, Lubwama R, Hannanchi H, Iglay K, Koro C. Chronic kidney disease among US adults with type 2 diabetes and cardiovascular diseases: a national estimate of prevalence by KDIGO 2012 classification. *Diabetes Metab Syndr*. 2019;13:612–615. doi: 10.1016/j.dsx.2018.11.026
139. Afkarian M, Zelnick LR, Hall YN, Heagerty PJ, Tuttle K, Weiss NS, de Boer IH. Clinical manifestations of kidney disease among US adults with diabetes, 1988-2014. *JAMA*. 2016;316:602–610. doi: 10.1001/jama.2016.10924
140. Cheng HT, Xu X, Lim PS, Hung KY. Worldwide epidemiology of diabetes-related end-stage renal disease, 2000-2015. *Diabetes Care*. 2021;44:89–97. doi: 10.2337/dc20-1913
141. Smidtslund P, Jansson Sigfrids F, Ylinen A, Elonen N, Harjutsalo V, Groop PH, Thorn LM. Prognosis after first-ever myocardial infarction in type 1 diabetes is strongly affected by chronic kidney disease. *Diabetes Care*. 2023;46:197–205. doi: 10.2337/dc22-1586
142. Fan Y, Lau ESH, Wu H, Yang A, Chow E, So WY, Kong APS, Ma RCW, Chan JCN, Luk AOY. Incidence of long-term diabetes complications and mortality in youth-onset type 2 diabetes: a systematic review. *Diabetes Res Clin Pract*. 2022;191:110030. doi: 10.1016/j.diabres.2022.110030
143. Mizokami-Stout KR, Li Z, Foster NC, Shah V, Aleppo G, McGill JB, Pratley R, Toschi E, Ang L, Pop-Busui R; T1D Exchange Clinic Network. The contemporary prevalence of diabetic neuropathy in type 1 diabetes: findings from the T1D Exchange. *Diabetes Care*. 2020;43:806–812. doi: 10.2337/dc19-1583
144. Coles B, Zaccardi F, Ling S, Davies MJ, Samani NJ, Khunti K. Cardiovascular events and mortality in people with and without type 2 diabetes: an observational study in a contemporary multi-ethnic population. *J Diabetes Investig*. 2021;12:1175–1182. doi: 10.1111/jdi.13464
145. Bjornstad P, Drews KL, Caprio S, Gubitosi-Klug R, Nathan DM, Tesfaldet B, Tryggestad J, White NH, Zeitler P; TODAY Study Group. Long-term complications in youth-onset type 2 diabetes. *N Engl J Med*. 2021;385:416–426. doi: 10.1056/NEJMoa2100165
146. Shah AD, Langenberg C, Rapsomaniki E, Denaxas S, Pujades-Rodriguez M, Gale CP, Deanfield J, Smeeth L, Timmis A, Hemingway H. Type 2 diabetes and incidence of cardiovascular diseases: a cohort study in 1.9 million people. *Lancet Diabetes Endocrinol*. 2015;3:105–113. doi: 10.1016/S2213-8587(14)70219-0
147. Kaze AD, Santhanam P, Erqou S, Ahima RS, Bertoni A, Echouffo-Tcheugui JB. Microvascular disease and incident heart failure among individuals with type 2 diabetes mellitus. *J Am Heart Assoc*. 2021;10:e018998. doi: 10.1161/JAHA.120.018998
148. Nanayakkara N, Curtis AJ, Heritier S, Gadowski AM, Pavkov ME, Kenealy T, Owens DR, Thomas RL, Song S, Wong J, et al. Impact of age at type 2 diabetes mellitus diagnosis on mortality and vascular complications: systematic review and meta-analyses. *Diabetologia*. 2021;64:275–287. doi: 10.1007/s00125-020-05319-w
149. Schwab U, Reynolds AN, Sallinen T, Rivellese AA, Riserus U. Dietary fat intakes and cardiovascular disease risk in adults with type 2 diabetes: a systematic review and meta-analysis. *Eur J Nutr*. 2021;60:3355–3363. doi: 10.1007/s00394-021-02507-1
150. Liu L, Simon B, Shi J, Mallhi AK, Eisen HJ. Impact of diabetes mellitus on risk of cardiovascular disease and all-cause mortality: evidence on health outcomes and antidiabetic treatment in United States adults. *World J Diabetes*. 2016;7:449–461. doi: 10.4239/wjd.v7.i18.449
151. Alfredsson J, Green JB, Stevens SR, Reed SD, Armstrong PW, Angelyn Bethel M, Engel SS, McGuire DK, Van de Werf F, Hramiak I, et al; TECOS Study Group. Sex differences in management and outcomes of patients with type 2 diabetes and cardiovascular disease: a report from TECOS. *Diabetes Obes Metab*. 2018;20:2379–2388. doi: 10.1111/dom.13377
152. de Jong M, Woodward M, Peters SAE. Diabetes, glycated hemoglobin, and the risk of myocardial infarction in women and men: a prospective cohort study of the UK Biobank. *Diabetes Care*. 2020;43:2050–2059. doi: 10.2337/dc19-2363
153. Mondesir FL, Brown TM, Muntner P, Durant RW, Carson AP, Safford MM, Levitan EB. Diabetes, diabetes severity, and coronary heart disease risk equivalence: REasons for Geographic and Racial Differences in Stroke (REGARDS). *Am Heart J*. 2016;181:43–51. doi: 10.1016/j.ahj.2016.08.002
154. Bancks MP, Ning H, Allen NB, Bertoni AG, Carnethon MR, Correa A, Echouffo-Tcheugui JB, Lange LA, Lloyd-Jones DM, Wilkins JT. Long-term absolute risk for cardiovascular disease stratified by fasting glucose level. *Diabetes Care*. 2019;42:457–465. doi: 10.2337/dc18-1773
155. Davis WA, Gregg EW, Davis TME. Temporal trends in cardiovascular complications in people with or without type 2 diabetes: the Fremantle Diabetes Study. *J Clin Endocrinol Metab*. 2020;105:dgaa215. doi: 10.1210/clinem/dgaa215
156. Bertoni AG, Kramer H, Watson K, Post WS. Diabetes and clinical and subclinical CVD. *Glob Heart*. 2016;11:337–342. doi: 10.1016/j.gheart.2016.07.005
157. Reis JP, Allen NB, Bancks MP, Carr JJ, Lewis CE, Lima JA, Rana JS, Gidding SS, Schreiner PJ. Duration of diabetes and prediabetes during adulthood and subclinical atherosclerosis and cardiac dysfunction in middle age: the CARDIA study. *Diabetes Care*. 2018;41:731–738. doi: 10.2337/dc17-2233
158. Seyed Ahmadi S, Svensson AM, Pivodic A, Rosengren A, Lind M. Risk of atrial fibrillation in persons with type 2 diabetes and the excess risk in relation to glycaemic control and renal function: a Swedish cohort study. *Cardiovasc Diabetol*. 2020;19:9. doi: 10.1186/s12933-019-0983-1
159. Braffett BH, Bebu I, El Ghormli L, Cowie CC, Sivitz WI, Pop-Busui R, Larkin ME, Gubitosi-Klug RA, Nathan DM, Lachin JM, et al; DCCT/EDIC Research Group. Cardiometabolic risk factors and incident cardiovascular disease events in women vs men with type 1 diabetes. *JAMA Netw Open*. 2022;5:e2230710. doi: 10.1001/jamanetworkopen.2022.30710
160. Davis SN, Duckworth W, Emanuele N, Hayward RA, Wiitala WL, Thottapurathu L, Reda DJ, Reaven PD; Investigators of the Veterans Affairs Diabetes Trial. Effects of severe hypoglycemia on cardiovascular outcomes and death in the Veterans Affairs Diabetes Trial. *Diabetes Care*. 2019;42:157–163. doi: 10.2337/dc18-1144
161. Zinman B, Marso SP, Christiansen E, Calanna S, Rasmussen S, Buse JB; LEADER Publication Committee on behalf of the LEADER Trial Investigators. Hypoglycemia, cardiovascular outcomes, and death: the LEADER experience. *Diabetes Care*. 2018;41:1783–1791. doi: 10.2337/dc17-2677
162. Heller SR, Bergenstal RM, White WB, Kupfer S, Bakris GL, Cushman WC, Mehta CR, Nissen SE, Wilson CA, Zannad F, et al; EXAMINE Investigators. Relationship of glycated haemoglobin and reported hypoglycaemia to cardiovascular outcomes in patients with type 2 diabetes and recent acute coronary syndrome events: the EXAMINE trial. *Diabetes Obes Metab*. 2017;19:664–671. doi: 10.1111/dom.12871
163. Lee AK, Warren B, Lee CJ, McEvoy JW, Matsushita K, Huang ES, Sharrett AR, Coresh J, Selvin E. The association of severe hypoglycemia with incident cardiovascular events and mortality in adults with type 2 diabetes. *Diabetes Care*. 2018;41:104–111. doi: 10.2337/dc17-1669
164. Echouffo-Tcheugui JB, Daya N, Lee AK, Tang O, Ndumele CE, Windham BG, Shah AM, Selvin E. Severe hypoglycemia, cardiac structure and function, and risk of cardiovascular events among older adults with diabetes. *Diabetes Care*. 2021;44:248–254. doi: 10.2337/dc20-0552
165. Rana JS, Moffet HH, Liu JY, Karter AJ. Severe hypoglycemia and risk of atherosclerotic cardiovascular disease in patients with diabetes. *Diabetes Care*. 2021;44:e40–e41. doi: 10.2337/dc20-2798
166. McCoy RG, Herrin J, Lipska KJ, Shah ND. Recurrent hospitalizations for severe hypoglycemia and hyperglycemia among U.S. adults with diabetes. *J Diabetes Complications*. 2018;32:693–701. doi: 10.1016/j.jdiacomp.2018.04.007
167. Echouffo-Tcheugui JB, Kaze AD, Fonarow GC, Dagogo-Jack S. Severe hypoglycemia and incident heart failure among adults with type 2 diabetes. *J Clin Endocrinol Metab*. 2022;107:e955–e962. doi: 10.1210/clinem/dgab794
168. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, Northwell COVID-19 Research Consortium, Barnaby DP, Becker LB, Chelico JD, Cohen SL, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA*. 2020;323:2052–2059. doi: 10.1001/jama.2020.6775
169. Cummings MJ, Baldwin MR, Abrams D, Jacobson SD, Meyer BJ, Balough EM, Aaron JG, Claassen J, Rabbani LE, Hastie J, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. *Lancet*. 2020;395:1763–1770. doi: 10.1016/S0140-6736(20)31189-2

170. Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, Tobin KA, Cerfolio RJ, Francois F, Horwitz LI. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. *BMJ*. 2020;369:m1966. doi: 10.1136/bmj.m1966
171. Myers LC, Parodi SM, Escobar GJ, Liu VX. Characteristics of hospitalized adults with COVID-19 in an integrated health care system in California. *JAMA*. 2020;323:2195–2198. doi: 10.1001/jama.2020.7202
172. Czeisler ME, Barrett CE, Siegel KR, Weaver MD, Czeisler CA, Rajaratnam SMW, Howard ME, Bullard KM. Health care access and use among adults with diabetes during the COVID-19 pandemic: United States, February-March 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70:1597–1602. doi: 10.15585/mmwr.mm7046a2
173. Kastora S, Patel M, Carter B, Delibegovic M, Myint PK. Impact of diabetes on COVID-19 mortality and hospital outcomes from a global perspective: an umbrella systematic review and meta-analysis. *Endocrinol Diabetes Metab*. 2022;5:e00338. doi: 10.1002/edm2.338
174. Gregory JM, Slaughter JC, Duffus SH, Smith TJ, LeStourgeon LM, Jaser SS, McCoy AB, Luther JM, Giovannetti ER, Boeder S, et al. COVID-19 severity is tripled in the diabetes community: a prospective analysis of the pandemic's impact in type 1 and type 2 diabetes. *Diabetes Care*. 2021;44:526–532. doi: 10.2337/dc20-2260
175. Seiglie J, Platt J, Cromer SJ, Bunda B, Foulkes AS, Bassett IV, Hsu J, Meigs JB, Leong A, Putman MS, et al. Diabetes as a risk factor for poor early outcomes in patients hospitalized with COVID-19. *Diabetes Care*. 2020;43:2938–2944. doi: 10.2337/dc20-1506
176. Barron E, Bakhai C, Kar P, Weaver A, Bradley D, Ismail H, Knighton P, Holman N, Khunti K, Sattar N, et al. Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study. *Lancet Diabetes Endocrinol*. 2020;8:813–822. doi: 10.1016/S2213-8587(20)30272-2
177. Dennis JM, Mateen BA, Sonabend R, Thomas NJ, Patel KA, Hattersley AT, Denaxas S, McGovern AP, Vollmer SJ. Type 2 diabetes and COVID-19-related mortality in the critical care setting: a national cohort study in England, March-July 2020. *Diabetes Care*. 2021;44:50–57. doi: 10.2337/dc20-1444
178. Benoit SR, Hora I, Pasquel FJ, Gregg EW, Albright AL, Imperatore G. Trends in emergency department visits and inpatient admissions for hyperglycemic crises in adults with diabetes in the U.S., 2006-2015. *Diabetes Care*. 2020;43:1057–1064. doi: 10.2337/dc19-2449
179. Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project (HCUP). Accessed April 1, 2023. http://hcupnet.ahrq.gov/
180. Collins J, Abbass IM, Harvey R, Suehs B, Uribe C, Bouchard J, Prewitt T, DeLuzio T, Allen E. Predictors of all-cause-30-day-readmission among Medicare patients with type 2 diabetes. *Curr Med Res Opin*. 2017;33:1517–1523. doi: 10.1080/03007995.2017.1330258
181. McCoy RG, Lipska KJ, Herrin J, Jeffery MM, Krumholz HM, Shah ND. Hospital readmissions among commercially insured and Medicare Advantage beneficiaries with diabetes and the impact of severe hypoglycemic and hyperglycemic events. *J Gen Intern Med*. 2017;32:1097–1105. doi: 10.1007/s11606-017-4095-x
182. Rodriguez-Gutierrez R, Herrin J, Lipska KJ, Montori VM, Shah ND, McCoy RG. Racial and ethnic differences in 30-day hospital readmissions among US adults with diabetes. *JAMA Netw Open*. 2019;2:e1913249. doi: 10.1001/jamanetworkopen.2019.13249
183. Zhou X, Shrestha SS, Shao H, Zhang P. Factors contributing to the rising national cost of glucose-lowering medicines for diabetes during 2005-2007 and 2015-2017. *Diabetes Care*. 2020;43:2396–2402. doi: 10.2337/dc19-2273
184. Hernandez I, San-Juan-Rodriguez A, Good CB, Gellad WF. Changes in list prices, net prices, and discounts for branded drugs in the US, 2007-2018. *JAMA*. 2020;323:854–862. doi: 10.1001/jama.2020.1012
185. McCoy RG, Van Houten HK, Deng Y, Mandic PK, Ross JS, Montori VM, Shah ND. Comparison of diabetes medications used by adults with commercial insurance vs Medicare Advantage, 2016 to 2019. *JAMA Netw Open*. 2021;4:e2035792. doi: 10.1001/jamanetworkopen.2020.35792
186. Dieleman JL, Cao J, Chapin A, Chen C, Li Z, Liu A, Horst C, Kaldjian A, Matyasz T, Scott KW, et al. US health care spending by payer and health condition, 1996-2016. *JAMA*. 2020;323:863–884. doi: 10.1001/jama.2020.0734
187. American Diabetes Association. Economic costs of diabetes in the U.S. in 2017. *Diabetes Care*. 2018;41:917–928. doi: 10.2337/dci18-0007
188. Joo H, Zhang P, Wang G. Cost of informal care for patients with cardiovascular disease or diabetes: current evidence and research challenges. *Qual Life Res*. 2017;26:1379–1386. doi: 10.1007/s11136-016-1478-0
189. Shrestha SS, Zhang P, Hora IA, Gregg EW. Trajectory of excess medical expenditures 10 years before and after diabetes diagnosis among U.S. adults aged 25-64 years, 2001-2013. *Diabetes Care*. 2019;42:62–68. doi: 10.2337/dc17-2683
190. Shrestha SS, Zhang P, Hora I, Geiss LS, Luman ET, Gregg EW. Factors contributing to increases in diabetes-related preventable hospitalization costs among U.S. adults during 2001-2014. *Diabetes Care*. 2019;42:77–84. doi: 10.2337/dc18-1078
191. Rubens M, Saxena A, Ramamoorthy V, Khera R, Hong J, Veledar E, Nasir K. Trends in diabetes-related preventable hospitalizations in the U.S., 2005-2014. *Diabetes Care*. 2018;41:e72–e73. doi: 10.2337/dc17-1942
192. Einarson TR, Acs A, Ludwig C, Panton UH. Economic burden of cardiovascular disease in type 2 diabetes: a systematic review. *Value Health*. 2018;21:881–890. doi: 10.1016/j.jval.2017.12.019
193. Global Burden of Disease Study and Institute for Health Metrics and Evaluation. University of Washington. Accessed August 2, 2023. http://ghdx.healthdata.org/
194. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, Stein C, Basit A, Chan JCN, Mbanya JC, et al. IDF Diabetes Atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res Clin Pract*. 2022;183:109119. doi: 10.1016/j.diabres.2021.109119
195. Saeedi P, Salpea P, Karuranga S, Petersohn I, Malanda B, Gregg EW, Unwin N, Wild SH, Williams R. Mortality attributable to diabetes in 20-79 years old adults, 2019 estimates: results from the International Diabetes Federation Diabetes Atlas, 9(th) edition. *Diabetes Res Clin Pract*. 2020;162:108086. doi: 10.1016/j.diabres.2020.108086
196. Bommer C, Sagalova V, Heesemann E, Manne-Goehler J, Atun R, Barnighausen T, Davies J, Vollmer S. Global economic burden of diabetes in adults: projections from 2015 to 2030. *Diabetes Care*. 2018;41:963–970. doi: 10.2337/dc17-1962
197. Stierman B, Afful J, Carroll M, Chen T, Davy O, Fink S, Fryar C, Gu Q, Hales C, Hughes J, et al. National Health and Nutrition Examination Survey 2017-March 2020 prepandemic data files: development of files and prevalence estimates for selected health outcomes. 2021. Accessed xxxx. https://stacks.cdc.gov/view/cdc/106273
198. Centers for Disease Control and Prevention and National Center for Health Statistics. National Health Interview Survey: public-use data files and documentation. Accessed March 15, 2023. https://cdc.gov/nchs/nhis/index.htm

# 10. METABOLIC SYNDROME

*See Charts 10-1 through 10-7*

Click here to return to the Table of Contents
Click here to return to the Abbreviations

## Definition

- MetS is a multicomponent risk factor for CVD and type 2 diabetes that reflects the clustering of individual cardiometabolic risk factors related to abdominal obesity and insulin resistance. MetS is a useful entity for communicating the nature of lifestyle-related cardiometabolic risk to both patients and clinicians. Although multiple definitions for MetS have been proposed, the IDF, NHLBI, AHA, and others recommended a harmonized definition for MetS based on the presence of any 3 of the following 5 risk factors[1]:
  - FPG ≥100 mg/dL or undergoing drug treatment for elevated glucose
  - HDL-C <40 mg/dL in males or <50 mg/dL in females or undergoing drug treatment for reduced HDL-C
  - Triglycerides ≥150 mg/dL or undergoing drug treatment for elevated triglycerides
  - WC >102 cm in males or >88 cm in females for people of most ancestries living in the United States. Ethnicity- and country-specific thresholds can be used for diagnosis in other groups, particularly Asian individuals and individuals of non-European ancestry who have resided predominantly outside the United States. Current recommendations for WC cut points also may overestimate MetS in US Hispanic/Latina females.[2]
  - SBP ≥130 mm Hg or DBP ≥85 mm Hg or undergoing drug treatment for hypertension or antihypertensive drug treatment in a patient with a history of hypertension
- Several adverse health conditions are related to MetS but are not part of its clinical definition. These include NAFLD, sexual/reproductive dysfunction (erectile dysfunction in males and polycystic ovarian syndrome in females), OSA, certain forms of cancer, and possibly osteoarthritis, as well as a general proinflammatory and prothrombotic state.[3]
- Type 2 diabetes, defined as FPG ≥126 mg/dL, random or 2-hour postchallenge glucose ≥200 mg/dL, HbA1c ≥6.5%, or taking hypoglycemic medication, is a separate clinical diagnosis distinct from MetS; however, many individuals with type 2 diabetes also have MetS.

## Prevalence

### *Youths*

*(See Chart 10-1)*

- In NHANES 1999 to 2014, the prevalence of MetS in adolescents 12 to 19 years of age in the United States varied by geographic region and was higher in adolescent males than females across all regions (Chart 10-1). According to data from NHANES 2011 to 2016, the prevalence of MetS according to the IDF definition in adolescents 12 to 19 years of age was estimated to be 4.24% (95% CI, 2.49%–5.99%) overall, 6.04% (95% CI, 2.92%–9.16%) in adolescent males, and 2.28% (95% CI, 2.08%–3.48%) in adolescent females.[4]
- According to data from NHANES 1999 to 2018, the prevalence of MetS among youths 12 to 19 years of age was 4.34% (95% CI, 3.33%–5.65%) for NH White, 3.66% (95% CI, 2.67%–4.99%) for NH Black, 7.70% (95% CI, 6.32%–9.36%) for Mexican American, 4.84% (95% CI, 2.89%–7.99%) for other Hispanic, and 1.84% (95% CI, 0.89%–3.76%) for other youths.[5]
- In HCHS/SOL Youth, the prevalence of MetS among children 10 to 15 years of age varied according to the clinical definition used from 0% (WHO) to 4.7% (95% CI, 1.7%–7.6%; ATP-III) for females and from 0.5% (95% CI, 0%–1.2%; WHO) to 2.4% (95% CI, 0.9%–3.9%; ATP-III) for males. Among children 16 years of age, the prevalence of MetS ranged from 0% (WHO) to 7.3% (95% CI, 0–17.8%; ATP-III) for females and from 0% (WHO) to 2.8% (95% CI, 0–6.7%; IDF) for males. Only 1 participant of 1137 was classified as having MetS by all 3 clinical definitions (ATP-III, IDF, and WHO).[6]
- The definition of the obesity component of MetS is uncertain in the pediatric population because it is age dependent. Therefore, the use of BMI percentiles[7] and waist-height ratio[8] has been recommended. When CDC and FitnessGram standards are used for pediatric obesity, the prevalence of MetS in youths with obesity ranges from 19% to 35%.[7]

The 2024 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2024. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

- The prevalence of MetS varied by parental educational attainment, level of family income, and household food security status. For example, the prevalence of MetS among youths 12 to 19 years of age was 6.53% (95% CI, 4.89%–8.69%) for parental education of less than high school and 2.51% (95% CI, 1.39%–4.50%) for parental education of college degree or above according to data from NHANES 1999 to 2018.[5]
- The prevalence of MetS significantly differed by BMI category according to data from NHANES 1999 to 2018. The prevalence of MetS was 0.18% (95% CI, 0.05%–0.62%) for children with underweight and normal weight, 2.56% (95% CI, 1.65%–3.96%) for children with overweight, and 20.1% (95% CI, 17.0%–23.6%) for children with obesity.[5]

### *Adults*

#### *(See Chart 10-2)*

The following estimates include many who also have diabetes, in addition to those with MetS without diabetes:

- In NHANES 2011 to 2016, the overall prevalence of MetS was 34.7% (95% CI, 33.1%–36.3%) and was similar for males (35.1% [95% CI, 32.9%–37.3%]) and females (34.3% [95% CI, 32.7%–36.0%]).[9] The prevalence of MetS was higher with older age, from 19.5% (95% CI, 17.8%–21.4%) among people 20 to 39 years of age to 39.4% (95% CI, 37.2%–41.7%) for people 40 to 59 years of age and 48.6% (95% CI, 46.0%–51.2%) among people ≥60 years of age.
- In 2017 to 2018, Mexican American adults generally had the highest prevalence of MetS at 52.2% (95% CI, 47.0%–54.2%), whereas NH White adults had 46.6% (95% CI, 42.9%–50.2%), NH Black adults had 47.6% (95% CI, 44.7%–50.5%), other Hispanic adults had 45.9% (95% CI, 41.9%–50.0%), and Asian/other including multiracial adults had 46.7% (95% CI, 41.9%–51.4%) prevalence.[10]
- In 2017 to 2018, the prevalence of MetS was the lowest among adults who were college graduates or above at 39.3% (95% CI, 34.9%–43.6%).[10] In contrast, adults with lower educational attainment had a higher prevalence of MetS at 49.1% (95% CI, 44.7%–53.6%) for those less than high school graduates, 51.9% (95% CI, 47.5%–56.2%) for those who were high school graduates, and 50.2% (95% CI, 46.9%–53.4%) for those with some college.
- In 2017 to 2018, adults with a higher family income (ratio of family income to the FPL≥3.0) had a lower prevalence of MetS at 44.2% (95% CI, 40.9%–47.6%) compared with those with lower family income (ratio <1.30) with a prevalence of MetS at 50.6% (95% CI, 47.0%–54.2%).[10]
- In a meta-analysis of 26 609 young adults (18–30 years of age) across 34 studies, the prevalence of MetS was 4.8% to 7.0%, depending on the definition used including harmonized, IDF, National Cholesterol Education Program–ATP II, and AHA/NHBLI.[11]
- The age-standardized prevalence of MetS by age and sex from 2008 to 2011 in Hispanic/Latino people in HCHS/SOL is shown in Chart 10-2.[12]
- Among Black people in the JHS, the overall prevalence of MetS was 34%, and it was higher in females than in males (40% versus 27%, respectively).[13]
- The prevalence of MetS has been noted to be higher in individuals with certain conditions, including schizophrenia spectrum disorders[14] and bipolar disorder[15]; prior solid organ transplantations[16]; prior hematopoietic cell transplantation[17,18]; HIV infection[19]; chronic obstructive pulmonary disease[20]; prior treatment for blood cancers[18,21]; systemic inflammatory disorders such as psoriasis,[22,23] systemic lupus erythematosus,[24] ankylosing spondylitis,[25] and rheumatoid arthritis[26,27]; multiple sclerosis[28]; type 1 diabetes[29,30]; latent autoimmune diabetes in adults[30]; prior gestational diabetes[31]; prior pregnancy-induced hypertension[32]; acne keloidalis nuchae[33]; periodontitis[34,35]; gallstones[36]; cerebral palsy[37]; war-related bilateral lower-limb amputation[38] or spinal cord injury[39] in veterans; and chronic opiate dependence,[40] as well as in individuals in select professions, including law enforcement,[41] commercial truck driving,[42] and firefighting.[43]

## Secular Trends

### *Youths*

#### *(See Chart 10-3)*

- A recent NHANES analysis from 1999 to 2018 among youths 12 to 19 years of age reported that the prevalence of MetS remained stable at 4.36% (95% CI, 3.65%–5.20%) over the study period (Chart 10-3).[5]

### *Adults*

#### *(See Charts 10-4 and 10-5)*

- Secular trends in MetS differ according to the definition used, including the harmonized MetS and ATP III criteria.[44–46] Chart 10-4 demonstrates trends using the harmonized MetS criteria between NHANES 2009 to 2010 and 2017 to 2018; Chart 10-5 demonstrates trends using ATP III criteria in NHANES 2007 to 2014.
- According to data from NHANES 1999 to 2018, the overall MetS prevalence (according to the AHA/NHLBI definition) increased from 36.2% (95% CI, 33.2%–39.1%) to 47.3% (95% CI, 45.3%–49.3%; $P_{trend}$<0.001).[10]

## Risk Factors

### Youths

- In the PREMA study, independent predictors of MetS from childhood to adolescence were LBW, small head circumference, and a parent with overweight or obesity.[47] When all 3 of these predictors were present, the sensitivity and specificity of identifying MetS were 91% and 98%, respectively, in both the derivation and validation cohorts.
- In an RCT of health care worker assistance to promote longer duration of exclusive breastfeeding in mother-child pairs, the risk of childhood MetS after 11.5 years of follow-up was increased among males who received longer breastfeeding (OR, 1.49 [95% CI, 1.01–2.22]) but not females who received longer breastfeeding (OR, 0.94 [95% CI, 0.63–1.42]) compared with control groups.[48]
- In a single-center retrospective case-control study among children and adolescents <18 years of age, bipolar disorder was associated with prevalent MetS compared with healthy controls (OR, 2.33 [95% CI, 1.37–4.0]).[49]
- Obesity and weight gain among children with obesity have been identified as important risk factors for MetS among youths.[50]

### Respiratory Exposures

- In NHANES 2007 to 2010, higher exposure to secondhand smoke was associated with prevalent MetS (OR, 5.4 [95% CI, 1.7–16.9]) among adolescents 12 to 19 years of age. In addition, higher secondhand smoke exposure interacted with low exposure to certain nutrients (vitamin E and omega-3 PUFAs) to increase the odds of MetS.[51]
- Among 9897 children and adolescents 10 to 18 years of age in China, long-term exposure to ambient air pollution (eg, PM2.5, fine particulate matter <10-μm diameter, and $NO_2$) was positively associated with the prevalence of MetS. For every 10–μg/$m^3$ increase in PM2.5, fine particulate matter <10-μm diameter, and $NO_2$, the odds of MetS increased by 31% (OR, 1.31 [95% CI, 1.05–1.64]), 32% (OR, 1.32 [95% CI, 1.08–1.62]), and 33% (OR, 1.33 [95% CI, 1.03–1.72]), respectively.[52]

### Diet and PA

- Daily intake of added sugar >186 g/d was associated with prevalent MetS (OR, 8.4 [95% CI, 4.7–12.1]) among adolescents 12 to 19 years of age in NHANES 2005 to 2012.[53] Higher consumption of ultraprocessed foods was associated with prevalent MetS. A study using data from NHANES 2009 to 2014 reported that a 10% increase in dietary contribution of ultraprocessed foods was associated with a 4% prevalence of MetS increase (PR, 1.04 [95% CI, 1.02–1.07]).[54] Furthermore, compared with ultraprocessed food contribution <40%, the dietary contribution of ultraprocessed foods >71% was associated with a 28% higher prevalence of MetS (PR, 1.28 [95% CI, 1.09–1.50]).
- Among 6009 children and adolescents 9 to 18 years of age with objectively measured accelerometer data from the International Children's Accelerometry Database, higher total PA and moderate to vigorous PA were inversely associated with prevalent MetS according to the IDF definition.[55] The odds of MetS decreased by 17% (OR, 0.83 [95% CI, 0.76–0.91]) for every 100–count/min increase in total PA and by 9% (OR, 0.91 [95% CI, 0.84–0.99]) for every 10-minute increase in moderate to vigorous PA independently of sedentary time.

### Serum Biomarkers

- Among Chinese adolescents 12 to 16 years of age, aspartate aminotransferase/alanine aminotransferase ratio was inversely associated with prevalent MetS. Students in the lowest tertile of aspartate aminotransferase/alanine aminotransferase ratio had a 6-fold higher odds of MetS compared with those in the highest tertile (aOR, 6.02 [95% CI, 1.93–18.76]).[56] In addition, a lower ratio of insulin-like growth factor 1 to insulin-like growth factor binding protein 3 was an independent risk factor for prevalent MetS (OR, 2.35 [95% CI, 1.04–5.30]) in Chinese adolescents 12 to 16 years of age. Lower baseline ratio of insulin-like growth factor 1 to insulin-like growth factor binding protein 3 in adolescence was an independent risk factor for MetS in adulthood (OR, 10.72 [95% CI, 1.03–11.40]).[57]
- In ERICA, a cross-sectional multicenter study of Brazilian adolescents 12 to 17 years of age, serum adiponectin levels were inversely associated with MetS *z* score (β=–0.40 [95% CI, –0.66 to –0.14]; *P*=0.005).[58] Total serum adiponectin, but not high-molecular-weight adiponectin, was inversely associated with MetS according to modified WHO criteria in Mexican children 8 to 11 years of age.[59]

## Incident MetS

### Diet

- Dietary habits are directly associated with incident MetS, including a Western dietary pattern,[60] high inflammatory diet pattern,[61–63] and consumption or intake of soft drinks,[64] energy-dense beverages,[65] SSBs,[66] fructose,[67] carbohydrates,[68] total fat,[69] meats (total, red, and processed but not white meat),[70,71] and fried foods.[72]
- Subjects in the highest versus lowest quintile of an unhealthful plant-based diet index, a composite measure of a diet with a higher intake of refined grains, potatoes, SSBs, sweets, and salty food and

lower intake of whole grains, fruits, vegetables, nuts, legumes, tea, and coffee, had a 50% higher risk of developing incident MetS.[73]
- Restrained and emotional eating behaviors[74] and a problematic relationship with eating and food[75] are risk factors for incident MetS.
- Dietary habits are also inversely associated with incident MetS, including alcohol use,[76] fiber intake,[77] Mediterranean diet,[78–80] fruit consumption (≥4 servings/d versus <1 serving/d),[81] dairy consumption (particularly yogurt and low-fat dairy products),[82,83] consumption of animal or fat protein,[84] coffee consumption,[61,62,85,86] vitamin D intake,[87] intake of tree nuts,[88] walnut intake,[89] and intake of long-chain omega-3 PUFAs.[90]

### Physical Activity

- In a meta-analysis that included 76 699 participants and 13 871 incident cases of MetS, there was a negative linear relationship between leisure-time PA and the development of MetS.[91] For every increase of 10 MET-h/wk (equal to ≈150 minutes of moderate PA per week), the risk of MetS was reduced by 10% (RR, 0.90 [95% CI, 0.86–0.94]).
- The following factors have been reported as being inversely associated with incident MetS, defined by 1 of the major definitions, in prospective or retrospective cohort studies: increased PA or physical fitness,[92] aerobic or resistance training,[93] and cardiorespiratory fitness (eg, maximal oxygen uptake).[94]
- Each 1000–steps/d increase is associated with lower odds of having MetS (OR, 0.90 [95% CI, 0.83–0.98]) in American males.[95] The long-term meeting of step-based guidelines or an increase in daily steps was associated with reduced risk of MetS from 39% to 12% over 7 years of follow-up among older European females.[96]

### Sleep

- The association between sleep duration and incident MetS appears U shaped, but compared with normal sleep duration (7–8 hours), only short duration of sleep was significantly associated with an increased risk of incident MetS (OR, 1.28 [95% CI, 1.07–1.53]); a long duration of sleep was not.[97]

### Blood Biomarkers

- In Chinese adults, increased high-sensitivity CRP levels were associated with a higher risk of MetS in females (OR, 4.82 [95% CI, 1.89–12.3] for highest versus lowest quartile) but not in males (OR, 3.15 [95% CI, 0.82–12.1]).[98]
- Blood biomarkers that are inversely associated with incident MetS include insulin sensitivity,[99] adiponectin,[100] total testosterone,[99,101] serum 25-hydroxyvitamin D,[102–106] total and indirect bilirubin,[107] follicle-stimulating hormone in postmenopausal females,[108] and sex hormone–binding globulin.[99,101]

### Other

- Risk factors for incident MetS include age,[109] smoking,[110,111] childhood MetS,[112] childhood cancer,[113] obesity or high BMI,[114] weight gain,[115] and weight fluctuation.[116]
- There is a bidirectional association between MetS and depression. In prospective studies, baseline depression increased the risk of MetS (OR, 1.49 [95% CI, 1.19–1.87]), and baseline MetS increased the risk of depression (OR, 1.52 [95% CI, 1.20–1.91]).[117] Furthermore, individuals with depression in America were at higher odds of MetS than those in Europe (OR, 1.46 [95% CI, 1.16–1.84]).[118]
- There is also a bidirectional association between MetS and osteoarthritis. In a meta-analysis, osteoarthritis increased the odds of incident MetS in females (OR, 2.34 [95% CI, 1.54–3.56]) but not in males (OR, 0.86 [95% CI, 0.61–1.16]), and MetS increased the odds of incident osteoarthritis for both males and females (pooled OR, 1.45 [95% CI, 1.27–1.66]).[119]
- In a meta-analysis, perinatal factors, including LBW (pooled OR, 1.79 [95% CI, 1.39–2.31]) and PTB (pooled OR, 1.72 [95% CI, 1.12–2.65]), were associated with incident MetS.[120]
- Among perimenopausal females (mean age, 55±5.4 years), >12 months of breastfeeding significantly reduced the odds of incident MetS in midlife (aOR, 0.76 [95% CI, 0.60–0.95]).[121]
- In a pooled population of 117 020 patients from 20 studies who were followed up for a median of 5 years (range, 3–14.7 years), NAFLD was associated with an increased risk of incident MetS when alanine aminotransferase (RR, 1.80 [95% CI, 1.72–1.89] for highest versus lowest quartile or quintile), γ-glutamyltransferase (RR, 1.98 [95% CI, 1.89–2.07] for highest versus lowest quartile or quintile), or ultrasonography (RR, 3.22 [95% CI, 3.05–3.41]) was used to assess NAFLD.[122]

## Prevalent MetS

### Diet

- In cross-sectional studies, prevalent MetS was directly associated with a high-salt diet,[123] white rice consumption,[124] a high DII score,[125,126] high dietary acid load,[127] high insulin load or insulin index diet,[128] a long-chain food supply (compared with a short-chain food supply),[129] excessive dietary calcium (>1200 mg/d) in males,[130] and inadequate energy intake among patients undergoing dialysis.[131]
- Prevalent MetS is inversely associated with total antioxidant capacity from diet and dietary supplements,[132] animal-based oils such as butter and ghee,[133] organic food consumption,[134] and Mediterranean–DASH Intervention for Neurodegenerative Delay diet, identified as a new

dietary pattern of the combination of Mediterranean and DASH diets.[135]

### Physical Activity

- In cross-sectional studies, a higher prevalence of MetS is associated with lower cardiorespiratory fitness[103,136] and lower levels of PA.[137,138] MetS is lower with "weekend warrior" and regular PA patterns,[139] any length of moderate- to vigorous-intensity PA,[138] and greater handgrip strength.[140–142]
- The relationship between PA and MetS may be moderated by lean muscle mass in males. Males and females with higher lean muscle mass had lower risk of MetS, regardless of PA. However, males with low lean muscle mass exhibited a U-shaped relationship between vigorous PA and MetS risk (0 h/wk versus 4–8 h/wk: aOR, 2.1 [95% CI, 1.1–4.3]; >12 h/wk versus 4–8 h/wk: aOR, 4.3 [95% CI, 1.7–11.0]). No interaction between lean muscle mass and PA was seen in females.[143]

### Sleep

- Associations between sleep duration and prevalent MetS were U shaped. Compared with normal sleep duration (7–8 hours), short durations of sleep were significantly associated with higher rates of prevalent MetS (OR, 1.36 [95% CI, 1.04–1.78] for <5 hours and 1.09 [95% CI, 1.01–1.16] for <6 hours), as were long durations of sleep (OR, 1.11 [95% CI, 1.02–1.21] for >9 hours and 1.31 [95% CI, 1.22–1.40] for >10 hours).[97]
- In data from 8272 adults in China, there was a U-shaped relationship between sleep duration and MetS. Sleep duration <6 or >9 hours was associated with higher risk of MetS (OR ranged from 1.10–2.15).[144]

### Blood Biomarkers

- Blood biomarkers directly associated with prevalent MetS include proinflammatory cytokines such as interleukin-6 and tumor necrosis factor-α[145]; retinol binding protein 4[146]; cancer antigen 19-9[136,147]; serum liver chemistries, including alanine transaminase,[148] aspartate transaminase, alanine transaminase/aspartate transaminase ratio, alkaline phosphatase, and γ-glutamyl transferase[149]; serum vitamin levels,[150] including retinol and α-tocopherol; serum thyrotropin in individuals with euthyroidism[151]; and erythrocyte parameters[152] such as hemoglobin level and red blood cell distribution width. For example, participants with elevated serum CA 19-9 (≥37 U/mL) had an increased risk of prevalent MetS compared with those with serum CA 19-9 <37 U/mL (multivariable aOR, 2.10 [95% CI, 1.21–3.65]).[147]
- In cross-sectional studies, prevalent MetS is inversely associated with anti-inflammatory cytokines (interleukin-10),[145] ghrelin,[145] adiponectin,[145] and antioxidant factors (paraoxonase-1).[145]

### Other

- Prevalent MetS is also directly associated with elevated urine sodium[153] and high heavy metal exposure.[154]
- In cross-sectional studies, prevalent MetS is inversely associated with the ratio of muscle mass to visceral fat in college students,[155] vacation frequency,[156] and marijuana use.[157]
- A systematic review and meta-analysis found that adults in psychological high-stress groups had a higher chance of having MetS than those in the low-stress group (OR, 1.45 [95% CI, 1.21–1.74]).[158] Occupational stress showed the strongest association with MetS (OR, 1.69 [95% CI, 1.18–2.42]), whereas perceived general stress showed the weakest association (OR, 1.22 [95% CI, 1.02–1.46]).
- In Korea NHANES 2013 to 2017, among 24 695 participants, a higher density of physicians (2.71 per 1000 population versus 2.64 per 1000 population) was significantly associated with a lower prevalence of MetS (OR, 0.86 [95% CI, 0.76–0.98]).[159]

## Social Determinants of Health/Health Equity

- Prior studies have reported higher MetS incidence among individuals with lower educational attainment, lower SES,[160] more experiences of everyday discrimination,[161] and long-term work stress. In HCHS/SOL, SES was inversely associated with prevalent MetS among Hispanic/Latino adults of diverse ancestry groups.[162] Higher versus lower income, higher versus lower education level, and full-time employment status versus unemployed status were associated with a 4%, 3%, and 24% decreased odds of having MetS, respectively. The association between income was significant only among females and those with current health insurance.
- In NHANES 2007 to 2014, females in households with low and very low food security were at increased risk for prevalent MetS compared with females in households with full food security (OR, 1.43 [95% CI, 1.13–1.80] and 1.71 [95% CI, 1.31–2.24], respectively).[163]
- In the HELENA study among 1037 European adolescents 12.5 to 17.5 years of age, those with mothers with low education showed a higher MetS risk (β estimate, 0.54 [95% CI, 0.09–0.98]) compared with those with highly educated mothers. Adolescents who accumulated >3 disadvantages (defined as parents with low education, low family affluence, migrant origin, unemployed parents, or nontraditional families) had a higher MetS risk score compared with those who did not experience disadvantage (β estimate, 0.69 [95% CI, 0.08–1.31]).[164]
- Using data from the Korean National Health and Nutrition Examination Survey (2016–2018), a

study reported that high SES was inversely associated with the prevalence of MetS after adjustment for covariates (OR, 0.67 [95% CI, 0.50–0.89]).[165]
- Similar findings were reported around the world on the association of socioeconomic inequalities with MetS.[166–168] In a Spanish working population, the prevalence of MetS by ATP III criteria among males was 8.01% for social class I (highest), 8.72% for social class II, and 9.82% for social class III (lowest; $P$=0.004); the values among females were 1.35%, 3.85%, and 4.6%, respectively. Individuals with no education or primary school education in the French West Indies had a higher risk of MetS (OR, 2.4 [95% CI, 1.3–4.4]) compared with those having equivalent to high school or higher than high school education.[167]

## Subclinical Disease

- In the ARIC study (1987–1998), 76% of ARIC participants had an increase in their sex- and race and ethnicity–specific MetS severity score over a mean 10-year follow-up, with faster progression observed in younger participants and in females.[169]
- Isolated MetS, which could be considered an early form of overt MetS, has been defined as ≥3 MetS components but without overt hypertension and diabetes. In a population-based random sample of 2042 residents of Olmsted County, Minnesota, those with isolated MetS compared with healthy control subjects had a higher incidence of hypertension (34% versus 14%; $P$<0.001) and diabetes (12% versus 1%; $P$<0.001).[170]

## Genetics and Family History

### *(See also Chapter 6 [Overweight and Obesity], Chapter 8 [High Blood Pressure], and Chapter 9 [Diabetes])*

- The combined genetic heritability in self-identified Black individuals and White individuals for ATP III–defined MetS is estimated to be ≈25%.[171]
- Genetic factors are associated with the individual components of MetS. In a candidate gene study of 3067 children, variants in the *FTO* gene were associated with MetS.[172] Several pleiotropic variants of genes of apolipoproteins (*APOE*, *APOC1*, *APOC3*, and *APOA5*), Wnt signaling pathway (*TCF7L2*), lipoproteins (*LPL*, *CETP*), mitochondrial proteins (*TOMM40*), gene transcription regulation (*PROX1*), cell proliferation (*DUSP9*), cAMP signaling (*ADCY5*), and oxidative LDL metabolism (*COLEC12*), as well as expression of liver-specific genes (*HNF1A*), have been identified across various racial and ethnic populations that could explain some of the correlated architecture of MetS traits.[173–177] A recent multiethnic GWAS for MetS components has identified ethnicity-specific genetic associations (6 loci in African American individuals, 3 loci in European American individuals, 3 loci in Japanese American individuals, 2 loci in Mexican American individuals) with substantial interethnic heterogeneity.[178]
- The A allele of the *TNFα* (−308 A/G) rs1800629 polymorphic gene, which is associated with higher levels of circulating tumor necrosis factor-α, has been associated with higher prevalence of MetS in Egyptians.[179]
- The minor G allele of the ANP genetic variant rs5068, which is associated with higher levels of circulating ANP, has been associated with lower prevalence of MetS in White and Black people.[180–182]
- SNPs of inflammatory genes (encoding interleukin-6, interleukin-1β, and interleukin-10) and plasma fatty acids, as well as interactions among these SNPs, are differentially associated with odds of MetS.[183]
- A UK Biobank study of 291 107 individuals performed GWASs for the clustering of MetS traits and found 3 loci associated with all 5 MetS components (near *LINC0112*, *C5orf67*, and *GIP*), of which *C5orf67* has been associated with individual MetS components.[184]
- Recently, 90 novel loci (cumulative 94 loci) have been identified for NAFLD.[185] A total of 8 common genetic loci (*MTARC1*, *ADH1B*, *TRIB1*, *GPAM*, *MAST3*, *TM6SF2*, *APOE*, and *PNPLA3*) have also been identified for association with hepatic steatosis, a leading risk factor for cardiometabolic diseases.[186]

## Prevention and Awareness of MetS

- Despite the high prevalence of MetS, the public's recognition of MetS is limited. A study showed that the average MetS Knowledge Scale score was 36.7±18.8 (range, 0–100).[187] Communicating with patients about MetS and its clinical assessment may increase risk perception and motivation toward healthier behaviors.[188]

## Morbidity and Mortality

### *Adults*

#### *CVD Morbidity and Mortality*

- MetS is associated with CVD morbidity and mortality. A meta-analysis of 87 studies comprising 951 083 subjects showed that MetS increased the risk of CVD (summary RR, 2.35 [95% CI, 2.02–2.73]), with significantly increased risks (RRs ranging from 1.6–2.9) for all-cause mortality, CVD mortality, MI, and stroke, even for those with MetS but without diabetes.[189]
- In the HAPIEE study of 4257 participants 45 to 72 years of age with a mean follow-up of 11 years,

MetS increased the risk of a first CVD event among males (HR, 1.53 [95% CI, 1.18–1.97]) and females (HR, 1.56 [95% CI, 1.14–2.15]).[190]

- The cardiovascular risk associated with MetS varies by the combination of MetS components present. Of all possible ways to have 3 MetS components, the combination of central obesity, elevated BP, and hyperglycemia conferred the greatest risk for CVD (HR, 2.36 [95% CI, 1.54–3.61]) and mortality (HR, 3.09 [95% CI, 1.93–4.94]) in the Framingham Offspring Study.[114]
- In the INTERHEART case-control study of 26 903 subjects from 52 countries, MetS was associated with an increased risk of MI, according to both the WHO (OR, 2.69 [95% CI, 2.45–2.95]) and IDF (OR, 2.20 [95% CI, 2.03–2.38]) definitions, with a PAR of 14.5% (95% CI, 12.7%–16.3%) and 16.8% (95% CI, 14.8%–18.8%), respectively. Associations were similar across all regions and ethnic groups. In addition, the presence of ≥3 versus <3 elevated risk factors was associated with an increased risk of MI (OR, 1.50 [95% CI, 1.24–1.81]). Similar results were observed when the IDF definition was used.[191]
- In the Three-City Study, among 7612 participants ≥65 years of age who were followed up for 5.2 years, MetS was associated with an increased risk of total CHD (HR, 1.78 [95% CI, 1.39–2.28]) and fatal CHD (HR, 2.40 [95% CI, 1.41–4.09]); however, MetS was not associated with CHD risk beyond its individual components.[192]
- Among 3414 patients with stable CVD and atherogenic dyslipidemia who were treated intensively with statins in the AIM-HIGH trial, neither the presence of MetS nor the number of MetS components was associated with cardiovascular outcomes, including coronary events, ischemic stroke, nonfatal MI, CAD death, or the composite end point.[193]
- In patients with chest pain undergoing invasive coronary angiography, presence of MetS and increasing number of MetS factors were independently associated with obstructive CAD in females (aOR, 1.92 [95% CI, 1.31–2.81]) but not in males (aOR, 0.97 [95% CI, 0.61–1.55]).[194]
- It is estimated that 13.3% to 44.0% of the excess CVD mortality in the United States compared with other countries such as Japan is explained by MetS or MetS-related existing CVD.[195]
- MetS is associated with risk of stroke.[196] In a meta-analysis of 16 studies including 116 496 participants who were initially free of CVD, those with MetS had an increased risk of stroke (pooled RR, 1.70 [95% CI, 1.49–1.95]) compared with those without MetS. The magnitude of the effect was stronger among females (RR, 1.83 [95% CI, 1.31–2.56]) than males (RR, 1.47 [95% CI, 1.22–1.78]). The risk was higher for ischemic stroke (RR, 2.12 [95% CI, 1.46–3.08]) than hemorrhagic stroke (RR, 1.48 [95% CI, 0.98–2.24]). In a combined analysis from the ARIC and JHS studies, among 13 141 White and Black individuals with a mean follow-up of 18.6 years, risk of ischemic stroke increased consistently with MetS severity *z* score (HR, 1.75 [95% CI, 1.35–2.27]) for those above the 75th percentile compared with those below the 25th percentile. Risk was highest for White females (HR, 2.63 [95% CI, 1.70–4.07]), although significant interactions by sex and race were not observed.[197]
- In the ARIC study, among 13 168 participants with a median follow-up of 23.6 years, MetS was independently associated with an increased risk of SCD (aHR, 1.70 [95% CI, 1.37–2.12]; $P<0.001$).[198] The risk of SCD varied according to the number of MetS components (HR, 1.31 per 1 additional component of the MetS [95% CI, 1.19–1.44]; $P<0.001$) independently of race or sex.
- In a recent meta-analysis of 13 cohort studies comprising 59 919 participants >60 years of age, MetS was significantly associated with stroke recurrence (RR, 1.46 [95% CI, 1.07–1.97]).[199]

### *All-Cause Mortality*

- In patients with impaired LV systolic function (EF <50%) who undergo CABG, MetS is associated with an increased risk of all-cause in-hospital mortality (OR, 5.99 [95% CI, 1.02–35.15]).[200]
- In a meta-analysis of 20 prospective cohort studies that included 57 202 adults ≥60 years of age, MetS was associated with increased risk of all-cause mortality (RR, 1.20 [95% CI, 1.05–1.38] for males; RR, 1.22 [95% CI, 1.02–1.44] for females) and CVD mortality (RR, 1.29 [95% CI, 1.09–1.53] for males; RR, 1.20 [95% CI, 0.91–1.60] for females).[201] There was significant heterogeneity across the studies (all-cause mortality, $I^2$=55.9%, $P$=0.001; CVD mortality, $I^2$=58.1%, $P$=0.008). In subgroup analyses, the association of MetS with CVD and all-cause mortality varied by geographic location, sample size, definition of MetS, and adjustment for frailty.
- In a recent meta-analysis of 13 cohort studies comprising 59 919 participants >60 years of age, MetS was significantly associated with all-cause mortality (RR, 1.27 [95% CI, 1.18–1.36]).[199]
- The impact of MetS on mortality has been shown to be modified by objective sleep duration.[202] Using data from the Penn State Adult Cohort, a prospective population-based study of 1344 males and females followed up for 16.6 years, the HRs of all-cause and CVD mortality associated with MetS were 1.29 (95% CI, 0.89–1.87) and 1.49 (95% CI, 0.75–2.97) for individuals who slept ≥6 hours and 1.99 (95% CI, 1.53–2.59) and 2.10 (95% CI, 1.39–3.16) for individuals who slept <6 hours.

### *Youths*

- Among 771 participants 6 to 19 years of age from the NHLBI's Lipid Research Clinics Princeton Prevalence Study and the Princeton Follow-Up Study, the risk of CVD was substantially higher among those with compared with those without MetS (OR, 14.6 [95% CI, 4.8–45.3]) over a 25-year follow-up.[203]
- In the Princeton Lipid Research Cohort Study, MetS severity scores during childhood were lowest among those who never developed CVD, intermediate among those who developed CVD later in life (mean, 50 years of age), and highest in those who developed early CVD (mean, 38 years of age).[204] MetS severity score was also strongly associated with early onset of diabetes.[205]
- In an International Childhood Cardiovascular Cohort Consortium that included 5803 participants in 4 cohort studies (Cardiovascular Risk in Young Finns, Bogalusa Heart Study, Princeton Lipid Research Study, and Minnesota Insulin Study) with a mean follow-up period of 22.3 years, childhood MetS and overweight were associated with a >2.4-fold risk for adult MetS from 5 years of age onward.[112] The risk for type 2 diabetes was increased beginning at 8 years of age (RR, 2.6 [95% CI, 1.4–6.8]) on the basis of international cutoff values for the definition of childhood MetS. Risk of high carotid IMT was increased beginning at 11 years of age (RR, 2.44 [95% CI, 1.55–3.55]) with the same definition.
- Among 2798 adolescents 11 to 19 years of age in the Tehran Lipid and Glucose Study with a mean follow-up of 11.3 years, those with MetS in adolescence had a 2.8 times increased hazard of incident type 2 diabetes in adulthood (HR, 2.82 [95% CI, 1.41–5.64]) independently of baseline age and sex, adulthood BMI, and family history of diabetes.[206]
- Among 1757 youths from the Bogalusa Heart Study and the Cardiovascular Risk in Young Finns Study, those with MetS in youth and adulthood were at 3.4 times increased risk of high carotid IMT and 12.2 times increased risk of type 2 diabetes in adulthood compared with those without MetS at either time. Adults whose MetS had resolved after their youth did not have an increased risk of having high IMT or type 2 diabetes.[207] An analysis of 5803 participants in 4 cohort studies (Cardiovascular Risk in Young Finns, Bogalusa Heart Study, Princeton Lipid Research Study, Insulin Study) showed that childhood MetS predicted high carotid IMT in adults from 11 years of age onward and type 2 diabetes in adults from 14 years of age onward.[112]
- MetS score, based on the number of MetS components, was associated with biomarkers of inflammation, endothelial damage, and CVD risk in a separate cohort of 677 prepubertal children.[208]

## MetS and Subclinical CVD

- MetS has also been associated with incident AF,[209,210] HF,[211] and PAD.[212] The aHR for incident AF was 1.38 (95% CI, 1.36–1.39). The aRR for incidence PAD was 1.76 (95% CI, 1.05–2.92).
- In MESA, among 6603 adults 45 to 84 years of age (1686 [25%] with MetS without diabetes and 881 [13%] with diabetes), subclinical atherosclerosis prevalence and progression assessed by CAC were more severe in people with MetS and diabetes than in those without these conditions, and the extent and progression of CAC were strong predictors of CHD and CVD events in these groups.[213,214] There appears to be a synergistic relationship among MetS, NAFLD, and prevalence of CAC,[215] as well as a synergistic relationship with smoking.[216]
- Individuals with MetS have a higher degree of endothelial dysfunction than individuals with a similar burden of traditional cardiovascular risk factors.[217] The aOR for the association of MetS with peripheral endothelial dysfunction was 2.06 ($P$=0.009). Furthermore, individuals with both MetS and diabetes have demonstrated increased microvascular and macrovascular dysfunction.[218] MetS is associated with increased thrombosis, including increased resistance to aspirin[219] and clopidogrel loading.[220]
- In a meta-analysis of 8 population-based studies that included 19 696 patients (22.2% with MetS), MetS was associated with higher carotid IMT (SMD, 0.28±0.06 [95% CI, 0.16–0.40]; $P$=0.00003) and higher prevalence of carotid plaques (pooled OR, 1.61 [95% CI, 1.29–2.01]; $P$<0.0001).[221]
- In modern imaging studies using echocardiography, MRI, cardiac CT, and positron emission tomography, MetS was closely related to increased epicardial adipose tissues[222]; increased visceral fat[223]; increased ascending aortic diameter[224]; high-risk coronary plaque features, including increased necrotic core[225]; impaired coronary flow reserve[226]; abnormal indices of LV strain[227]; LV diastolic dysfunction[228]; LV dyssynchrony[229]; and subclinical RV dysfunction.[230] For example, the epicardial adipose thickness was higher in patients with MetS than in those without MetS (difference in means, 1.15 mm [95% CI, 0.78–1.53]).[222]

## MetS and Non-CVD Complications

### *Diabetes*

- In data from ARIC and JHS, MetS was associated with an increased risk of diabetes (HR, 4.36 [95% CI, 3.83–4.97]), although the association was attenuated after adjustment for the individual components of MetS.[231] However, use of a continuous sex- and race-specific MetS severity $z$ score was

associated with an increased risk of diabetes that was independent of individual MetS components, with increases in this score over time conferring additional risk for diabetes. Among White males and females, compared with below the 25th percentile of a MetS severity score, the risk of incident diabetes was 0.97 (95% CI, 0.62–1.53) for the 25th to 50th percentile, 1.29 (95% CI, 0.76–2.19) for the 50th to 75th percentile, and 2.24 (95% CI, 1.21–4.15) for above the 75th percentile. Among Black males and females, compared with below the 25th percentile of a MetS severity score, the risk of incident diabetes was 2.15 (95% CI, 1.28–3.62) for the 25th to 50th percentile, 4.00 (95% CI, 2.22–7.18) for the 50th to 75th percentile, and 5.30 (95% CI, 2.73–10.29) for above the 75th percentile.

- In the Korean Genome Epidemiology Project, incident MetS and persistent MetS over 2 years were significantly associated with 10-year incident diabetes even after adjustment for confounding factors (aHR, 1.75 [95% CI, 1.30–2.37] and 1.98 [95% CI, 1.50–2.61], respectively), whereas resolved MetS over 2 years did not significantly increase the risk of diabetes after adjustment for confounders (aHR, 1.28 [95% CI, 0.92–1.75]).[232] Similar findings were also reported in the Korean nationwide cohort study.[233] When the reference group was set as subjects having 4 to 5 components of MetS, subjects having ≤1 component of MetS had the lowest risk of incident type 2 diabetes (aHR, 0.27 [95% CI, 0.266–0.271]), and the risk increased as components of MetS increased.

### Kidney Disease

- Among 633 nondiabetic Chinese adults receiving a first renal transplantation, presence of pretransplantation MetS was an independent predictor of prevalent (aOR, 1.28 [95% CI, 1.04–1.51]) and incident (aOR, 2.75 [95% CI, 1.45–6.05]) posttransplantation diabetes.[234]
- In RENIS-T6, MetS was associated with a mean 0.30–mL/min per year (95% CI, 0.02–0.58) faster decline in GFR than in individuals without MetS.[235]

### Cancer

- MetS is also associated with breast, endometrial, prostate, pancreatic, hepatic, colorectal, and renal cancers,[236–238] as well as with gastroenteropancreatic neuroendocrine tumors.[239] A nationwide cohort study conducted among Korean individuals found that, compared with the sustained non-MetS group, the aHR for breast cancer was 1.11 (95% CI, 1.04–1.19) in the transition to MetS group, 1.05 (95% CI, 0.96–1.14) in the transition to non-MetS group, and 1.18 (95% CI, 1.12–1.25) in the sustained MetS group.[240]
- MetS is linked to poorer cancer outcomes, including increased risk of recurrence and overall mortality.[241,242] In a meta-analysis of 24 studies that included 132 589 males with prostate cancer (17.4% with MetS), MetS was associated with worse oncological outcomes, including biochemical recurrence and more aggressive tumor features.[243] Among 94 555 females free of cancer at baseline in the prospective NIH-AARP cohort, MetS was associated with increased risk of breast cancer mortality (HR, 1.73 [95% CI, 1.09–2.75]), particularly among postmenopausal females (HR, 2.07 [95% CI, 1.32–3.25]).[244]
- In a meta-analysis of 17 prospective longitudinal studies that included 602 195 females and 15 945 cases of breast cancer, MetS was associated with increased risk of incident breast cancer in postmenopausal females (aRR, 1.25 [95% CI, 1.12–1.39]) but significantly reduced breast cancer risk in premenopausal females (aRR, 0.82 [95% CI, 0.76–0.89]). The association between MetS and increased risk of breast cancer was observed only among White and Asian females, whereas there was no association in Black females.[245]
- In data obtained from HCUP, hospitalized patients with a diagnosis of MetS and cancer had significantly increased odds of adverse health outcomes, including increased postsurgical complications (breast cancer: OR, 1.20 [95% CI, 1.03–1.39]; prostate cancer: OR, 1.22 [95% CI, 1.09–1.37]).[246]
- In 25 038 Black and White individuals in the REGARDS study, MetS was associated with increased risk of cancer-related mortality (HR, 1.22 [95% CI, 1.03–1.45]).[236] For those with all 5 MetS components present, the risk of cancer mortality was 59% higher than for those without a MetS component present (HR, 1.59 [95% CI, 1.01–2.51]).
- In NHANES III, MetS was associated with total cancer mortality (HR, 1.33 [95% CI, 1.04–1.70]) and breast cancer mortality (HR, 2.1 [95% CI, 1.09–4.11]).[247]

### Gastrointestinal

- NAFLD, a spectrum of liver disease that ranges from isolated fatty liver to fatty liver plus inflammation (nonalcoholic steatohepatitis), is hypothesized to represent the hepatic manifestation of MetS. According to data from NHANES 2011 to 2014, the overall prevalence of NAFLD among US adults is 21.9%.[248] The global prevalence of NAFLD is estimated to be 25.2%.[249] In a prospective study of 4401 Japanese adults 21 to 80 years of age who were free of NAFLD at baseline, the presence of MetS increased the risk for NAFLD in both males (OR, 4.00 [95% CI, 2.63–6.08]) and females (OR, 11.20 [95% CI, 4.85–25.87]).[250] In cross-sectional

studies, an increase in the number of MetS components was associated with underlying nonalcoholic steatohepatitis and advanced fibrosis in NAFLD in adults and children.[248,251]
- MetS has been associated with cirrhosis,[252] colorectal adenomas,[253] acute pancreatitis,[254] and Barrett esophagus.[255]

### *Other*

- Among 725 Chinese adults ≥90 years of age, MetS was associated with prevalent disability in activities of daily living (OR, 1.65 [95% CI, 1.10–3.21]) and instrumental activities of daily living (OR, 2.09 [95% CI, 1.17–4.32]).[256]
- In a cross-sectional analysis of data from the PREDIMED-Plus multicenter randomized trial, MetS was associated with adverse health-related quality of life as measured by the Short Form-36 in the aggregated physical dimensions, body pain in females, and general health in males; however, this adverse association was absent for the psychological dimensions of health-related quality of life.[257]
- MetS is associated with dementia[258] (particularly Alzheimer dementia[259]), cognitive decline,[260] and lower cognitive performance in older adults at risk for cognitive decline.[261] For example, during the mean follow-up of 4.9 years, the aHRs in a non-MetS group that progressed to MetS compared with the sustained normal group were 1.11 (95% CI, 1.08–1.13) for total dementia, 1.08 (95% CI, 1.05–1.11) for AD, and 1.20 (95% CI, 1.13–1.28) for vascular dementia.[258] The aHRs in the improved group (MetS to normal) compared with the sustained normal group were 1.12 (95% CI, 1.10–1.15) for total dementia, 1.10 (95% CI, 1.07–1.13) for AD, and 1.19 (95% CI, 1.12–1.27) for vascular dementia. The aHRs in the sustained group (MetS to MetS) compared with the sustained normal group were 1.18 (95% CI, 1.16–1.20) for total dementia, 1.13 (95% CI, 1.11–1.15) for AD, and 1.38 (95% CI, 1.32–1.44) for vascular dementia.
- MetS is associated with higher bone mineral density and, in some but not all studies, a decreased risk of bone fractures, depending on the definition of MetS used, fracture site, and sex.[262,263]
- In males, MetS has been associated with decreased sperm total count, sperm concentration, sperm normal morphology, sperm progressive motility, and sperm vitality and an increase in sperm DNA fragmentation and mitochondrial membrane potential, as well as lower semen quality, which may contribute to male infertility.[264]
- MetS and its components are associated with more severe infection with SARS-CoV-2 and high risk for poor outcomes in COVID-19 illness.[265–268]

## Cost and Health Care Use

- MetS is associated with increased health care use and health care–related costs among individuals with and without diabetes. Overall, health care costs increase by ≈24% for each additional MetS component present.[269]
- The presence of MetS increases the risk for postoperative complications, including prolonged hospital stay and risk for postsurgical complications (OR, 1.20 [95% CI, 1.03–1.09] and 1.22 [95% CI, 1.09–1.37] for patients with breast and prostate cancer with MetS undergoing tumor removal, respectively), blood transfusion, surgical site infection, and respiratory failure, across various surgical populations.[246,270–274]

## Global Burden of MetS

- MetS is becoming hyperendemic around the world. Published evidence has described an increasing prevalence of MetS in Canada,[275] Latin America,[276] Aruba,[277] India,[278–281] Bangladesh,[282] Iran,[283–285] Ghana,[286] the Gaza Strip,[287] Jordan,[288] Ethiopia,[289,290] Nigeria,[291,292] South Africa,[293] Ecuador,[294] and Vietnam,[295] as well as many other countries.
- Global prevalence of MetS in military personnel is estimated at 21% (95% CI, 17%–25%; N=37 studies: 15 in America, 13 in Europe, and 9 in Asia).[296]
- MetS among children and adolescents is an emerging public health challenge in low- to middle-income countries. In a meta-analysis including data from 76 studies with 142 142 children and adolescents residing in low- to middle-income countries, the pooled prevalence of MetS was 4.0% (IDF), 6.7% (ATP III), and 8.9% (de Ferranti).[297] Among children and adolescents with obesity or overweight, the pooled prevalence was estimated at 24.1%, 36.5%, and 56.3% with the IDF, ATP III, and de Ferranti criteria, respectively.
- A recent systematic review has synthesized the prevalence of MetS according to different definitions in the pediatric population across the world.[298] According to the IDF, the prevalence of MetS was 3.1% to 5.4% in the United States, 2.1% in Canada, 0.3% to 0.9% in Colombia, 1.5% in Venezuela, 2.1% to 2.6% in Brazil, 9.5% in Chile, 0.4% to 2.7% in Europe, 3.8% in Spain, 1.9% in South Africa, 1.1% to 7.6% in China, 1.0 to 2.1% in Korea, 2.6% in Malaysia, 2.0% in Saudi Arabia, 8.4% in Iran, and 2.7% in Australia.

### *Latin America*

- In a systematic review of 10 Brazilian studies, the weighted mean prevalence of MetS in Brazil was 29.6%.[299]
- In a meta-analysis of 10 191 participants across 6 studies, the prevalence of MetS in Argentina was

27.5% (95% CI, 21.3%–34.1%), and the prevalence was higher in males than in females (29.4% versus 27.4%; *P*=0.02).[300]

- In a report from a representative survey of the northern state of Nuevo León, Mexico, the prevalence of MetS in adults (≥16 years of age) for 2011 to 2012 was 54.8%. In adults with obesity, the prevalence reached 73.8%. The prevalence in adult North Mexican females (60.4%) was higher than in adult North Mexican males (48.9%).[301] Among older Mexican adults (≥65 years of age), the prevalence was 72.9% (75.7% in males, 70.4% in females).[302]
- MetS is highly prevalent in modern Indigenous populations, notably in Brazil and Australia. The prevalence of MetS was estimated to be 41.5% in Indigenous groups in Brazil,[299,301] 33.0% in Australian Aborigine individuals, and 50.3% in Torres Strait Islander individuals.[303]

### Europe

#### (See Chart 10-6)

- The prevalence of MetS and MHO in subjects with obesity varied considerably by European country in the BioSHaRE consortium, which harmonizes modern data from 10 different population-based cohorts in 7 European countries (Chart 10-6).[304]
- The prevalence of MetS has been reported to be low (14.6%) in a population-representative study in France (French Nutrition and Health Survey, 2006–2007) compared with other industrialized countries.[305]

### Asia

- From NIPPON DATA (1990–2005), the age-adjusted prevalence of MetS in a Japanese population was 19.3%.[195]
- Based on a systematic review and meta-analysis of data from 734 511 Chinese individuals ≥15 years of age, the prevalence of MetS in China was 22.0% (95% CI, 19.9%–24.1%). The prevalence of MetS was 27.6% (95% CI, 23.9%–31.6%) among people >40 years of age, whereas the prevalence was 8.3% (95% CI, 2.8%–17.7%) among those 15 to 40 years of age. The prevalence was higher in females (23.6% [95% CI, 21.0%–26.3%]) than males (21.0% [95% CI, 18.8%–23.3%]).[306]
- In 2018, the prevalence of MetS in Chinese adults in Hong Kong was 14.1%.[307]

### Middle East

#### (See Chart 10-7)

- In a meta-analysis of cross-sectional studies that assessed the prevalence of MetS in 15 Middle Eastern countries, the pooled prevalence estimate for MetS was 31.2% (95% CI, 28.4%–33.9%). Pooled prevalence estimates ranged from a low of 23.6% in Kuwait to 40.1% in the United Arab Emirates, depending on the time frame, country studied, and definition of MetS used (Chart 10-7). There was high heterogeneity among the 61 included studies.[308]

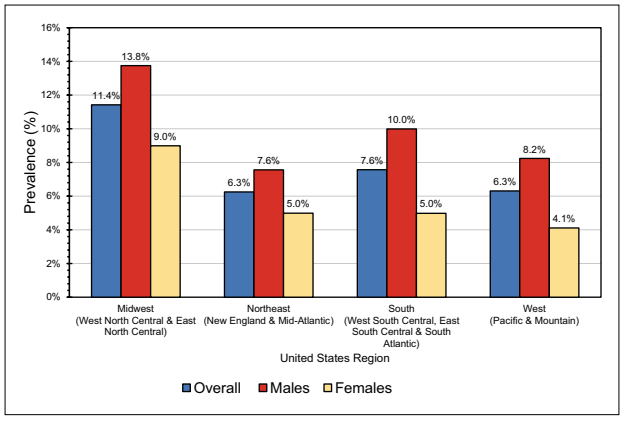



**Chart 10-1. Prevalence of MetS by sex and US region among adolescents 12 to 19 years of age (NHANES, 1999–2014).**
MetS indicates metabolic syndrome; and NHANES, National Health and Nutrition Examination Survey.
Source: Data derived from DeBoer et al.[309]

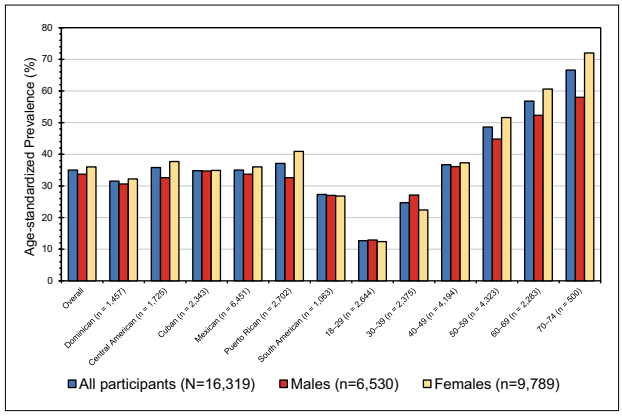



**Chart 10-2. Age-standardized prevalence of MetS by age and sex in Hispanic/Latino people in HCHS/SOL, United States, 2008 to 2011.**
Values were weighted for survey design and nonresponse and were age standardized to the population described by the 2010 US census. HCHS/SOL indicates Hispanic Community Health Study/Study of Latinos; and MetS, metabolic syndrome.
Source: Data derived from Heiss et al.[12]

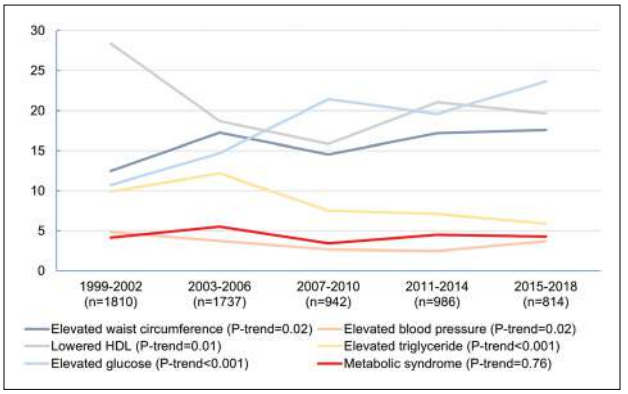



**Chart 10-3. Trends in estimated prevalence of MetS and its subcomponents among US youths 2 to 19 years of age from 1999 to 2018.**

Data were adjusted for NHANES weights to be nationally representative.

HDL indicates high-density lipoprotein; MetS, metabolic syndrome; and NHANES, National Health and Nutrition Examination Survey.

Source: Reprinted from Liu et al.[5]

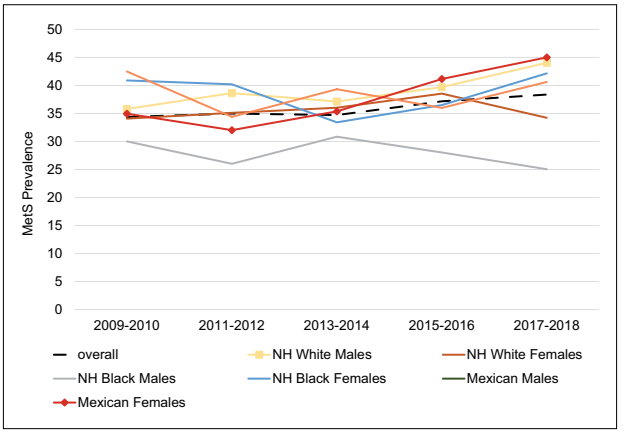



**Chart 10-4. Prevalence of MetS among US adults using the harmonized MetS criteria (NHANES, 2009–2018).**

MetS was defined using the criteria agreed to jointly by the IDF; the NHLBI; the AHA; the World Heart Federation; the International Atherosclerosis Society; and the International Association for the Study of Obesity.

AHA indicates American Heart Association; IDF, International Diabetes Federation; MetS, metabolic syndrome; NH, non-Hispanic; NHANES, National Health and Nutrition Examination Survey; and NHLBI, National Heart, Lung, and Blood Institute.

Source: Data courtesy of Junxiu Liu using NHANES.[310]

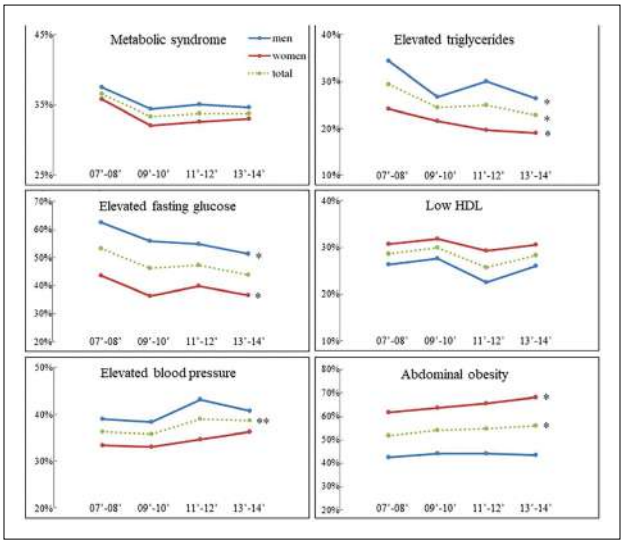



**Chart 10-5. Sex-stratified trends in the age-adjusted weighted prevalence of MetS using ATP III criteria and its components among US adults (NHANES, 2007–2014).**

MetS was defined using modified National Cholesterol Education Program–ATP III criteria.

ATP III indicates Adult Treatment Panel III; HDL, high-density lipoprotein; MetS, metabolic syndrome; and NHANES, National Health and Nutrition Examination Survey.

*$P_{trend}$<0.05.

**$P_{trend}$=0.05 after adjustment for age, sex, and race as appropriate.

Source: Reprinted from Shin et al[44] with permission from Elsevier. Copyright © 2018 Elsevier.

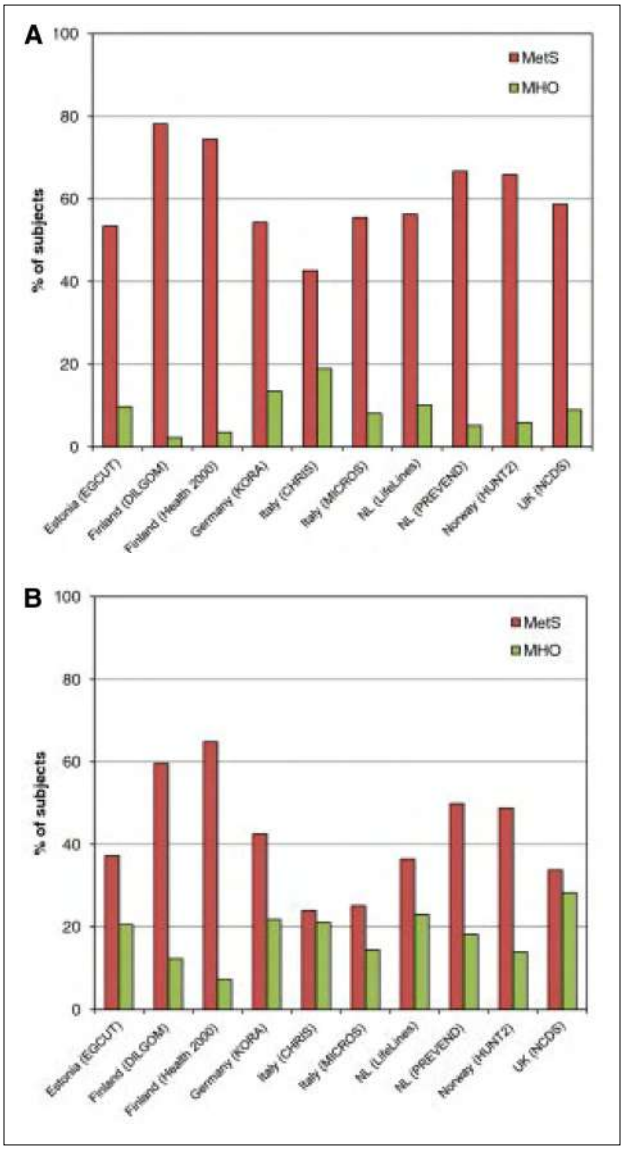



**Chart 10-6. Age-standardized prevalence of MetS and MHO among people with obesity (BMI ≥30 kg/m2) in different European cohorts, 1995 to 2012 (global data).**
**A**, Males. **B**, Females.
BMI indicates body mass index; CHRIS, Collaborative Health Research in South Tyrol Study; DILGOM, Dietary, Lifestyle, and Genetics Determinants of Obesity and Metabolic Syndrome; EGCUT, Estonian Genome Center of the University of Tartu; HUNT2, Nord-Trøndelag Health Study; KORA, Cooperative Health Research in the Region of Augsburg; MetS, metabolic syndrome; MHO, metabolically healthy obesity; MICROS, Microisolates in South Tyrol Study; NCDS, National Child Development Study; NL, the Netherlands; and PREVEND, Prevention of Renal and Vascular End-Stage Disease.
Source: Reprinted from van Vliet-Ostaptchouk et al.[304] Copyright © 2014 van Vliet-Ostaptchouk et al; licensee BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided that the original work is properly credited.

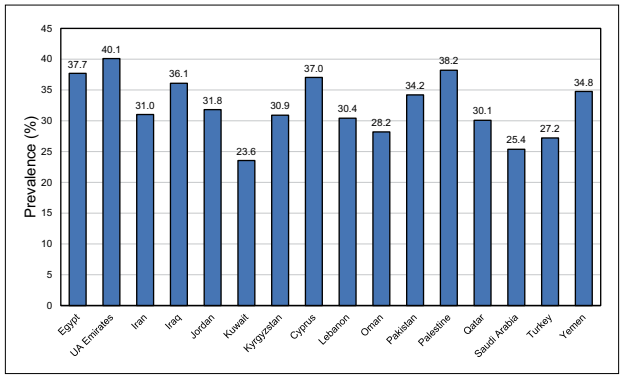



**Chart 10-7. Estimated pooled prevalence* of MetS in countries in the Middle East (2001–2018).**
MetS indicates metabolic syndrome; and UA, United Arab.
*Pooled prevalence estimates obtained with the random-effects model.
Source: Data derived from Ansari-Moghaddam et al.[308]

## REFERENCES


1. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM, Smith SC Jr; International Diabetes Federation Task Force on Epidemiology and Prevention. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*. 2009;120:1640–1645. doi: 10.1161/CIRCULATIONAHA.109.192644
2. Chirinos DA, Llabre MM, Goldberg R, Gellman M, Mendez A, Cai J, Sotres-Alvarez D, Daviglus M, Gallo LC, Schneiderman N. Defining abdominal obesity as a risk factor for coronary heart disease in the U.S.: results from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). *Diabetes Care*. 2020;43:1774–1780. doi: 10.2337/dc19-1855
3. Mendrick DL, Diehl AM, Topor LS, Dietert RR, Will Y, La Merrill MA, Bouret S, Varma V, Hastings KL, Schug TT, et al. Metabolic syndrome and associated diseases: from the bench to the clinic. *Toxicol Sci*. 2018;162:36–42. doi: 10.1093/toxsci/kfx233
4. Gaston SA, Tulve NS, Ferguson TF. Abdominal obesity, metabolic dysfunction, and metabolic syndrome in U.S. adolescents: National Health and Nutrition Examination Survey 2011-2016. *Ann Epidemiol*. 2019;30:30–36. doi: 10.1016/j.annepidem.2018.11.009
5. Liu J, Ma J, Orekoya O, Vangeepuram N, Liu J. Trends in metabolic syndrome among US youth, from 1999 to 2018. *JAMA Pediatr*. 2022;176:1043–1045. doi: 10.1001/jamapediatrics.2022.1850
6. Reina SA, Llabre MM, Vidot DC, Isasi CR, Perreira K, Carnethon M, Parrinello CM, Gallo LC, Ayala GX, Delamater A. Metabolic syndrome in Hispanic youth: results from the Hispanic Community Children's Health Study/Study of Latino Youth. *Metab Syndr Relat Disord*. 2017;15:400–406. doi: 10.1089/met.2017.0054
7. Laurson KR, Welk GJ, Eisenmann JC. Diagnostic performance of BMI percentiles to identify adolescents with metabolic syndrome. *Pediatrics*. 2014;133:e330–e338. doi: 10.1542/peds.2013-1308
8. Khoury M, Manlhiot C, McCrindle BW. Role of the waist/height ratio in the cardiometabolic risk assessment of children classified by body mass index. *J Am Coll Cardiol*. 2013;62:742–751. doi: 10.1016/j.jacc.2013.01.026
9. Hirode G, Wong RJ. Trends in the prevalence of metabolic syndrome in the United States, 2011-2016. *JAMA*. 2020;323:2526–2528. doi: 10.1001/jama.2020.4501
10. O'Hearn M, Lauren BN, Wong JB, Kim DD, Mozaffarian D. Trends and disparities in cardiometabolic health among U.S. adults, 1999-2018. *J Am Coll Cardiol*. 2022;80:138–151. doi: 10.1016/j.jacc.2022.04.046
11. Nolan PB, Carrick-Ranson G, Stinear JW, Reading SA, Dalleck LC. Prevalence of metabolic syndrome and metabolic syndrome components in young adults: a pooled analysis. *Prev Med Rep*. 2017;7:211–215. doi: 10.1016/j.pmedr.2017.07.004
12. Heiss G, Snyder ML, Teng Y, Schneiderman N, Llabre MM, Cowie C, Carnethon M, Kaplan R, Giachello A, Gallo L, et al. Prevalence of metabolic syndrome among Hispanics/Latinos of diverse background: the Hispanic Community Health Study/Study of Latinos. *Diabetes Care*. 2014;37:2391–2399. doi: 10.2337/dc13-2505
13. Khan RJ, Gebreab SY, Sims M, Riestra P, Xu R, Davis SK. Prevalence, associated factors and heritabilities of metabolic syndrome and its individual components in African Americans: the Jackson Heart Study. *BMJ Open*. 2015;5:e008675. doi: 10.1136/bmjopen-2015-008675
14. Abou Kassm S, Hoertel N, Naja W, McMahon K, Barriere S, Blumenstock Y, Portefaix C, Raucher-Chene D, Bera-Potelle C, Cuervo-Lombard C, et al; CSA Study group. Metabolic syndrome among older adults with schizophrenia spectrum disorder: prevalence and associated factors in a multicenter study. *Psychiatry Res*. 2019;275:238–246. doi: 10.1016/j.psychres.2019.03.036
15. Coello K, Vinberg M, Knop FK, Pedersen BK, McIntyre RS, Kessing LV, Munkholm K. Metabolic profile in patients with newly diagnosed bipolar disorder and their unaffected first-degree relatives. *Int J Bipolar Disord*. 2019;7:8. doi: 10.1186/s40345-019-0142-3
16. Thoefner LB, Rostved AA, Pommergaard HC, Rasmussen A. Risk factors for metabolic syndrome after liver transplantation: a systematic review and meta-analysis. *Transplant Rev (Orlando)*. 2018;32:69–77. doi: 10.1016/j.trre.2017.03.004
17. DeFilipp Z, Duarte RF, Snowden JA, Majhail NS, Greenfield DM, Miranda JL, Arat M, Baker KS, Burns LJ, Duncan CN, et al. Metabolic syndrome and cardiovascular disease following hematopoietic cell transplantation: screening and preventive practice recommendations from CIBMTR and EBMT. *Bone Marrow Transplant*. 2017;52:173–182. doi: 10.1038/bmt.2016.203
18. Bielorai B, Pinhas-Hamiel O. Type 2 diabetes mellitus, the metabolic syndrome, and its components in adult survivors of acute lymphoblastic leukemia and hematopoietic stem cell transplantations. *Curr Diab Rep*. 2018;18:32. doi: 10.1007/s11892-018-0998-0
19. Calza L, Colangeli V, Magistrelli E, Rossi N, Rosselli Del Turco E, Bussini L, Borderi M, Viale P. Prevalence of metabolic syndrome in HIV-infected patients naive to antiretroviral therapy or receiving a first-line treatment. *HIV Clin Trials*. 2017;18:110–117. doi: 10.1080/15284336.2017.1311502
20. Ahmed MES, Elnaby HEHA, Hussein MAR, Abo-Ghabsha ME. Metabolic syndrome in patients with chronic obstructive pulmonary disease. *Egypt J Chest Dis Tuberc*. 2020;69:316–322.
21. Oudin C, Berbis J, Bertrand Y, Vercasson C, Thomas F, Chastagner P, Ducassou S, Kanold J, Tabone MD, Paillard C, et al. Prevalence and characteristics of metabolic syndrome in adults from the French Childhood Leukemia Survivors' cohort: a comparison with controls from the French population. *Haematologica*. 2018;103:645–654. doi: 10.3324/haematol.2017.176123
22. Rodriguez-Zuniga MJM, Garcia-Perdomo HA. Systematic review and meta-analysis of the association between psoriasis and metabolic syndrome. *J Am Acad Dermatol*. 2017;77:657–666.e8. doi: 10.1016/j.jaad.2017.04.1133
23. Fernandez-Armenteros JM, Gomez-Arbones X, Buti-Soler M, Betriu-Bars A, Sanmartin-Novell V, Ortega-Bravo M, Martinez-Alonso M, Gari E, Portero-Otin M, Santamaria-Babi L, et al. Psoriasis, metabolic syndrome and cardiovascular risk factors: a population-based study. *J Eur Acad Dermatol Venereol*. 2019;33:128–135. doi: 10.1111/jdv.15159
24. Sun C, Qin W, Zhang YH, Wu Y, Li Q, Liu M, He CD. Prevalence and risk of metabolic syndrome in patients with systemic lupus erythematosus: a meta-analysis. *Int J Rheum Dis*. 2017;20:917–928. doi: 10.1111/1756-185X.13153
25. Liu M, Huang Y, Huang Z, Huang Q, Guo X, Wang Y, Deng W, Huang Z, Li T. Prevalence of metabolic syndrome and its associated factors in Chinese patients with ankylosing spondylitis. *Diabetes Metab Syndr Obes*. 2019;12:477–484. doi: 10.2147/DMSO.S197745
26. Gomes KWP, Luz AJP, Felipe MRB, Beltrao LA, Sampaio AXC, Rodrigues CEM. Prevalence of metabolic syndrome in rheumatoid arthritis patients from northeastern Brazil: association with disease activity. *Mod Rheumatol*. 2018;28:258–263. doi: 10.1080/14397595.2017.1316813
27. Bhattacharya PK, Barman B, Jamil M, Bora K. Metabolic syndrome and atherogenic indices in rheumatoid arthritis and their relationship with disease activity: a hospital-based study from northeast India. *J Transl Int Med*. 2020;8:99–105. doi: 10.2478/jtim-2020-0015
28. Sicras-Mainar A, Ruiz-Beato E, Navarro-Artieda R, Maurino J. Comorbidity and metabolic syndrome in patients with multiple sclerosis from Asturias and Catalonia, Spain. *BMC Neurol*. 2017;17:134. doi: 10.1186/s12883-017-0914-2
29. Simoniene D, Platukiene A, Prakapiene E, Radzeviciene L, Velickiene D. Insulin resistance in type 1 diabetes mellitus and its association with patient's micro- and macrovascular complications, sex hormones, and other clinical data. *Diabetes Ther*. 2020;11:161–174. doi: 10.1007/s13300-019-00729-5
30. Li X, Cao C, Tang X, Yan X, Zhou H, Liu J, Ji L, Yang X, Zhou Z. Prevalence of metabolic syndrome and its determinants in newly-diagnosed adult-onset diabetes in China: a multi-center, cross-sectional survey. *Front Endocrinol (Lausanne)*. 2019;10:661. doi: 10.3389/fendo.2019.00661
31. Noctor E, Crowe C, Carmody LA, Kirwan B, O'Dea A, Glynn LG, McGuire BE, O'Shea PM, Dunne FP. ATLANTIC-DIP: prevalence of metabolic syndrome and insulin resistance in women with previous gestational diabetes mellitus by International Association of Diabetes in Pregnancy Study Groups criteria. *Acta Diabetol*. 2015;52:153–160. doi: 10.1007/s00592-014-0621-z
32. Facca TA, Mastroianni-Kirsztajn G, Sabino ARP, Passos MT, Dos Santos LF, Fama EAB, Nishida SK, Sass N. Pregnancy as an early stress test for cardiovascular and kidney disease diagnosis. *Pregnancy Hypertens*. 2017;12:169–173. doi: 10.1016/j.preghy.2017.11.008
33. Kridin K, Solomon A, Tzur-Bitan D, Damiani G, Comaneshter D, Cohen AD. Acne keloidalis nuchae and the metabolic syndrome: a population-based study. *Am J Clin Dermatol*. 2020;21:733–739. doi: 10.1007/s40257-020-00541-z
34. Montero E, Molina A, Carasol M, Fernández-Meseguer A, Calvo-Bonacho E, García-Margallo MT, Sanz M, Herrera D. The association between metabolic syndrome and periodontitis in Spain: results from the WORALTH (Workers' ORAL healTH) Study. *J Clin Periodontol*. 2021;48:38–50. doi: 10.1111/jcpe.13391

35. Gobin R, Tian D, Liu Q, Wang J. Periodontal diseases and the risk of metabolic syndrome: an updated systematic review and meta-analysis. *Front Endocrinol*. 2020;11:1035–1057.
36. Almobarak AO, Jervase A, Fadl AA, Garelnabi NIA, Hakem SA, Hussein TM, Ahmad AAA, El-Den Ahmed IS, Badi S, Ahmed MH. The prevalence of diabetes and metabolic syndrome and associated risk factors in Sudanese individuals with gallstones: a cross sectional survey. *Transl Gastroenterol Hepatol*. 2020;5:14. doi: 10.21037/tgh.2019.10.09
37. Heyn PC, Tagawa A, Pan Z, Thomas S, Carollo JJ. Prevalence of metabolic syndrome and cardiovascular disease risk factors in adults with cerebral palsy. *Dev Med Child Neurol*. 2019;61:477–483. doi: 10.1111/dmcn.14148
38. Ejtahed HS, Soroush MR, Hasani-Ranjbar S, Angoorani P, Mousavi B, Masumi M, Edjtehadi F, Soveid M. Prevalence of metabolic syndrome and health-related quality of life in war-related bilateral lower limb amputees. *J Diabetes Metab Disord*. 2017;16:17. doi: 10.1186/s40200-017-0298-2
39. Gater DR Jr, Farkas GJ, Berg AS, Castillo C. Prevalence of metabolic syndrome in veterans with spinal cord injury. *J Spinal Cord Med*. 2018;42:86–93. doi: 10.1080/10790268.2017.1423266
40. Dwivedi S, Purohit P, Nebhinani N, Sharma P. Effect of severity of opiate use on cardiometabolic profile of chronic opiate dependents of western Rajasthan. *Indian J Clin Biochem*. 2019;34:280–287. doi: 10.1007/s12291-018-0759-5
41. Zimmerman FH. Cardiovascular disease and risk factors in law enforcement personnel: a comprehensive review. *Cardiol Rev*. 2012;20:159–166. doi: 10.1097/CRD.0b013e318248d631
42. Robbins RB, Thiese MS, Ott U, Wood EM, Effiong A, Murtaugh M, Kapellusch J, Cheng M, Hegmann K. Metabolic syndrome in commercial truck drivers: prevalence; associated factors, and comparison with the general population. *J Occup Environ Med*. 2020;62:453–459. doi: 10.1097/JOM.0000000000001863
43. Li K, Lipsey T, Leach HJ, Nelson TL. Cardiac health and fitness of Colorado male/female firefighters. *Occup Med (Lond)*. 2017;67:268–273. doi: 10.1093/occmed/kqx033
44. Shin D, Kongpakpaisarn K, Bohra C. Trends in the prevalence of metabolic syndrome and its components in the United States 2007-2014. *Int J Cardiol*. 2018;259:216–219. doi: 10.1016/j.ijcard.2018.01.139
45. Moore JX, Chaudhary N, Akinyemiju T. Metabolic syndrome prevalence by race/ethnicity and sex in the United States, National Health and Nutrition Examination Survey, 1988-2012. *Prev Chronic Dis*. 2017;14:E24. doi: 10.5888/pcd14.16028
46. Palmer MK, Toth PP. Trends in lipids, obesity, metabolic syndrome, and diabetes mellitus in the United States: an NHANES analysis (2003-2004 to 2013-2014). *Obesity (Silver Spring)*. 2019;27:309–314. doi: 10.1002/oby.22370
47. Efstathiou SP, Skeva II, Zorbala E, Georgiou E, Mountokalakis TD. Metabolic syndrome in adolescence: can it be predicted from natal and parental profile? The Prediction of Metabolic Syndrome in Adolescence (PREMA) study. *Circulation*. 2012;125:902–910. doi: 10.1161/CIRCULATIONAHA.111.034546
48. Martin RM, Patel R, Kramer MS, Vilchuck K, Bogdanovich N, Sergeichick N, Gusina N, Foo Y, Palmer T, Thompson J, et al. Effects of promoting longer-term and exclusive breastfeeding on cardiometabolic risk factors at age 11.5 years: a cluster-randomized, controlled trial. *Circulation*. 2014;129:321–329. doi: 10.1161/CIRCULATIONAHA.113.005160
49. Mohite S, Wu H, Sharma S, Lavagnino L, Zeni CP, Currie TT, Soares JC, Pigott TA. Higher prevalence of metabolic syndrome in child-adolescent patients with bipolar disorder. *Clin Psychopharmacol Neurosci*. 2020;18:279–288. doi: 10.9758/cpn.2020.18.2.279
50. Gepstein V, Weiss R. Obesity as the main risk factor for metabolic syndrome in children. *Front Endocrinol (Lausanne)*. 2019;10:568. doi: 10.3389/fendo.2019.00568
51. Moore BF, Clark ML, Bachand A, Reynolds SJ, Nelson TL, Peel JL. Interactions between diet and exposure to secondhand smoke on metabolic syndrome among children: NHANES 2007-2010. *J Clin Endocrinol Metab*. 2016;101:52–58. doi: 10.1210/jc.2015-2477
52. Zhang JS, Gui ZH, Zou ZY, Yang BY, Ma J, Jing J, Wang HJ, Luo JY, Zhang X, Luo CY, et al. Long-term exposure to ambient air pollution and metabolic syndrome in children and adolescents: a national cross-sectional study in China. *Environ Int*. 2021;148:106383. doi: 10.1016/j.envint.2021.106383
53. Rodriguez LA, Madsen KA, Cotterman C, Lustig RH. Added sugar intake and metabolic syndrome in US adolescents: cross-sectional analysis of the National Health and Nutrition Examination Survey 2005-2012. *Public Health Nutr*. 2016;19:2424–2434. doi: 10.1017/S1368980016000057
54. Martinez Steele E, Juul F, Neri D, Rauber F, Monteiro CA. Dietary share of ultra-processed foods and metabolic syndrome in the US adult population. *Prev Med*. 2019;125:40–48. doi: 10.1016/j.ypmed.2019.05.004
55. Renninger M, Hansen BH, Steene-Johannessen J, Kriemler S, Froberg K, Northstone K, Sardinha L, Anderssen SA, Andersen LB, Ekelund U. Associations between accelerometry measured physical activity and sedentary time and the metabolic syndrome: a meta-analysis of more than 6000 children and adolescents. *Pediatr Obes*. 2020;15:e12578. doi: 10.1111/ijpo.12578
56. Lin S, Tang L, Jiang R, Chen Y, Yang S, Li L, Li P. The relationship between aspartate aminotransferase to alanine aminotransferase ratio and metabolic syndrome in adolescents in Northeast China. *Diabetes Metab Syndr Obes*. 2019;12:2387–2394. doi: 10.2147/DMSO.S217127
57. Xie S, Jiang R, Xu W, Chen Y, Tang L, Li L, Li P. The relationship between serum-free insulinlike growth factor-1 and metabolic syndrome in school adolescents of northeast China. *Diabetes Metab Syndr Obes*. 2019;12:305–313. doi: 10.2147/dmso.s195625
58. Sparrenberger K, Sbaraini M, Cureau FV, Teló GH, Bahia L, Schaan BD. Higher adiponectin concentrations are associated with reduced metabolic syndrome risk independently of weight status in Brazilian adolescents. *Diabetol Metab Syndr*. 2019;11:40. doi: 10.1186/s13098-019-0435-9
59. Gomez JAM, Moreno-Mascareño D, Rojo CEA, de la Peña GD. Association of total and high molecular weight adiponectin with components of metabolic syndrome in Mexican children. *J Clin Res Pediatr Endocrinol*. 2020;12:180–188. doi: 10.4274/jcrpe.galenos.2019.2019.0113
60. Drake I, Sonestedt E, Ericson U, Wallström P, Orho-Melander M. A Western dietary pattern is prospectively associated with cardio-metabolic traits and incidence of the metabolic syndrome. *Br J Nutr*. 2018;119:1168–1176. doi: 10.1017/S000711451800079X
61. Kouvari M, Panagiotakos DB, Naumovski N, Chrysohoou C, Georgousopoulou EN, Yannakoulia M, Tousoulis D, Pitsavos C; ATTICA Study Investigators. Dietary anti-inflammatory index, metabolic syndrome and transition in metabolic status; a gender-specific analysis of ATTICA prospective study. *Diabetes Res Clin Pract*. 2020;161:108031. doi: 10.1016/j.diabres.2020.108031
62. Canto-Osorio F, Denova-Gutierrez E, Sánchez-Romero LM, Salmerón J, Barrientos-Gutierrez T. Dietary Inflammatory Index and metabolic syndrome in Mexican adult population. *Am J Clin Nutr*. 2020;112:373–380. doi: 10.1093/ajcn/nqaa135
63. Gallardo-Alfaro L, Bibiloni MM, Mascaró CM, Montemayor S, Ruiz-Canela M, Salas-Salvadó J, Corella D, Fitó M, Romaguera D, Vioque J, et al. Leisure-time physical activity, sedentary behaviour and diet quality are associated with metabolic syndrome severity: the PREDIMED-Plus Study. *Nutrients*. 2020;12:1013–1013. doi: 10.3390/nu12041013
64. Narain A, Kwok CS, Mamas MA. Soft drink intake and the risk of metabolic syndrome: a systematic review and meta-analysis. *Int J Clin Pract*. 2017;71:e12927. doi: 10.1111/ijcp.12927
65. Appelhans BM, Baylin A, Huang M-H, Li H, Janssen I, Kazlauskaite R, Avery EF, Kravitz HM. Beverage intake and metabolic syndrome risk over 14 years: the Study of Women's Health Across the Nation. *J Acad Nutr Diet*. 2017;117:554–562. doi: 10.1016/j.jand.2016.10.011
66. Shin S, Kim S-A, Ha J, Lim K. Sugar-sweetened beverage consumption in relation to obesity and metabolic syndrome among Korean adults: a cross-sectional study from the 2012–2016 Korean National Health and Nutrition Examination Survey (KNHANES). *Nutrients*. 2018;10:1467. doi: 10.3390/nu10101467
67. Kelishadi R, Mansourian M, Heidari-Beni M. Association of fructose consumption and components of metabolic syndrome in human studies: a systematic review and meta-analysis. *Nutrition*. 2014;30:503–510. doi: 10.1016/j.nut.2013.08.014
68. Kwon YJ, Lee HS, Lee JW. Association of carbohydrate and fat intake with metabolic syndrome. *Clin Nutr*. 2018;37:746–751. doi: 10.1016/j.clnu.2017.06.022
69. Julibert A, Bibiloni MDM, Bouzas C, Martinez-Gonzalez MA, Salas-Salvado J, Corella D, Zomeno MD, Romaguera D, Vioque J, Alonso-Gomez AM, et al; PREDIMED-Plus Investigators. Total and subtypes of dietary fat intake and its association with components of the metabolic syndrome in a Mediterranean population at high cardiovascular risk. *Nutrients*. 2019;11:1493. doi: 10.3390/nu11071493
70. Kim Y, Je Y. Meat Consumption and risk of metabolic syndrome: results from the Korean population and a meta-analysis of observational studies. *Nutrients*. 2018;10:390. doi: 10.3390/nu10040390
71. Luan D, Wang D, Campos H, Baylin A. Red meat consumption and metabolic syndrome in the Costa Rica Heart Study. *Eur J Nutr*. 2019;59:185–193. doi: 10.1007/s00394-019-01898-6

72. Lutsey PL, Steffen LM, Stevens J. Dietary intake and the development of the metabolic syndrome: the Atherosclerosis Risk in Communities study. *Circulation*. 2008;117:754–761. doi: 10.1161/CIRCULATIONAHA.107.716159
73. Kim H, Lee K, Rebholz CM, Kim J. Plant-based diets and incident metabolic syndrome: results from a South Korean prospective cohort study. *PLoS Med*. 2020;17:e1003371. doi: 10.1371/journal.pmed.1003371
74. Song YM, Lee K. Eating behavior and metabolic syndrome over time. *Eat Weight Disord*. 2019;25:545–552. doi: 10.1007/s40519-019-00640-9
75. Yoon C, Jacobs DR, Duprez DA, Neumark-Sztainer D, Steffen LM, Mason SM. Problematic eating behaviors and attitudes predict long-term incident metabolic syndrome and diabetes: the Coronary Artery Risk Development in Young Adults Study. *Int J Eating Disord*. 2019;52:304–308. doi: 10.1002/eat.23020
76. Stoutenberg M, Lee DC, Sui X, Hooker S, Horigian V, Perrino T, Blair S. Prospective study of alcohol consumption and the incidence of the metabolic syndrome in US men. *Br J Nutr*. 2013;110:901–910. doi: 10.1017/S0007114512005764
77. Wei B, Liu Y, Lin X, Fang Y, Cui J, Wan J. Dietary fiber intake and risk of metabolic syndrome: a meta-analysis of observational studies. *Clin Nutr*. 2017;37:1935–1942. doi: 10.1016/j.clnu.2017.10.019
78. Echeverria G, McGee EE, Urquiaga I, Jimenez P, D'Acuna S, Villarroel L, Velasco N, Leighton F, Rigotti A. Inverse associations between a locally validated Mediterranean diet index, overweight/obesity, and metabolic syndrome in Chilean adults. *Nutrients*. 2017;9:E862. doi: 10.3390/nu9080862
79. Carlos S, De La Fuente-Arrillaga C, Bes-Rastrollo M, Razquin C, Rico-Campà A, Martínez-González MA, Ruiz-Canela M. Mediterranean diet and health outcomes in the SUN cohort. *Nutrients*. 2018;10:439. doi: 10.3390/nu10040439
80. Franquesa M, Pujol-Busquets G, Garcia-Fernandez E, Rico L, Shamirian-Pulido L, Aguilar-Martinez A, Medina FX, Serra-Majem L, Bach-Faig A. Mediterranean diet and cardiodiabesity: a systematic review through evidence-based answers to key clinical questions. *Nutrients*. 2019;11:655. doi: 10.3390/nu11030655
81. Lim M, Kim J. Association between fruit and vegetable consumption and risk of metabolic syndrome determined using the Korean Genome and Epidemiology Study (KoGES). *Eur J Nutr*. 2020;59:1667–1678. doi: 10.1007/s00394-019-02021-5
82. Babio N, Becerra-Tomas N, Martinez-Gonzalez MA, Corella D, Estruch R, Ros E, Sayon-Orea C, Fito M, Serra-Majem L, Aros F, et al; PREDIMED Investigators. Consumption of yogurt, low-fat milk, and other low-fat dairy products is associated with lower risk of metabolic syndrome incidence in an elderly Mediterranean population. *J Nutr*. 2015;145:2308–2316. doi: 10.3945/jn.115.214593
83. Hidayat K, Yu L-G, Yang J-R, Zhang X-Y, Zhou H, Shi Y-J, Liu B, Qin L-Q. The association between milk consumption and the metabolic syndrome: a cross-sectional study of the residents of Suzhou, China and a meta-analysis. *Br J Nutr*. 2020;123:1013–1023. doi: 10.1017/S0007114520000227
84. Hill AM, Harris Jackson KA, Roussell MA, West SG, Kris-Etherton PM. Type and amount of dietary protein in the treatment of metabolic syndrome: a randomized controlled trial. *Am J Clin Nutr*. 2015;102:757–770. doi: 10.3945/ajcn.114.104026
85. Shang F, Li X, Jiang X. Coffee consumption and risk of the metabolic syndrome: a meta-analysis. *Diabetes Metab*. 2016;42:80–87. doi: 10.1016/j.diabet.2015.09.001
86. Koyama T, Maekawa M, Ozaki E, Kuriyama N, Uehara R. Daily consumption of coffee and eating bread at breakfast time is associated with lower visceral adipose tissue and with lower prevalence of both visceral obesity and metabolic syndrome in Japanese populations: a cross-sectional study. *Nutrients*. 2020;12:3090. doi: 10.3390/nu12103090
87. Lee K, Kim J. Serum vitamin D status and metabolic syndrome: a systematic review and dose-response meta-analysis. *Nutr Res Pract*. 2021;15:329–345. doi: 10.4162/nrp.2021.15.3.329
88. O'Neil CE, Fulgoni VL 3rd, Nicklas TA. Tree Nut consumption is associated with better adiposity measures and cardiovascular and metabolic syndrome health risk factors in U.S. adults: NHANES 2005-2010. *Nutr J*. 2015;14:64. doi: 10.1186/s12937-015-0052-x
89. Hosseinpour-Niazi S, Hosseini S, Mirmiran P, Azizi F. Prospective study of nut consumption and incidence of metabolic syndrome: Tehran Lipid and Glucose Study. *Nutrients*. 2017;9:1056. doi: 10.3390/nu9101056
90. Kim YS, Xun P, He K. Fish consumption, long-chain omega-3 polyunsaturated fatty acid intake and risk of metabolic syndrome: a meta-analysis. *Nutrients*. 2015;7:2085–2100. doi: 10.3390/nu7042085
91. Zhang D, Liu X, Liu Y, Sun X, Wang B, Ren Y, Zhao Y, Zhou J, Han C, Yin L, et al. Leisure-time physical activity and incident metabolic syndrome: a systematic review and dose-response meta-analysis of cohort studies. *Metabolism*. 2017;75:36–44. doi: 10.1016/j.metabol.2017.08.001
92. Lin X, Zhang X, Guo J, Roberts CK, McKenzie S, Wu WC, Liu S, Song Y. Effects of exercise training on cardiorespiratory fitness and biomarkers of cardiometabolic health: a systematic review and meta-analysis of randomized controlled trials. *J Am Heart Assoc*. 2015;4:e002014. doi: 10.1161/JAHA.115.002014
93. Said MA, Abdelmoneim MA, Alibrahim MS, Kotb AAH. Aerobic training, resistance training, or their combination as a means to fight against excess weight and metabolic syndrome in obese students: which is the most effective modality? A randomized controlled trial. *Appl Physiol Nutr Metab*. 2021;46:952–963. doi: 10.1139/apnm-2020-0972
94. Kelley E, Imboden MT, Harber MP, Finch H, Kaminsky LA, Whaley MH. Cardiorespiratory fitness is inversely associated with clustering of metabolic syndrome risk factors: the Ball State Adult Fitness Program Longitudinal Lifestyle Study. *Mayo Clin Proc Innov Qual Outcomes*. 2018;2:155–164. doi: 10.1016/j.mayocpiqo.2018.03.001
95. Sagawa N, Rockette-Wagner B, Azuma K, Ueshima H, Hisamatsu T, Takamiya T, El-Saed A, Miura K, Kriska A, Sekikawa A. Physical activity levels in American and Japanese men from the ERA-JUMP study and associations with metabolic syndrome. *J Sport Health Sci*. 2019;9:170–178. doi: 10.1016/j.jshs.2019.09.007
96. Zajac-Gawlak I, Pelclova J, Groffik D, Pridalova M, Nawrat-Szoltysik A, Kroemeke A, Gaba A, Sadowska-Krepa E. Does physical activity lower the risk for metabolic syndrome: a longitudinal study of physically active older women. *BMC Geriatr*. 2021;21:11. doi: 10.1186/s12877-020-01952-7
97. Xie J, Li Y, Zhang Y, Vgontzas AN, Basta M, Chen B, Xu C, Tang X. Sleep duration and metabolic syndrome: an updated systematic review and meta-analysis. *Sleep Med Rev*. 2021;59:101451. doi: 10.1016/j.smrv.2021.101451
98. Hong GB, Gao PC, Chen YY, Xia Y, Ke XS, Shao XF, Xiong CX, Chen HS, Xiao H, Ning J, et al. High-sensitivity C-reactive protein leads to increased incident metabolic syndrome in women but not in men: a five-year follow-up study in a Chinese population. *Diabetes Metab Syndr Obes*. 2020;13:581–590. doi: 10.2147/DMSO.S241774
99. Palaniappan L, Carnethon MR, Wang Y, Hanley AJ, Fortmann SP, Haffner SM, Wagenknecht L; Insulin Resistance Atherosclerosis Study. Predictors of the incident metabolic syndrome in adults: the Insulin Resistance Atherosclerosis Study. *Diabetes Care*. 2004;27:788–793. doi: 10.2337/diacare.27.3.788
100. Liu Z, Liang S, Que S, Zhou L, Zheng S, Mardinoglu A. Meta-analysis of adiponectin as a biomarker for the detection of metabolic syndrome. *Front Physiol*. 2018;9:1238. doi: 10.3389/fphys.2018.01238
101. Liu S, Sun Q. Sex differences, endogenous sex-hormone hormones, sex-hormone binding globulin, and exogenous disruptors in diabetes and related metabolic outcomes. *J Diabetes*. 2018;10:428–441. doi: 10.1111/1753-0407.12517
102. Al-Khalidi B, Kimball SM, Rotondi MA, Ardern CI. Standardized serum 25-hydroxyvitamin D concentrations are inversely associated with cardiometabolic disease in U.S. adults: a cross-sectional analysis of NHANES, 2001-2010. *Nutr J*. 2017;16:16. doi: 10.1186/s12937-017-0237-6
103. Farrell SW, Leonard D, Barlow CE, Willis BL, Pavlovic A, Defina LF, Haskell WL. Cardiorespiratory fitness, serum vitamin D, and prevalence of metabolic syndrome in men. *Med Sci Sports Exerc*. 2021;53:68–73. doi: 10.1249/MSS.0000000000002445
104. Ganji V, Tangpricha V, Zhang X. Serum vitamin D concentration ≥75 nmol/L is related to decreased cardiometabolic and inflammatory biomarkers, metabolic syndrome, and diabetes; and increased cardiorespiratory fitness in US adults. *Nutrients*. 2020;12:730. doi: 10.3390/nu12030730
105. Liu L, Cao Z, Lu F, Liu Y, Lv Y, Qu Y, Gu H, Li C, Cai J, Ji S, et al. Vitamin D deficiency and metabolic syndrome in elderly Chinese individuals: evidence from CLHLS. *Nutr Metab*. 2020;17:1–11. doi: 10.1186/s12986-020-00479-3
106. Pott-Junior H, Nascimento CMC, Costa-Guarisco LP, Gomes GAO, Gramani-Say K, Orlandi FS, Gratão ACM, Orlandi AAS, Pavarini SCI, Vasilceac FA, et al. Vitamin D deficient older adults are more prone to have metabolic syndrome, but not to a greater number of metabolic syndrome parameters. *Nutrients*. 2020;12:748. doi: 10.3390/nu12030748
107. Hao H, Guo H, Ma RL, Yan YZ, Hu YH, Ma JL, Zhang XH, Wang XP, Wang K, Mu LT, et al. Association of total bilirubin and indirect bilirubin content with metabolic syndrome among Kazakhs in Xinjiang. *BMC Endocr Disord*. 2020;20:110. doi: 10.1186/s12902-020-00563-y

108. Jung ES, Choi EK, Park BH, Chae SW. Serum follicle-stimulating hormone levels are associated with cardiometabolic risk factors in post-menopausal Korean women. *J Clin Med*. 2020;9:1161. doi: 10.3390/jcm9041161
109. Beltran-Sanchez H, Harhay MO, Harhay MM, McElligott S. Prevalence and trends of metabolic syndrome in the adult U.S. population, 1999-2010. *J Am Coll Cardiol*. 2013;62:697–703. doi: 10.1016/j.jacc.2013.05.064
110. Cheng E, Burrows R, Correa P, Güichapani CG, Blanco E, Gahagan S. Light smoking is associated with metabolic syndrome risk factors in Chilean young adults. *Acta Diabetol*. 2019;56:473–479. doi: 10.1007/s00592-018-1264-2
111. Kim BJ, Kang JG, Han JM, Kim JH, Lee SJ, Seo DC, Lee SH, Kim BS, Kang JH. Association of self-reported and cotinine-verified smoking status with incidence of metabolic syndrome in 47 379 Korean adults. *J Diabetes*. 2019;11:402–409. doi: 10.1111/1753-0407.12868
112. Koskinen J, Magnussen CG, Sinaiko A, Woo J, Urbina E, Jacobs DR Jr, Steinberger J, Prineas R, Sabin MA, Burns T, et al. Childhood age and associations between childhood metabolic syndrome and adult risk for metabolic syndrome, type 2 diabetes mellitus and carotid intima media thickness: the International Childhood Cardiovascular Cohort Consortium. *J Am Heart Assoc*. 2017;6:e005632. doi: 10.1161/JAHA.117.005632
113. Pluimakers VG, van Waas M, Looman CWN, de Maat MP, de Jonge R, Delhanty P, Huisman M, Mattace-Raso FUS, van den Heuvel-Eibrink MM, Neggers SJCMM. Metabolic syndrome detection with biomarkers in childhood cancer survivors. *Endocr Connect*. 2020;9:676–686. doi: 10.1530/EC-20-0144
114. Franco OH, Massaro JM, Civil J, Cobain MR, O'Malley B, D'Agostino RB Sr. Trajectories of entering the metabolic syndrome: the Framingham Heart Study. *Circulation*. 2009;120:1943–1950. doi: 10.1161/CIRCULATIONAHA.109.855817
115. Ferreira I, Twisk JW, van Mechelen W, Kemper HC, Stehouwer CD. Development of fatness, fitness, and lifestyle from adolescence to the age of 36 years: determinants of the metabolic syndrome in young adults: the Amsterdam Growth and Health Longitudinal Study. *Arch Intern Med*. 2005;165:42–48. doi: 10.1001/archinte.165.1.42
116. Vergnaud AC, Bertrais S, Oppert JM, Maillard-Teyssier L, Galan P, Hercberg S, Czernichow S. Weight fluctuations and risk for metabolic syndrome in an adult cohort. *Int J Obes (Lond)*. 2008;32:315–321. doi: 10.1038/sj.ijo.0803739
117. Pan A, Keum N, Okereke OI, Sun Q, Kivimaki M, Rubin RR, Hu FB. Bidirectional association between depression and metabolic syndrome: a systematic review and meta-analysis of epidemiological studies. *Diabetes Care*. 2012;35:1171–1180. doi: 10.2337/dc11-2055
118. Moradi Y, Albatineh AN, Mahmoodi H, Gheshlagh RG. The relationship between depression and risk of metabolic syndrome: a meta-analysis of observational studies. *Clin Diabetes Endocrinol*. 2021;7:4. doi: 10.1186/s40842-021-00117-8
119. Liu SY, Zhu WT, Chen BW, Chen YH, Ni GX. Bidirectional association between metabolic syndrome and osteoarthritis: a meta-analysis of observational studies. *Diabetol Metab Syndr*. 2020;12:38. doi: 10.1186/s13098-020-00547-x
120. Liao L, Deng Y, Zhao D. Association of low birth weight and premature birth with the risk of metabolic syndrome: a meta-analysis. *Front Pediatr*. 2020;8:405. doi: 10.3389/fped.2020.00405
121. Suliga E, Ciesla E, Gluszek-Osuch M, Lysek-Gladysinska M, Wawrzycka I, Gluszek S. Breastfeeding and prevalence of metabolic syndrome among perimenopausal Women. *Nutrients*. 2020;12:2691. doi: 10.3390/nu12092691
122. Ballestri S, Zona S, Targher G, Romagnoli D, Baldelli E, Nascimbeni F, Roverato A, Guaraldi G, Lonardo A. Nonalcoholic fatty liver disease is associated with an almost twofold increased risk of incident type 2 diabetes and metabolic syndrome. Evidence from a systematic review and meta-analysis. *J Gastroenterol Hepatol*. 2016;31:936–944. doi: 10.1111/jgh.13264
123. Oh SW, Han KH, Han SY, Koo HS, Kim S, Chin HJ. Association of sodium excretion with metabolic syndrome, insulin resistance, and body fat. *Medicine (Baltimore)*. 2015;94:e1650. doi: 10.1097/MD.0000000000001650
124. Krittanawong C, Tunhasiriwet A, Zhang H, Prokop LJ, Chirapongsathorn S, Sun T, Wang Z. Is white rice consumption a risk for metabolic and cardiovascular outcomes? A systematic review and meta-analysis. *Heart Asia*. 2019;9:e010909. doi: 10.1136/heartasia-2017-010909
125. Kim HY, Lee J, Kim J. Association between Dietary Inflammatory Index and metabolic syndrome in the general Korean population. *Nutrients*. 2018;10:F648. doi: 10.3390/nu10050648
126. Aslani Z, Sadeghi O, Heidari-Beni M, Zahedi H, Baygi F, Shivappa N, Hébert JR, Moradi S, Sotoudeh G, Asayesh H, et al. Association of dietary inflammatory potential with cardiometabolic risk factors and diseases: a systematic review and dose–response meta-analysis of observational studies. *Diabetol Metab Syndr*. 2020;12:106. doi: 10.1186/s13098-020-00615-2
127. Arisawa K, Katsuura-Kamano S, Uemura H, Van Tien N, Hishida A, Tamura T, Kubo Y, Tsukamoto M, Tanaka K, Hara M, et al. Association of dietary acid load with the prevalence of metabolic syndrome among participants in baseline survey of the Japan Multi-Institutional Collaborative Cohort Study. *Nutrients*. 2020;12:1605. doi: 10.3390/nu12061605
128. Sadeghi O, Hasani H, Mozaffari-Khosravi H, Maleki V, Lotfi MH, Mirzaei M. Dietary Insulin Index and dietary insulin load in relation to metabolic syndrome: the Shahedieh Cohort Study. *J Acad Nutr Diet*. 2020;120:1672–1686.e4. doi: 10.1016/j.jand.2020.03.008
129. Santulli G, Pascale V, Finelli R, Visco V, Giannotti R, Massari A, Morisco C, Ciccarelli M, Illario M, Iaccarino G, et al. We are what we eat: impact of food from short supply chain on metabolic syndrome. *J Clin Med*. 2019;8:2061. doi: 10.3390/jcm8122061
130. Kim MK, Chon SJ, Noe EB, Roh YH, Yun BH, Cho S, Choi YS, Lee BS, Seo SK. Associations of dietary calcium intake with metabolic syndrome and bone mineral density among the Korean population: KNHANES 2008-2011. *Osteoporos Int*. 2017;28:299–308. doi: 10.1007/s00198-016-3717-1
131. Duong TV, Wong TC, Chen HH, Chen TW, Chen TH, Hsu YH, Peng SJ, Kuo KL, Liu HC, Lin ET, et al. Inadequate dietary energy intake associates with higher prevalence of metabolic syndrome in different groups of hemodialysis patients: a clinical observational study in multiple dialysis centers. *BMC Nephrol*. 2018;19:236. doi: 10.1186/s12882-018-1041-z
132. Kim S, Song Y, Lee JE, Jun S, Shin S, Wie GA, Cho YH, Joung H. Total antioxidant capacity from dietary supplement decreases the likelihood of having metabolic syndrome in Korean adults. *Nutrients*. 2017;9:1055. doi: 10.3390/nu9101055
133. Ahmadi E, Abdollahzad H, Pasdar Y, Rezaeian S, Moludi J, Nachvak SM, Mostafai R. Relationship between the consumption of milk-based oils including butter and kermanshah ghee with metabolic syndrome: Ravansar Non-Communicable Disease Cohort Study. *Diabetes Metab Syndr Obes*. 2020;13:1519–1530. doi: 10.2147/DMSO.S247412
134. Baudry J, Lelong H, Adriouch S, Julia C, Alles B, Hercberg S, Touvier M, Lairon D, Galan P, Kesse-Guyot E. Association between organic food consumption and metabolic syndrome: cross-sectional results from the NutriNet-Sante study. *Eur J Nutr*. 2018;57:2477–2488. doi: 10.1007/s00394-017-1520-1
135. Mohammadpour S, Ghorbaninejad P, Janbozorgi N, Shab-Bidar S. Associations between adherence to MIND diet and metabolic syndrome and general and abdominal obesity: a cross-sectional study. *Diabetol Metab Syndr*. 2020;12:101. doi: 10.1186/s13098-020-00611-6
136. Edwards MK, Loprinzi PD. High amounts of sitting, low cardiorespiratory fitness, and low physical activity levels: 3 key ingredients in the recipe for influencing metabolic syndrome prevalence. *Am J Health Promot*. 2018;32:587–594. doi: 10.1177/0890117116684889
137. Aljuhani O, Alkahtani S, Alhussain M, Smith L, Habib SS. Associations of physical activity and sedentary time with metabolic syndrome in Saudi adult males. *Risk Manag Healthc Policy*. 2020;13:1839–1847. doi: 10.2147/RMHP.S267575
138. Colpitts BH, Smith S, Bouchard DR, Boudreau J, Sénéchal M. Are physical activity and sedentary behavior patterns contributing to diabetes and metabolic syndrome simultaneously? *Transl Sports Med*. 2020;4:231–240. doi: 10.1002/tsm2.216
139. Xiao J, Chu M, Shen H, Ren W, Li Z, Hua T, Xu H, Liang Y, Gao Y, Zhuang X. Relationship of "weekend warrior" and regular physical activity patterns with metabolic syndrome and its associated diseases among Chinese rural adults. *J Sports Sci*. 2018;36:1963–1971. doi: 10.1080/02640414.2018.1428883
140. Yi D, Khang AR, Lee HW, Son SM, Kang YH. Relative handgrip strength as a marker of metabolic syndrome: the Korea National Health and Nutrition Examination Survey (KNHANES) VI (2014–2015). *Diabetes Metab Syndr Obes*. 2018;11:227–240. doi: 10.2147/dmso.s166875
141. Churilla JR, Summerlin M, Richardson MR, Boltz AJ. Mean combined relative grip strength and metabolic syndrome: 2011-2014 National Health and Nutrition Examination Survey. *J Strength Cond Res*. 2020;34:995–1000. doi: 10.1519/JSC.0000000000003515
142. Merchant RA, Chan YH, Lim JY, Emorley J. Prevalence of metabolic syndrome and association with grip strength in older adults: findings from the HOPE study. *Diabetes Metab Syndr Obes*. 2020;13:2677–2686. doi: 10.2147/DMSO.S260544
143. Yeap BB, Dedic D, Budgeon CA, Murray K, Knuiman MW, Hunter M, Zhu K, Cooke BR, Lim EM, Mulrennan S, et al. U-shaped association of vigorous

physical activity with risk of metabolic syndrome in men with low lean mass, and no interaction of physical activity and serum 25-hydroxyvitamin D with metabolic syndrome risk. *Intern Med J*. 2020;50:460–469. doi: 10.1111/imj.14379
144. Fan L, Hao Z, Gao L, Qi M, Feng S, Zhou G. Non-linear relationship between sleep duration and metabolic syndrome: a population-based study. *Medicine (Baltimore)*. 2020;99:e18753. doi: 10.1097/MD.0000000000018753
145. Srikanthan K, Feyh A, Visweshwar H, Shapiro JI, Sodhi K. Systematic review of metabolic syndrome biomarkers: a panel for early detection, management, and risk stratification in the West Virginian population. *Int J Med Sci*. 2016;13:25–38. doi: 10.7150/ijms.13800
146. Klisic A, Kavaric N, Soldatovic I, Ninic A, Kotur-Stevuljevic J. Retinol-binding protein 4 better correlates with metabolic syndrome than cystatin C. *J Lab Med*. 2019;43:29–34. doi: 10.1515/labmed-2018-0325
147. Du R, Cheng D, Lin L, Sun J, Peng K, Xu Y, Xu M, Chen Y, Bi Y, Wang W, et al. Association between serum CA 19-9 and metabolic syndrome: a cross-sectional study. *J Diabetes*. 2017;9:1040–1047. doi: 10.1111/1753-0407.12523
148. Chen Y-F, Lin Y-A, Yeh W-C, Tsao Y-C, Li W-C, Fang W-C, Chen IJ, Chen J-Y. The association between metabolic syndrome and elevated alanine aminotransferase levels in an Indigenous population in Northern Taiwan: a community-based and cross-sectional study. *Evid Based Complement Alternat Med*. 2020;2020:6612447. doi: 10.1155/2020/6612447
149. Gaeini Z, Bahadoran Z, Mirmiran P, Azizi F. The association between liver function tests and some metabolic outcomes: Tehran Lipid and Glucose Study. *Hepat Mon*. 2020;20:e98535. doi: 10.5812/hepatmon.98535
150. Kim T, Kang J. Association between serum retinol and α-tocopherol levels and metabolic syndrome in Korean general population: analysis of population-based nationally representative data. *Nutrients*. 2020;12:1689. doi: 10.3390/nu12061689
151. Li M, Zhang X, Zhou X, Han X, Zhang R, Fu Z, Wang L, Gao Y, Li Y, Ji L. The association between serum thyrotropin within the reference range and metabolic syndrome in a community-based Chinese population. *Diabetes Metab Syndr Obes*. 2020;13:2001–2011. doi: 10.2147/DMSO.S252154
152. Huang LL, Dou D-M, Liu N, Wang XX, Fu L-Y, Wu X, Wang P. Association of erythrocyte parameters with metabolic syndrome in the Pearl River Delta region of China: a cross sectional study. *BMJ Open*. 2018;8:e019792. doi: 10.1136/bmjopen-2017-019792
153. Naser AM, Rahman M, Unicomb L, Doza S, Selim S, Chaity M, Luby SP, Anand S, Staimez L, Clasen TF, et al. Past sodium intake, contemporary sodium intake, and cardiometabolic health in southwest coastal Bangladesh. *J Am Heart Assoc*. 2020;9:e014978. doi: 10.1161/JAHA.119.014978
154. Xu P, Liu A, Li F, Tinkov AA, Liu L, Zhou JC. Associations between metabolic syndrome and four heavy metals: a systematic review and meta-analysis. *Environ Pollut*. 2021;273:116480. doi: 10.1016/j.envpol.2021.116480
155. Ramírez-Vélez R, Garcia-Hermoso A, Prieto-Benavides DH, Correa-Bautista JE, Quino-Ávila AC, Rubio-Barreto CM, González-Ruíz K, Carrillo HA, Correa-Rodríguez M, González-Jiménez E, et al. Muscle mass to visceral fat ratio is an important predictor of the metabolic syndrome in college students. *Br J Nutr*. 2019;121:330–339. doi: 10.1017/S0007114518003392
156. Hruska B, Pressman SD, Bendinskas K, Gump BB. Vacation frequency is associated with metabolic syndrome and symptoms. *Psychol Health*. 2020;35:1–15. doi: 10.1080/08870446.2019.1628962
157. Vidot DC, Prado G, Hlaing WM, Florez HJ, Arheart KL, Messiah SE. Metabolic syndrome among marijuana users in the United States: an analysis of National Health and Nutrition Examination Survey Data. *Am J Med*. 2016;129:173–179. doi: 10.1016/j.amjmed.2015.10.019
158. Kuo WC, Bratzke LC, Oakley LD, Kuo F, Wang H, Brown RL. The association between psychological stress and metabolic syndrome: a systematic review and meta-analysis. *Obes Rev*. 2019;20:1651–1664. doi: 10.1111/obr.12915
159. Han KT, Kim SJ. Regional factors associated with the prevalence of metabolic syndrome: focusing on the role of healthcare providers. *Health Soc Care Community*. 2021;29:104–112. doi: 10.1111/hsc.13073
160. Wu HF, Tam T, Jin L, Lao XQ, Chung RY, Su XF, Zee B. Age, gender, and socioeconomic gradients in metabolic syndrome: biomarker evidence from a large sample in Taiwan, 2005-2013. *Ann Epidemiol*. 2017;27:315–322.e2. doi: 10.1016/j.annepidem.2017.04.003
161. Beatty Moody DL, Chang Y, Brown C, Bromberger JT, Matthews KA. Everyday discrimination and metabolic syndrome incidence in a racially/ethnically diverse sample: Study of Women's Health Across the Nation. *Psychosom Med*. 2018;80:114–121. doi: 10.1097/PSY.0000000000000516
162. Khambaty T, Schneiderman N, Llabre MM, Elfassy T, Moncrieft AE, Daviglus M, Talavera GA, Isasi CR, Gallo LC, Reina SA, et al. Elucidating the multidimensionality of socioeconomic status in relation to metabolic syndrome in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). *Int J Behav Med*. 2020;27:188–199. doi: 10.1007/s12529-020-09847-y
163. Park SH, Strauss SM. Food insecurity as a predictor of metabolic syndrome in U.S. female adults. *Public Health Nurs*. 2020;37:663–670. doi: 10.1111/phn.12781
164. Iguacel I, Börnhorst C, Michels N, Breidenassel C, Dallongeville J, González-Gross M, Gottrand F, Kafatos A, Karaglani E, Kersting M, et al. Socioeconomically disadvantaged groups and metabolic syndrome in european adolescents: the HELENA study. *J Adolesc Health*. 2021;68:146–154. doi: 10.1016/j.jadohealth.2020.05.027
165. Chung J, Choi H, Jung J, Kong MG. Association between socioeconomic status and metabolic syndrome in Korean adults: data from the Korean National Health and Nutrition Examination Survey. *CardioMetab Syndr J*. 2021;1:168–179. doi: 10.51789/cmsj.2021.1.e16
166. Abbate M, Pericas J, Yanez AM, Lopez-Gonzalez AA, De Pedro-Gomez J, Aguilo A, Morales-Asencio JM, Bennasar-Veny M. Socioeconomic inequalities in metabolic syndrome by age and gender in a Spanish working population. *Int J Environ Res Public Health*. 2021;18:10333. doi: 10.3390/ijerph181910333
167. Colombet Z, Perignon M, Salanave B, Landais E, Martin-Prevel Y, Alles B, Drogue S, Amiot MJ, Mejean C. Socioeconomic inequalities in metabolic syndrome in the French West Indies. *BMC Public Health*. 2019;19:1620. doi: 10.1186/s12889-019-7970-z
168. Ying X, Yang S, Li S, Su M, Wang N, Chen Y, Jiang Q, Fu C. Prevalences of metabolic syndrome and its sex-specific association with socioeconomic status in rural China: a cross-sectional study. *BMC Public Health*. 2021;21:2033. doi: 10.1186/s12889-021-12074-z
169. Vishnu A, Gurka MJ, DeBoer MD. The severity of the metabolic syndrome increases over time within individuals, independent of baseline metabolic syndrome status and medication use: the Atherosclerosis Risk in Communities Study. *Atherosclerosis*. 2015;243:278–285. doi: 10.1016/j.atherosclerosis.2015.09.025
170. Patel PA, Scott CG, Rodeheffer RJ, Chen HH. The natural history of patients with isolated metabolic syndrome. *Mayo Clin Proc*. 2016;91:623–633. doi: 10.1016/j.mayocp.2016.02.026
171. Musani SK, Martin LJ, Woo JG, Olivier M, Gurka MJ, DeBoer MD. Heritability of the severity of the metabolic syndrome in Whites and Blacks in 3 large cohorts. *Circ Cardiovasc Genet*. 2017;10:e001621. doi: 10.1161/CIRCGENETICS.116.001621
172. Nagrani R, Foraita R, Gianfagna F, Iacoviello L, Marild S, Michels N, Molnar D, Moreno L, Russo P, Veidebaum T, et al. Common genetic variation in obesity, lipid transfer genes and risk of metabolic syndrome: results from IDEFICS/I.Family study and meta-analysis. *Sci Rep*. 2020;10:7189. doi: 10.1038/s41598-020-64031-2
173. Lin E, Kuo PH, Liu YL, Yang AC, Tsai SJ. Detection of susceptibility loci on *APOA5* and *COLEC12* associated with metabolic syndrome using a genome-wide association study in a Taiwanese population. *Oncotarget*. 2017;8:93349–93359. doi: 10.18632/oncotarget.20967
174. Morjane I, Kefi R, Charoute H, Lakbakbi El Yaagoubi F, Hechmi M, Saile R, Abdelhak S, Barakat A. Association study of *HNF1A* polymorphisms with metabolic syndrome in the Moroccan population. *Diabetes Metab Syndr*. 2017;11:S853–S857. doi: 10.1016/j.dsx.2017.07.005
175. Lakbakbi El Yaagoubi F, Charoute H, Morjane I, Sefri H, Rouba H, Ainahi A, Kandil M, Benrahma H, Barakat A. Association analysis of genetic variants with metabolic syndrome components in the Moroccan population. *Curr Res Transl Med*. 2017;65:121–125. doi: 10.1016/j.retram.2017.08.001
176. Carty CL, Bhattacharjee S, Haessler J, Cheng I, Hindorff LA, Aroda V, Carlson CS, Hsu CN, Wilkens L, Liu S, et al. Analysis of metabolic syndrome components in >15 000 African Americans identifies pleiotropic variants: results from the Population Architecture Using Genomics and Epidemiology Study. *Circ Cardiovasc Genet*. 2014;7:505–513. doi: 10.1161/CIRCGENETICS.113.000386
177. Zafar U, Khaliq S, Lone KP. Genetic association of apolipoprotein A5-1131T>C polymorphism with traits of metabolic syndrome. *J Coll Physicians Surg Pak*. 2019;29:626–630. doi: 10.29271/jcpsp.2019.07.626
178. Wan JY, Goodman DL, Willems EL, Freedland AR, Norden-Krichmar TM, Santorico SA, Edwards KL; American Diabetes GENNID Study Group. Genome-wide association analysis of metabolic syndrome quantitative traits in the GENNID multiethnic family study. *Diabetol Metab Syndr*. 2021;13:59. doi: 10.1186/s13098-021-00670-3
179. Ghareeb D, Abdelazem AS, Hussein EM, Al-Karamany AS. Association of TNF-α-308 G>A (rs1800629) polymorphism with susceptibility of

metabolic syndrome. *J Diabetes Metab Disord*. 2021;20:209–215. doi: 10.1007/s40200-021-00732-3
180. Cannone V, Cefalu AB, Noto D, Scott CG, Bailey KR, Cavera G, Pagano M, Sapienza M, Averna MR, Burnett JC Jr. The atrial natriuretic peptide genetic variant rs5068 is associated with a favorable cardiometabolic phenotype in a Mediterranean population. *Diabetes Care*. 2013;36:2850–2856. 10.2337/dc12-2337
181. Cannone V, Cabassi A, Volpi R, Burnett JC Jr. Atrial natriuretic peptide: a molecular target of novel therapeutic approaches to cardio-metabolic disease. *Int J Mol Sci* . 2019;20:3265. doi: 10.3390/ijms20133265
182. Cannone V, Scott CG, Decker PA, Larson NB, Palmas W, Taylor KD, Wang TJ, Gupta DK, Bielinski SJ, Burnett JC Jr. A favorable cardiometabolic profile is associated with the G allele of the genetic variant rs5068 in African Americans: the Multi-Ethnic Study of Atherosclerosis (MESA). *PLoS One*. 2017;12:e0189858. doi: 10.1371/journal.pone.0189858
183. Maintinguer Norde M, Oki E, Ferreira Carioca AA, Teixeira Damasceno NR, Fisberg RM, Lobo Marchioni DM, Rogero MM. Influence of IL1B, IL6 and IL10 gene variants and plasma fatty acid interaction on metabolic syndrome risk in a cross-sectional population-based study. *Clin Nutr*. 2018;37:659–666. doi: 10.1016/j.clnu.2017.02.009
184. Lind L. Genetic determinants of clustering of cardiometabolic risk factors in U.K. Biobank. *Metab Syndr Relat Disord*. 2020;18:121–127. doi: 10.1089/met.2019.0096
185. Miao Z, Garske KM, Pan DZ, Koka A, Kaminska D, Mannisto V, Sinsheimer JS, Pihlajamaki J, Pajukanta P. Identification of 90 NAFLD GWAS loci and establishment of NAFLD PRS and causal role of NAFLD in coronary artery disease. *HGG Adv*. 2022;3:100056. doi: 10.1016/j.xhgg.2021.100056
186. Haas ME, Pirruccello JP, Friedman SN, Wang M, Emdin CA, Ajmera VH, Simon TG, Homburger JR, Guo X, Budoff M, et al. Machine learning enables new insights into genetic contributions to liver fat accumulation. *Cell Genom*. 2021;1:100066. doi: 10.1016/j.xgen.2021.100066
187. Wang Q, Chair SY, Wong EM, Taylor-Piliae RE, Qiu XCH, Li XM. Metabolic syndrome knowledge among adults with cardiometabolic risk factors: a cross-sectional study. *Int J Environ Res Public Health*. 2019;16:159. doi: 10.3390/ijerph16010159
188. Jumean MF, Korenfeld Y, Somers VK, Vickers KS, Thomas RJ, Lopez-Jimenez F. Impact of diagnosing metabolic syndrome on risk perception. *Am J Health Behav*. 2012;36:522–532. doi: 10.5993/AJHB.36.4.9
189. Mottillo S, Filion KB, Genest J, Joseph L, Pilote L, Poirier P, Rinfret S, Schiffrin EL, Eisenberg MJ. The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. *J Am Coll Cardiol*. 2010;56:1113–1132. doi: 10.1016/j.jacc.2010.05.034
190. Jasiukaitienė V, Lukšienė D, Tamošiūnas A, Radišauskas R, Bobak M. The impact of metabolic syndrome and lifestyle habits on the risk of the first event of cardiovascular disease: results from a cohort study in Lithuanian urban population. *Medicina (Kaunas)*. 2020;56:18. doi: 10.3390/medicina56010018
191. Mente A, Yusuf S, Islam S, McQueen MJ, Tanomsup S, Onen CL, Rangarajan S, Gerstein HC, Anand SS; INTERHEART Investigators. Metabolic syndrome and risk of acute myocardial infarction a case-control study of 26,903 subjects from 52 countries. *J Am Coll Cardiol*. 2010;55:2390–2398. doi: 10.1016/j.jacc.2009.12.053
192. Rachas A, Raffaitin C, Barberger-Gateau P, Helmer C, Ritchie K, Tzourio C, Amouyel P, Ducimetiere P, Empana JP. Clinical usefulness of the metabolic syndrome for the risk of coronary heart disease does not exceed the sum of its individual components in older men and women: the Three-City (3C) Study. *Heart*. 2012;98:650–655. doi: 10.1136/heartjnl-2011-301185
193. Lyubarova R, Robinson JG, Miller M, Simmons DL, Xu P, Abramson BL, Elam MB, Brown TM, McBride R, Fleg JL, et al; Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes (AIM-HIGH) Investigators. Metabolic syndrome cluster does not provide incremental prognostic information in patients with stable cardiovascular disease: a post hoc analysis of the AIM-HIGH trial. *J Clin Lipidol*. 2017;11:1201–1211. doi: 10.1016/j.jacl.2017.06.017
194. Lee HS, Kim HL, Kim MA, Oh S, Kim M, Park SM, Yoon HJ, Byun YS, Park SM, Shin MS, et al. Sex difference in the association between metabolic syndrome and obstructive coronary artery disease: analysis of data from the KoRean wOmen'S chest pain rEgistry (KoROSE). *J Womens Health (Larchmt)*. 2020;29:1500–1506. doi: 10.1089/jwh.2020.8488
195. Liu L, Miura K, Fujiyoshi A, Kadota A, Miyagawa N, Nakamura Y, Ohkubo T, Okayama A, Okamura T, Ueshima H. Impact of metabolic syndrome on the risk of cardiovascular disease mortality in the United States and in Japan. *Am J Cardiol*. 2014;113:84–89. doi: 10.1016/j.amjcard.2013.08.042
196. Li X, Li X, Lin H, Fu X, Lin W, Li M, Zeng X, Gao Q. Metabolic syndrome and stroke: a meta-analysis of prospective cohort studies. *J Clin Neurosci*. 2017;40:34–38. doi: 10.1016/j.jocn.2017.01.018
197. DeBoer MD, Filipp SL, Sims M, Musani SK, Gurka MJ. Risk of ischemic stroke increases over the spectrum of metabolic syndrome severity. *Stroke*. 2020;51:2548–2552. doi: 10.1161/STROKEAHA.120.028944
198. Hess PL, Al-Khalidi HR, Friedman DJ, Mulder H, Kucharska-Newton A, Rosamond WR, Lopes RD, Gersh BJ, Mark DB, Curtis LH, et al. The metabolic syndrome and risk of sudden cardiac death: the Atherosclerosis Risk in Communities study. *J Am Heart Assoc*. 2017;6:e006103. doi: 10.1161/JAHA.117.006103
199. Zhang F, Liu L, Zhang C, Ji S, Mei Z, Li T. Association of metabolic syndrome and its components with risk of stroke recurrence and mortality: a meta-analysis. *Neurology*. 2021;97:e695–e705. doi: 10.1212/WNL.0000000000012415
200. Chen S, Li J, Li Q, Qiu Z, Wu X, Chen L. Metabolic syndrome increases operative mortality in patients with impaired left ventricular systolic function who undergo coronary artery bypass grafting: a retrospective observational study. *BMC Cardiovasc Disord*. 2019;19:25. doi: 10.1186/s12872-019-1004-8
201. Ju SY, Lee JY, Kim DH. Association of metabolic syndrome and its components with all-cause and cardiovascular mortality in the elderly: a meta-analysis of prospective cohort studies. *Medicine (Baltimore)*. 2017;96:e8491. doi: 10.1097/MD.0000000000008491
202. Fernandez-Mendoza J, He F, LaGrotte C, Vgontzas AN, Liao D, Bixler EO. Impact of the metabolic syndrome on mortality is modified by objective short sleep duration. *J Am Heart Assoc*. 2017;6:e005479. doi: 10.1161/JAHA.117.005479
203. Morrison JA, Friedman LA, Gray-McGuire C. Metabolic syndrome in childhood predicts adult cardiovascular disease 25 years later: the Princeton Lipid Research Clinics Follow-up Study. *Pediatrics*. 2007;120:340–345. doi: 10.1542/peds.2006-1699
204. DeBoer MD, Gurka MJ, Woo JG, Morrison JA. Severity of metabolic syndrome as a predictor of cardiovascular disease between childhood and adulthood: the Princeton Lipid Research Cohort Study. *J Am Coll Cardiol*. 2015;66:755–757. doi: 10.1016/j.jacc.2015.05.061
205. DeBoer MD, Gurka MJ, Woo JG, Morrison JA. Severity of the metabolic syndrome as a predictor of type 2 diabetes between childhood and adulthood: the Princeton Lipid Research Cohort Study. *Diabetologia*. 2015;58:2745–2752. doi: 10.1007/s00125-015-3759-5
206. Asghari G, Hasheminia M, Heidari A, Mirmiran P, Guity K, Shahrzad MK, Azizi F, Hadaegh F. Adolescent metabolic syndrome and its components associations with incidence of type 2 diabetes in early adulthood: Tehran Lipid and Glucose Study. *Diabetol Metab Syndr*. 2021;13:1. doi: 10.1186/s13098-020-00608-1
207. Magnussen CG, Koskinen J, Juonala M, Chen W, Srinivasan SR, Sabin MA, Thomson R, Schmidt MD, Nguyen QM, Xu JH, et al. A diagnosis of the metabolic syndrome in youth that resolves by adult life is associated with a normalization of high carotid intima-media thickness and type 2 diabetes mellitus risk: the Bogalusa Heart and Cardiovascular Risk in Young Finns studies. *J Am Coll Cardiol*. 2012;60:1631–1639. doi: 10.1016/j.jacc.2012.05.056
208. Olza J, Aguilera CM, Gil-Campos M, Leis R, Bueno G, Valle M, Canete R, Tojo R, Moreno LA, Gil A. A continuous metabolic syndrome score is associated with specific biomarkers of inflammation and CVD risk in prepubertal children. *Ann Nutr Metab*. 2015;66:72–79. doi: 10.1159/000369981
209. Choe WS, Choi EK, Han KD, Lee EJ, Lee SR, Cha MJ, Oh S. Association of metabolic syndrome and chronic kidney disease with atrial fibrillation: a nationwide population-based study in Korea. *Diabetes Res Clin Pract*. 2019;148:14–22. doi: 10.1016/j.diabres.2018.12.004
210. Wang Z, Wang B, Li X, Zhang S, Wu S, Xia Y. Metabolic syndrome, high-sensitivity C-reactive protein levels and the risk of new-onset atrial fibrillation: results from the Kailuan Study. *Nutr Metab Cardiovasc Dis*. 2021;31:102–109. doi: 10.1016/j.numecd.2020.06.026
211. Perrone-Filardi P, Paolillo S, Costanzo P, Savarese G, Trimarco B, Bonow RO. The role of metabolic syndrome in heart failure. *Eur Heart J*. 2015;36:2630–2634. doi: 10.1093/eurheartj/ehv350
212. Vidula H, Liu K, Criqui MH, Szklo M, Allison M, Sibley C, Ouyang P, Tracy RP, Chan C, McDermott MM. Metabolic syndrome and incident peripheral artery disease: the Multi-Ethnic Study of Atherosclerosis. *Atherosclerosis*. 2015;243:198–203. doi: 10.1016/j.atherosclerosis.2015.08.044
213. Malik S, Budoff MJ, Katz R, Blumenthal RS, Bertoni AG, Nasir K, Szklo M, Barr RG, Wong ND. Impact of subclinical atherosclerosis on cardiovascular disease events in individuals with metabolic syndrome and

diabetes: the Multi-Ethnic Study of Atherosclerosis. *Diabetes Care*. 2011;34:2285–2290. doi: 10.2337/dc11-0816
214. Wong ND, Nelson JC, Granston T, Bertoni AG, Blumenthal RS, Carr JJ, Guerci A, Jacobs DR Jr, Kronmal R, Liu K, et al. Metabolic syndrome, diabetes, and incidence and progression of coronary calcium: the Multiethnic Study of Atherosclerosis study. *JACC Cardiovasc Imaging*. 2012;5:358–366. doi: 10.1016/j.jcmg.2011.12.015
215. Al Rifai M, Silverman MG, Nasir K, Budoff MJ, Blankstein R, Szklo M, Katz R, Blumenthal RS, Blaha MJ. The association of nonalcoholic fatty liver disease, obesity, and metabolic syndrome, with systemic inflammation and subclinical atherosclerosis: the Multi-Ethnic Study of Atherosclerosis (MESA). *Atherosclerosis*. 2015;239:629–633. doi: 10.1016/j.atherosclerosis.2015.02.011
216. Lee YA, Kang SG, Song SW, Rho JS, Kim EK. Association between metabolic syndrome, smoking status and coronary artery calcification. *PLoS One*. 2015;10:e0122430. doi: 10.1371/journal.pone.0122430
217. Taher R, Sara JD, Heidari B, Toya T, Lerman LO, Lerman A. Metabolic syndrome is associated with peripheral endothelial dysfunction amongst men. *Diabetes Metab Syndr Obes*. 2019;12:1035–1045. doi: 10.2147/DMSO.S204666
218. Walther G, Obert P, Dutheil F, Chapier R, Lesourd B, Naughton G, Courteix D, Vinet A. Metabolic syndrome individuals with and without type 2 diabetes mellitus present generalized vascular dysfunction: cross-sectional study. *Arterioscler Thromb Vasc Biol*. 2015;35:1022–1029. doi: 10.1161/ATVBAHA.114.304591
219. Smith JP, Haddad EV, Taylor MB, Oram D, Blakemore D, Chen Q, Boutaud O, Oates JA. Suboptimal inhibition of platelet cyclooxygenase-1 by aspirin in metabolic syndrome. *Hypertension*. 2012;59:719–725. doi: 10.1161/HYPERTENSIONAHA.111.181404
220. Feldman L, Tubach F, Juliard JM, Himbert D, Ducrocq G, Sorbets E, Triantafyllou K, Kerner A, Abergel H, Huisse MG, et al. Impact of diabetes mellitus and metabolic syndrome on acute and chronic on-clopidogrel platelet reactivity in patients with stable coronary artery disease undergoing drug-eluting stent placement. *Am Heart J*. 2014;168:940–947.e5. doi: 10.1016/j.ahj.2014.08.014
221. Cuspidi C, Sala C, Tadic M, Gherbesi E, Grassi G, Mancia G. Association of metabolic syndrome with carotid thickening and plaque in the general population: a meta-analysis. *J Clin Hypertens (Greenwich)*. 2018;20:4–10. doi: 10.1111/jch.13138
222. Pierdomenico SD, Pierdomenico AM, Cuccurullo F, Iacobellis G. Meta-analysis of the relation of echocardiographic epicardial adipose tissue thickness and the metabolic syndrome. *Am J Cardiol*. 2013;111:73–78. doi: 10.1016/j.amjcard.2012.08.044
223. van der Meer RW, Lamb HJ, Smit JW, de Roos A. MR imaging evaluation of cardiovascular risk in metabolic syndrome. *Radiology*. 2012;264:21–37. doi: 10.1148/radiol.12110772
224. Chun H. Ascending aortic diameter and metabolic syndrome in Korean men. *J Investig Med*. 2017;65:1125–1130. doi: 10.1136/jim-2016-000367
225. Marso SP, Mercado N, Maehara A, Weisz G, Mintz GS, McPherson J, Schiele F, Dudek D, Fahy M, Xu K, et al. Plaque composition and clinical outcomes in acute coronary syndrome patients with metabolic syndrome or diabetes. *JACC Cardiovasc Imaging*. 2012;5:S42–S52. doi: 10.1016/j.jcmg.2012.01.008
226. Di Carli MF, Charytan D, McMahon GT, Ganz P, Dorbala S, Schelbert HR. Coronary circulatory function in patients with the metabolic syndrome. *J Nucl Med*. 2011;52:1369–1377. doi: 10.2967/jnumed.110.082883
227. Canon-Montanez W, Santos ABS, Nunes LA, Pires JCG, Freire CMV, Ribeiro ALP, Mill JG, Bessel M, Duncan BB, Schmidt MI, et al. Central obesity is the key component in the association of metabolic syndrome with left ventricular global longitudinal strain impairment. *Rev Esp Cardiol (Engl Ed)*. 2018;71:524–530. doi: 10.1016/j.rec.2017.10.008
228. Aksoy S, Durmus G, Ozcan S, Toprak E, Gurkan U, Oz D, Canga Y, Karatas B, Duman D. Is left ventricular diastolic dysfunction independent from presence of hypertension in metabolic syndrome? An echocardiographic study. *J Cardiol*. 2014;64:194–198. doi: 10.1016/j.jjcc.2014.01.002
229. Crendal E, Walther G, Dutheil F, Courteix D, Lesourd B, Chapier R, Naughton G, Vinet A, Obert P. Left ventricular myocardial dyssynchrony is already present in nondiabetic patients with metabolic syndrome. *Can J Cardiol*. 2014;30:320–324. doi: 10.1016/j.cjca.2013.10.019
230. Tadic M, Cuspidi C, Sljivic A, Andric A, Ivanovic B, Scepanovic R, Ilic I, Jozika L, Marjanovic T, Celic V. Effects of the metabolic syndrome on right heart mechanics and function. *Can J Cardiol*. 2014;30:325–331. doi: 10.1016/j.cjca.2013.12.006
231. Gurka MJ, Golden SH, Musani SK, Sims M, Vishnu A, Guo Y, Cardel M, Pearson TA, DeBoer MD. Independent associations between a metabolic syndrome severity score and future diabetes by sex and race: the Atherosclerosis Risk in Communities study and Jackson Heart Study. *Diabetologia*. 2017;60:1261–1270. doi: 10.1007/s00125-017-4267-6
232. Huh JH, Ahn SG, Kim YI, Go T, Sung KC, Choi JH, Koh KK, Kim JY. Impact of longitudinal changes in metabolic syndrome status over 2 years on 10-year incident diabetes mellitus. *Diabetes Metab J*. 2019;43:530–538. doi: 10.4093/dmj.2018.0111
233. Lee MK, Han K, Kim MK, Koh ES, Kim ES, Nam GE, Kwon HS. Changes in metabolic syndrome and its components and the risk of type 2 diabetes: a nationwide cohort study. *Sci Rep*. 2020;10:2313. doi: 10.1038/s41598-020-59203-z
234. Cai R, Wu M, Xing Y. Pretransplant metabolic syndrome and its components predict post-transplantation diabetes mellitus in Chinese patients receiving a first renal transplant. *Ther Clin Risk Manag*. 2019;15:497–503. doi: 10.2147/TCRM.S190185
235. Stefansson VTN, Schei J, Solbu MD, Jenssen TG, Melsom T, Eriksen BO. Metabolic syndrome but not obesity measures are risk factors for accelerated age-related glomerular filtration rate decline in the general population. *Kidney Int*. 2018;93:1183–1190. doi: 10.1016/j.kint.2017.11.012
236. Akinyemiju T, Moore JX, Judd S, Lakoski S, Goodman M, Safford MM, Pisu M. Metabolic dysregulation and cancer mortality in a national cohort of blacks and whites. *BMC Cancer*. 2017;17:856. doi: 10.1186/s12885-017-3807-2
237. Esmaeili ES, Asadollahi K, Delpisheh A, Sayehmiri K, Azizi H. Metabolic syndrome and risk of colorectal cancer: a case-control study. *Int J Cancer Manag*. 2019;12:e84627. doi: 10.5812/ijcm.84627
238. Zhao P, Xia N, Zhang H, Deng T. The metabolic syndrome is a risk factor for breast cancer: a systematic review and meta-analysis. *Obes Facts*. 2020;13:384–396. doi: 10.1159/000507554
239. Santos AP, Santos AC, Castro C, Raposo L, Pereira SS, Torres I, Henrique R, Cardoso H, Monteiro MP. Visceral obesity and metabolic syndrome are associated with well-differentiated gastroenteropancreatic neuroendocrine tumors. *Cancers*. 2018;10:293. doi: 10.3390/cancers10090293
240. Choi IY, Chun S, Shin DW, Han K, Jeon KH, Yu J, Chae BJ, Suh M, Park YM. Changes in metabolic syndrome status and breast cancer risk: a nationwide cohort study. *Cancers (Basel)*. 2021;13:1177. doi: 10.3390/cancers13051177
241. Watanabe J, Kakehi E, Kotani K, Kayaba K, Nakamura Y, Ishikawa S. Metabolic syndrome is a risk factor for cancer mortality in the general Japanese population: the Jichi Medical School Cohort Study. *Diabetol Metabol Syndr*. 2019;11:3. doi: 10.1186/s13098-018-0398-2
242. Liu Y, Wang L, Liu H, Li C, He J. The prognostic significance of metabolic syndrome and a related six-lncRNA signature in esophageal squamous cell carcinoma. *Front Oncol*. 2020;10:61. doi: 10.3389/fonc.2020.00061
243. Gacci M, Russo GI, De Nunzio C, Sebastianelli A, Salvi M, Vignozzi L, Tubaro A, Morgia G, Serni S. Meta-analysis of metabolic syndrome and prostate cancer. *Prostate Cancer Prostatic Dis*. 2017;20:146–155. doi: 10.1038/pcan.2017.1
244. Dibaba DT, Ogunsina K, Braithwaite D, Akinyemiju T. Metabolic syndrome and risk of breast cancer mortality by menopause, obesity, and subtype. *Breast Cancer Res Treat*. 2018;174:209–218. doi: 10.1007/s10549-018-5056-8
245. Li Y, Liu T, Ivan C, Huang J, Shen DY, Kavanagh JJ, Bast RC Jr, Fu S, Hu W, Sood AK. Corrigendum: Enhanced cytotoxic effects of combined valproic acid and the aurora kinase inhibitor VE465 on gynecologic cancer cells. *Front Oncol*. 2018;8:9. doi: 10.3389/fonc.2018.00009
246. Akinyemiju T, Sakhuja S, Vin-Raviv N. In-hospital mortality and post-surgical complications among cancer patients with metabolic syndrome. *Obes Surg*. 2018;28:683–692. doi: 10.1007/s11695-017-2900-6
247. Gathirua-Mwangi WG, Song Y, Monahan PO, Champion VL, Zollinger TW. Associations of metabolic syndrome and C-reactive protein with mortality from total cancer, obesity-linked cancers and breast cancer among women in NHANES III. *Int J Cancer*. 2018;143:535–542. doi: 10.1002/ijc.31344
248. Wong RJ, Liu B, Bhuket T. Significant burden of nonalcoholic fatty liver disease with advanced fibrosis in the US: a cross-sectional analysis of 2011-2014 National Health and Nutrition Examination Survey. *Aliment Pharmacol Ther*. 2017;46:974–980. doi: 10.1111/apt.14327
249. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease: meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology*. 2016;64:73–84. doi: 10.1002/hep.28431
250. Hamaguchi M, Kojima T, Takeda N, Nakagawa T, Taniguchi H, Fujii K, Omatsu T, Nakajima T, Sarui H, Shimazaki M, et al. The metabolic syndrome as a predictor of nonalcoholic fatty liver disease. *Ann Intern Med*. 2005;143:722–728. doi: 10.7326/0003-4819-143-10-200511150-00009

251. Ting YW, Wong SW, Anuar Zaini A, Mohamed R, Jalaludin MY. Metabolic syndrome is associated with advanced liver fibrosis among pediatric patients with non-alcoholic fatty liver disease. *Front Pediatr*. 2019;7:491. doi: 10.3389/fped.2019.00491
252. Aberg F, Helenius-Hietala J, Puukka P, Farkkila M, Jula A. Interaction between alcohol consumption and metabolic syndrome in predicting severe liver disease in the general population. *Hepatology*. 2018;67:2141–2149. doi: 10.1002/hep.29631
253. Milano A, Bianco MA, Buri L, Cipolletta L, Grossi E, Rotondano G, Tessari F, Efthymakis K, Neri M. Metabolic syndrome is a risk factor for colorectal adenoma and cancer: a study in a White population using the harmonized criteria. *Therap Adv Gastroenterol*. 2019;12:1756284819867839. doi: 10.1177/1756284819867839
254. Niknam R, Moradi J, Jahanshahi KA, Mahmoudi L, Ejtehadi F. Association between metabolic syndrome and its components with severity of acute pancreatitis. *Diabetes Metab Syndro Obes*. 2020;13:1289–1296. doi: 10.2147/DMSO.S249128
255. Di J, Cheng Y, Chang D, Liu Y. A meta-analysis of the impact of obesity, metabolic syndrome, insulin resistance, and microbiome on the diagnosis of Barrett's esophagus. *Dig Dis*. 2019;38:165–177. doi: 10.1159/000502376
256. Yang M, Xu H, Yang L, Jiang J, Dong B. Metabolic syndrome and disability in Chinese nonagenarians and centenarians. *Aging Clin Exp Res*. 2018;30:943–949. doi: 10.1007/s40520-017-0877-6
257. Marcos-Delgado A, Lopez-Garcia E, Martinez-Gonzalez MA, Salas-Salvado J, Corella D, Fito M, Romaguera D, Vioque J, Alonso-Gomez AM, Warnberg J, et al. Health-related quality of life in individuals with metabolic syndrome: a cross-sectional study. *Semergen*. 2020;46:524–537. doi: 10.1016/j.semerg.2020.03.003
258. Lee JE, Shin DW, Han K, Kim D, Yoo JE, Lee J, Kim S, Son KY, Cho B, Kim MJ. Changes in metabolic syndrome status and risk of dementia. *J Clin Med*. 2020;9:122. doi: 10.3390/jcm9010122
259. Kim YJ, Kim SM, Jeong DH, Lee SK, Ahn ME, Ryu OH. Associations between metabolic syndrome and type of dementia: analysis based on the National Health Insurance Service database of Gangwon province in South Korea. *Diabetol Metab Syndr*. 2021;13:4. doi: 10.1186/s13098-020-00620-5
260. Lee EY, Lee SJ, Kim KM, Yun YM, Song BM, Kim JE, Kim HC, Rhee Y, Youm Y, Kim CO. Association of metabolic syndrome and 25-hydroxyvitamin D with cognitive impairment among elderly Koreans. *Geriatr Gerontol Int*. 2017;17:1069–1075. doi: 10.1111/ggi.12826
261. Lai MMY, Ames DJ, Cox KL, Ellis KA, Sharman MJ, Hepworth G, Desmond P, Cyarto EV, Szoeke C, Martins R, et al. Association between cognitive function and clustered cardiovascular risk of metabolic syndrome in older adults at risk of cognitive decline. *J Nutr Health Aging*. 2020;24:300–304. doi: 10.1007/s12603-020-1333-4
262. Yang L, Lv X, Wei D, Yue F, Guo J, Zhang T. Metabolic syndrome and the risk of bone fractures: a meta-analysis of prospective cohort studies. *Bone*. 2016;84:52–56. doi: 10.1016/j.bone.2015.12.008
263. Muka T, Trajanoska K, Kiefte-de Jong JC, Oei L, Uitterlinden AG, Hofman A, Dehghan A, Zillikens MC, Franco OH, Rivadeneira F. The association between metabolic syndrome, bone mineral density, hip bone geometry and fracture risk: the Rotterdam Study. *PLoS One*. 2015;10:e0129116. doi: 10.1371/journal.pone.0129116
264. Zhao L, Pang A. Effects of metabolic syndrome on semen quality and circulating sex hormones: a systematic review and meta-analysis. *Front Endocrinol*. 2020;11:428. doi: 10.3389/fendo.2020.00428
265. Bansal R, Gubbi S, Muniyappa R. Metabolic syndrome and COVID 19: endocrine-immune-vascular interactions shapes clinical course. *Endocrinology*. 2020;161:bqaa112. doi: 10.1210/endocr/bqaa112
266. Mechanick JI, Rosenson RS, Pinney SP, Mancini DM, Narula J, Fuster V. Coronavirus and cardiometabolic syndrome: JACC focus seminar. *J Am Coll Cardiol*. 2020;76:2024–2035. doi: 10.1016/j.jacc.2020.07.069
267. Costa FF, Rosário WR, Ribeiro Farias AC, de Souza RG, Duarte Gondim RS, Barroso WA. Metabolic syndrome and COVID-19: an update on the associated comorbidities and proposed therapies. *Diabetes Metab Syndr*. 2020;14:809–814. doi: 10.1016/j.dsx.2020.06.016
268. Li B, Yang J, Zhao F, Zhi L, Wang X, Liu L, Bi Z, Zhao Y. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. *Clin Res Cardiol*. 2020;109:531–538. doi: 10.1007/s00392-020-01626-9
269. Boudreau DM, Malone DC, Raebel MA, Fishman PA, Nichols GA, Feldstein AC, Boscoe AN, Ben-Joseph RH, Magid DJ, Okamoto LJ. Health care utilization and costs by metabolic syndrome risk factors. *Metab Syndr Relat Disord*. 2009;7:305–314. doi: 10.1089/met.2008.0070
270. Shariq OA, Fruth KM, Hanson KT, Cronin PA, Richards ML, Farley DR, Thompson GB, Habermann EB, McKenzie TJ. Metabolic syndrome is associated with increased postoperative complications and use of hospital resources in patients undergoing laparoscopic adrenalectomy. *Surgery*. 2018;163:167–175. doi: 10.1016/j.surg.2017.06.023
271. Tee MC, Ubl DS, Habermann EB, Nagorney DM, Kendrick ML, Sarr MG, Truty MJ, Que FG, Reid-Lombardo K, Smoot RL, et al. Metabolic syndrome is associated with increased postoperative morbidity and hospital resource utilization in patients undergoing elective pancreatectomy. *J Gastrointest Surg*. 2016;20:189–198. doi: 10.1007/s11605-015-3007-9
272. He X, Fei Q, Sun T. Metabolic syndrome increases risk for perioperative outcomes following posterior lumbar interbody fusion. *Medicine (Baltimore)*. 2020;99:e21786. doi: 10.1097/MD.0000000000021786
273. Chen X, Zhang W, Sun X, Shi M, Xu L, Cai Y, Chen W, Mao C, Shen X. Metabolic syndrome predicts postoperative complications after gastrectomy in gastric cancer patients: development of an individualized usable nomogram and rating model. *Cancer Med*. 2020;9:7116–7124. doi: 10.1002/cam4.3352
274. Guofeng C, Chen Y, Rong W, Ruiyu L, Kunzheng W. Patients with metabolic syndrome have a greater rate of complications after arthroplasty. *Bone Joint Res*. 2020;9:120–129. doi: 10.1302/2046-3758.93.BJR-2019-0138.R1
275. Leiter LA, Fitchett DH, Gilbert RE, Gupta M, Mancini GB, McFarlane PA, Ross R, Teoh H, Verma S, Anand S, et al; Cardiometabolic Risk Working Group: Executive Committee. Cardiometabolic risk in Canada: a detailed analysis and position paper by the Cardiometabolic Risk Working Group. *Can J Cardiol*. 2011;27:e1–e33. doi: 10.1016/j.cjca.2010.12.054
276. Lopez-Jaramillo P, Sanchez RA, Diaz M, Cobos L, Bryce A, Parra Carrillo JZ, Lizcano F, Lanas F, Sinay I, Sierra ID, et al; Latin America Expert Group. Latin American consensus on hypertension in patients with diabetes type 2 and metabolic syndrome. *J Hypertens*. 2013;31:223–238. doi: 10.1097/HJH.0b013e32835c5444
277. Ramdass PVAK, Ford T, Sidhu T, Ogbonnia CF, Gomez A. Prevalence of metabolic syndrome and obesity among adults in Aruba. *Int Public Health J*. 2020;12:75–82.
278. Barik A, Das K, Chowdhury A, Rai RK. Metabolic syndrome among rural Indian adults. *Clin Nutr ESPEN*. 2018;23:129–135. doi: 10.1016/j.clnesp.2017.11.002
279. Gupta A, Sachdeva A, Mahajan N, Gupta A, Sareen N, Pandey RM, Ramakrishnan L, Sati HC, Sharma B, Sharma N, et al. Prevalence of pediatric metabolic syndrome and associated risk factors among school-age children of 10-16 years living in District Shimla, Himachal Pradesh, India. *Indian J Endocrinol Metabol*. 2018;22:373–378. doi: 10.4103/ijem.IJEM_251_17
280. Lin BY, Genden K, Shen W, Wu P-S, Yang W-C, Hung H-F, Fu C-M, Yang K-C. The prevalence of obesity and metabolic syndrome in Tibetan immigrants living in high altitude areas in Ladakh, India. *Obes Res Clin Pract*. 2018;12:365–371. doi: 10.1016/j.orcp.2017.03.002
281. Mini GK, Sarma PS, Thankappan KR. Overweight, the major determinant of metabolic syndrome among industrial workers in Kerala, India: results of a cross-sectional study. *Diabetes Metab Syndr*. 2018;13:3025–3030. doi: 10.1016/j.dsx.2018.07.009
282. Chowdhury MZI, Anik AM, Farhana Z, Bristi PD, Abu Al Mamun BM, Uddin MJ, Fatema J, Akter T, Tani TA, Rahman M, et al. Prevalence of metabolic syndrome in Bangladesh: a systematic review and meta-analysis of the studies. *BMC Public Health*. 2018;18:308. doi: 10.1186/s12889-018-5209-z
283. Heshmat R, Hemati Z, Qorbani M, Asl LN, Motlagh ME, Ziaodini H, Taheri M, Ahadi Z, Shafiee G, Aminaei T, et al. Metabolic syndrome and associated factors in Iranian children and adolescents: the CASPIAN-V study. *J Cardiovasc Thorac Res*. 2018;10:214–220. doi: 10.15171/jcvtr.2018.37
284. Bakhshayeshkaram M, Heydari ST, Honarvar B, Keshani P, Roozbeh J, Dabbaghmanesh MH, Lankarani KB. Incidence of metabolic syndrome and determinants of its progression in southern Iran: a 5-year longitudinal follow-up study. *J Res Med Sci*. 2020;25:103. doi: 10.4103/jrms.JRMS_884_19
285. Fatahi A, Doosti-Irani A, Cheraghi Z. Prevalence and incidence of metabolic syndrome in Iran: a systematic review and meta-analysis. *Int J Prev Med*. 2020;11:64. doi: 10.4103/ijpvm.IJPVM_489_18
286. Annani-Akollor ME, Laing EF, Osei H, Mensah E, Owiredu EW, Afranie BO, Anto EO. Prevalence of metabolic syndrome and the comparison of fasting plasma glucose and HbA1c as the glycemic criterion for MetS definition in non-diabetic population in Ghana. *Diabetol Metab Syndr*. 2019;11:26. doi: 10.1186/s13098-019-0423-0
287. Jamee AS, Aboyans V, Magne J, Preux PM, Lacroix P. The epidemic of the metabolic syndrome among the Palestinians in the Gaza Strip. *Diabetes Metab Syndr Obes*. 2019;12:2201–2208. doi: 10.2147/DMSO.S207781
288. Ajlouni K, Khader Y, Alyousfi M, Al Nsour M, Batieha A, Jaddou H. Metabolic syndrome amongst adults in Jordan: prevalence, trend, and its association with socio-demographic characteristics. *Diabetol Metab Syndr*. 2020;12:100. doi: 10.1186/s13098-020-00610-7

289. Motuma A, Gobena T, Roba KT, Berhane Y, Worku A. Metabolic syndrome among working adults in eastern Ethiopia. *Diabetes Metab Syndr Obes*. 2020;13:4941–4951. doi: 10.2147/DMSO.S283270
290. Ambachew S, Endalamaw A, Worede A, Tegegne Y, Melku M, Biadgo B. The prevalence of metabolic syndrome in Ethiopian population: a systematic review and meta-analysis. *J Obes*. 2020;2020:1–14. doi: 10.1155/2020/2701309
291. Oguoma VM, Nwose EU, Richards RS. Prevalence of cardio-metabolic syndrome in Nigeria: a systematic review. *Public Health*. 2015;129:413–423. doi: 10.1016/j.puhe.2015.01.017
292. Raimi TH, Odusan O, Fasanmade OA, Odewabi AO, Ohwovoriole AE. Metabolic syndrome among apparently healthy Nigerians with the harmonized criteria: prevalence and concordance with the International Diabetes Federation (IDF) and Third Report of the National Cholesterol Education Programme-Adult Treatment Panel III (NCEP-ATP III) criteria. *J Cardiovasc Disease Res*. 2017;8:145–150. doi: 10.5530/jcdr.2017.4.32
293. Peer N, Lombard C, Steyn K, Levitt N. High prevalence of metabolic syndrome in the Black population of Cape Town: the Cardiovascular Risk in Black South Africans (CRIBSA) study. *Eur J Prev Cardiol*. 2015;22:1036–1042. doi: 10.1177/2047487314549744
294. Orces CH, Gavilanez EL. The prevalence of metabolic syndrome among older adults in Ecuador: results of the SABE survey. *Diabetes Metab Syndr*. 2017;11(suppl 2):S555–S560. doi: 10.1016/j.dsx.2017.04.004
295. Binh TQ, Phuong PT, Nhung BT, Tung do D. Metabolic syndrome among a middle-aged population in the Red River Delta region of Vietnam. *BMC Endocr Disord*. 2014;14:77. doi: 10.1186/1472-6823-14-77
296. Baygi F, Herttua K, Jensen OC, Djalalinia S, Mahdavi Ghorabi A, Asayesh H, Qorbani M. Global prevalence of cardiometabolic risk factors in the military population: a systematic review and meta-analysis. *BMC Endocr Disord*. 2020;20:8. doi: 10.1186/s12902-020-0489-6
297. Bitew ZW, Alemu A, Ayele EG, Tenaw Z, Alebel A, Worku T. Metabolic syndrome among children and adolescents in low and middle income countries: a systematic review and meta-analysis. *Diabetol Metab Syndr*. 2020;12:93. doi: 10.1186/s13098-020-00601-8
298. Reisinger C, Nkeh-Chungag BN, Fredriksen PM, Goswami N. The prevalence of pediatric metabolic syndrome: a critical look on the discrepancies between definitions and its clinical importance. *Int J Obes (Lond)*. 2021;45:12–24. doi: 10.1038/s41366-020-00713-1
299. de Carvalho Vidigal F, Bressan J, Babio N, Salas-Salvado J. Prevalence of metabolic syndrome in Brazilian adults: a systematic review. *BMC Public Health*. 2013;13:1198. doi: 10.1186/1471-2458-13-1198
300. Diaz A, Espeche W, March C, Flores R, Parodi R, Genesio MA, Sabio R, Poppe S. Prevalence of metabolic syndrome in Argentina in the last 25 years: systematic review of population observational studies. *Hipertens y Riesgo Vasc*. 2018;35:64–69. doi: 10.1016/j.hipert.2017.08.003
301. Salas R, del Mar Bibiloni M, Ramos E, Villarreal JZ, Pons A, Tur JA, Sureda A. Metabolic syndrome prevalence among northern Mexican adult population. *PLoS One*. 2014;9:e105581. doi: 10.1371/journal.pone.0105581
302. Ortiz-Rodríguez MA, Yáñez-Velasco L, Carnevale A, Romero-Hidalgo S, Bernal D, Aguilar-Salinas C, Rojas R, Villa A, Tur JA. Prevalence of metabolic syndrome among elderly Mexicans. *Arch Gerontol Geriatr*. 2017;73:288–293. doi: 10.1016/j.archger.2017.09.001
303. Li M, McCulloch B, McDermott R. Metabolic syndrome and incident coronary heart disease in Australian indigenous populations. *Obesity (Silver Spring)*. 2012;20:1308–1312. doi: 10.1038/oby.2011.156
304. van Vliet-Ostaptchouk JV, Nuotio ML, Slagter SN, Doiron D, Fischer K, Foco L, Gaye A, Gogele M, Heier M, Hiekkalinna T, et al. The prevalence of metabolic syndrome and metabolically healthy obesity in Europe: a collaborative analysis of ten large cohort studies. *BMC Endocr Disord*. 2014;14:9. doi: 10.1186/1472-6823-14-9
305. Vernay M, Salanave B, de Peretti C, Druet C, Malon A, Deschamps V, Hercberg S, Castetbon K. Metabolic syndrome and socioeconomic status in France: the French Nutrition and Health Survey (ENNS, 2006-2007). *Int J Public Health*. 2013;58:855–864. doi: 10.1007/s00038-013-0501-2
306. Huang J, Huang JLW, Withers M, Chien K, Trihandi I, Elcarte E, Chung V, Wong MCS. Prevalence of metabolic syndrome in Chinese women and men: a systematic review and meta-analysis of data from 734 511 individuals. *Lancet*. 2018;392:S14. doi: 10.1016/S0140-6736(18)32643-6
307. Ng S-M, Su X. Prevalence and correlates of metabolic syndrome in Hong Kong Chinese adults: a random community sample study. *Psychol Health Med*. 2018;23:485–495. doi: 10.1080/13548506.2017.1395057
308. Ansari-Moghaddam A, Adineh HA, Zareban I, Kalan Farmanfarma KH. Prevalence of metabolic syndrome and population attributable risk for cardiovascular, stroke, and coronary heart diseases as well as myocardial infarction and all-cause mortality in middle-east: systematic review & meta-analysis. *Obes Med*. 2019;14:100086. doi: 10.1016/j.obmed.2019.100086
309. DeBoer MD, Filipp SL, Gurka MJ. Geographical variation in the prevalence of obesity and metabolic syndrome among US adolescents. *Pediatr Obes*. 2019;14:e12483. doi: 10.1111/ijpo.12483
310. Centers for Disease Control and Prevention and National Center for Health Statistics. National Health and Nutrition Examination Survey (NHANES) public use data files. Accessed April 1, 2023. https://cdc.gov/nchs/nhanes/

# 11. ADVERSE PREGNANCY OUTCOMES

*See Charts 11-1 through 11-9*

Click here to return to the Table of Contents

Click here to return to the Abbreviations

APOs include gestational hypertension, preeclampsia, gestational diabetes, PTB, delivery of an infant who is SGA, pregnancy loss (eg, miscarriage or stillbirth), and placental abruption. The processes leading to these interrelated disorders reflect a response to the "stress test" of pregnancy, and they are associated with risk of poor future CVH outcomes in females and offspring, including CHD, stroke, and HF. Furthermore, growing rates of pregnancy-related morbidity and mortality in the United States are attributed predominantly to CVD. Because of this, the AHA has recognized the importance of raising awareness about these disorders in comprehensive CVH promotion and CVD prevention in females.[1] Furthermore, the AHA, in partnership with the American College of Obstetricians and Gynecologists, has encouraged collaboration between cardiologists and obstetricians/gynecologists to promote CVH in females across the reproductive life course with a special focus on pregnancy, given the intergenerational impact on health for both females and offspring.[2,3]

This chapter focuses only on complications of pregnancy-related mortality, CVD, CVH (risk factors), and brain health in females and offspring; complications in other organ systems are important sources of APO-related morbidity and mortality in females (eg, acute kidney injury) and offspring (eg, necrotizing enterocolitis in infancy or accumulation of cardiometabolic risk factors later in life) but are beyond the scope of this chapter. In addition, pregnancy complications related to PPCM and risk associated with congenital malformations are addressed elsewhere (see Chapter 22 [Cardiomyopathy and Heart Failure] for pregnancy-related HF and PPCM and Chapter 17 [Congenital Cardiovascular Defects and Kawasaki Disease] for pregnancy-related risk factors for congenital HD).

The 2024 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2024. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

## Classification of APOs

- HDP
  - Gestational hypertension: De novo hypertension that develops after week 20 of pregnancy without protein in the urine or evidence of end-organ involvement is defined as gestational hypertension.
  - Preeclampsia/eclampsia: Hypertension after week 20 of pregnancy, most often de novo, with protein in the urine or other evidence of end-organ involvement is defined as preeclampsia and may progress to the convulsive phase or eclampsia.
  - Chronic (ie, prepregnancy) hypertension is hypertension that is present before week 20 of pregnancy; note that preeclampsia/eclampsia can develop on top of chronic hypertension.
  - The threshold for treatment of BP differs in pregnant and nonpregnant individuals. The American College of Obstetricians and Gynecologists defines HDP as a BP of ≥140/90 mm Hg in pregnancy. In contrast, the AHA and ACC adopted a lower threshold in nonpregnant adults of ≥130/80 mm Hg in 2017. In a retrospective cohort study, lowering the BP threshold to diagnose gestational hypertension would increase the prevalence from 6.0% to 13.8% in a sample of 137 398 females from an integrated health system between 2009 and 2014.[4]
- Gestational diabetes: De novo diabetes that develops after week 20 of pregnancy is considered gestational diabetes. Gestational diabetes often initially resolves after delivery but is strongly associated with future type 2 diabetes risk.
- PTB: PTB includes spontaneous or indicated delivery before 37 weeks' gestation.
- Infant with SGA: An infant with a birth weight ≤10th percentile for gestational age is considered to be SGA. SGA is called intrauterine growth restriction during gestation; an alternative definition for an infant with LBW includes birth weight <2500 g.
- Pregnancy loss: Spontaneous loss of an intrauterine pregnancy is classified as pregnancy loss and is further categorized according to gestational age at which loss occurs.
  - Stillbirth: loss occurs at ≥20 weeks' gestational age; also called late fetal death and intrauterine fetal demise
  - Miscarriage: loss occurs before 20 weeks' gestational age; also called spontaneous abortion
- Placental abruption: Premature separation of a normally implanted placenta from the uterus before delivery.

## Any APO

### *Incidence*

- APOs (including HDP, gestational diabetes, PTB, and SGA at birth) occur in 10% to 20% of pregnancies globally.[5]

## Risk Factors (Including Social Determinants)

### (See Chart 11-1)

- According to a meta-analysis of individual participant data from 265 270 females from 39 European, North American, and Oceanic cohort studies, the risk of any APO was greater with higher categories of prepregnancy BMI and greater degree of gestational weight gain, with an aOR of 2.51 (95% CI, 2.31–2.74) for females with prepregnancy obesity and high (≥1.0 SD) gestational weight gain (Chart 11-1).[6]
- Similar findings were observed in a separate meta-analysis of individual participant data from 196 670 females from 25 European and North American cohort studies, with estimates that 23.9% of pregnancy complications were attributable to prepregnancy overweight or obesity, defined as BMI ≥25.0 kg/m$^2$.[7]
- A meta-analysis of 17 403 participants from 30 cross-sectional or case-control studies examined risk factors for PTB in Ethiopia (PTB prevalence is 11% in Ethiopia).[8] This study showed that pregnancy-induced hypertension (aOR, 5.11 [95% CI, 3.73–7.01]), living with HIV (aOR, 4.74 [95% CI, 2.79–8.05]), rural residence (aOR, 2.35 [95% CI, 1.56–3.55]), premature rupture of membrane, history of abortion, multiple pregnancies, and anemia during pregnancy were associated with PTB.
- In 24 369 females from 12 studies (case-control, cohort, and cross-sectional) in sub-Saharan Africa, chronic hypertension (OR from 5 studies ranged from 2.2–10.5), overweight (OR from 3 studies ranged from 1.4–7.0), obesity (OR from 5 studies ranged from 1.8–3.9), diabetes (OR from 1 study was 5.4 [95% CI, 1.1–27.0]), and alcohol use (OR from 1 study was 4.0 [95% CI, 1.8–8.8]) were significantly associated with a high risk of preeclampsia.[9]

## Pregnancy-Related Complications: Mortality and CVD

### Pregnancy-Related Mortality

### (See Chart 11-2)

- In 2021, maternal death rate per 100 000 live births was highest in NH Black females (69.9), followed by Hispanic females (28.0) and NH White females (26.6; Chart 11-2).[10]
- The pregnancy-related mortality rate was 32.9 per 100 000 live births in 2021.[10] Maternal or pregnancy-related mortality is defined by the WHO as death while pregnant or within 42 days of the end of pregnancy; late maternal or pregnancy-related deaths occurring between 43 days and 1 year are not included as part of the definition.
  - Pregnancy-related mortality rates were higher in older age groups for females ≥40 years of age compared with females <25 years of age (138.5 versus 20.4 per 100 000 live births) in 2021.[10]
  - Significant disparities were present, with the pregnancy-related mortality rate for NH Black females being 2.6-fold and 2.5-fold greater than for NH White and Hispanic females, respectively (69.9 versus 26.6 and 28.0 per 100 000 live births) in 2021.[10]
- From 2016 to 2018, the maternal mortality rate was lowest (13.8 deaths per 100 000 live births) for women living in large fringe metro counties and highest (24.4 deaths per 100 000 live births) for women living in noncore counties (ie, those not in proximity to a metro core).[11]
- Cardiovascular maternal deaths (eg, from cardiomyopathy, arrhythmia, and congenital HD) are the most common cause of maternal or pregnancy-related mortality in high-income countries. In the United States, these accounted for 26.6% of maternal deaths from 2017 to 2019; HDP contributed an additional 6.3% of maternal deaths.[12] In low- to middle-income countries, the second leading cause of death is HDP, accounting for 14% of maternal deaths.[13]

### Long-Term Mortality

- The Collaborative Perinatal Project was a prospective cohort 48 197 pregnant females at 12 US clinical centers during the years 1959 to 1966 (45% were Black and 46% were White females).[14] After a median of 52 years after pregnancy, the following APOs were associated with all-cause mortality: preterm spontaneous labor (HR, 1.07 [95% CI, 1.03–1.1]); premature rupture of membranes (HR, 1.23 [95% CI, 1.05–1.44]); gestational hypertension (HR, 1.09 [95% CI, 0.97–1.22]); preeclampsia or eclampsia (HR, 1.14 [95% CI, 0.99–1.32]) and superimposed preeclampsia or eclampsia (HR, 1.32 [95% CI, 1.20–1.46]) compared with normotension; and gestational diabetes or impaired fasting glucose (HR, 1.14 [95% CI, 1.00–1.30]) compared with normoglycemia. Preterm induced labor was associated with greater mortality risk among Black (HR, 1.64 [95% CI, 1.10–2.46]) compared with White (HR, 1.29 [95% CI, 0.97–1.73]) participants.

### Associations With Cardiovascular Risk Factors and CVD

- A cohort study of 2 195 989 Swedish females demonstrated a higher risk of hypertension within 10 years among those who had preterm delivery (gestational age <37 weeks; HR, 1.67 [95% CI, 1.61–1.74]) compared with full-term delivery (39–41 weeks' gestation).[15] There were also elevated risks of hypertension among females who experienced extremely preterm (22–27 weeks' gestation; HR, 2.23 [95% CI, 1.98–2.5]) and moderately preterm (28–33 weeks' gestation; HR, 1.85 [95% CI, 1.74–1.97]) deliveries.

- Among 4484 females from the nuMoM2b Heart Health Study, a prospective observational cohort, APOs occurred in 1017 females (22.7%). In short-term follow-up over a mean of 3.2 years, the overall incidence of hypertension was 5.4% (95% CI, 4.7%–6.1%) with an increased risk among females with any APO (RR, 2.4 [95% CI, 1.8–3.1]) and by subtype (HDP: RR, 2.7 [95% CI, 2.0–3.6]; preeclampsia: RR, 2.8 [95% CI, 2.0–4.0]; PTB; RR, 2.7 [95% CI, 1.9–3.8]). Females who experienced both HDP and PTB had the highest risk of incident hypertension (RR, 4.3 [95% CI, 2.7–6.7]).[16]
- Among 48 113 participants from the WHI, 13 482 (28.8%) reported ≥1 APOs (defined as HDP, gestational diabetes, PTB, LBW, and high birth weight).[17] Females who reported any APO were more likely to have ASCVD (1028 [7.6%]) compared with those without APOs (1758 [5.8%]), and each APO was individually associated with future ASCVD (gestational diabetes: aOR, 1.32 [95% CI, 1.02–1.67]; LBW: aOR, 1.25 [95% CI, 1.12–1.39]; PTB: aOR, 1.23 [95% CI, 1.10–1.36]; HDP: aOR, 1.38 [95% CI, 1.19–1.58]; except for high birth weight).
- In a study of 10 292 females in the WHI with APO data and adjudicated HF outcomes, only HDP was significantly associated with HF (aOR, 1.75 [95% CI, 1.22–2.50]) and HFpEF (aOR,2.06 [95% CI, 1.29–3.27]).[18] In mediation analyses, hypertension explained 24% (95% CI, 12%–73%), CHD explained 23% (95% CI, 11%–68%), and BMI explained 20% (95% CI, 10%–64%) of the association between HDP and HF.

## Hypertensive Disorders of Pregnancy

### *Incidence, Prevalence, and Secular Trends*

#### *(See Charts 11-3 and 11-4)*

- Rates of overall HDP are increasing. During 2017 to 2019, the prevalence of HDP among delivery hospitalizations increased from 13.3% to 15.9% (Chart 11-3). The highest prevalence was among females 35 to 44 and 45 to 55 years of age (18% and 31%, respectively) and those who were Black (20.9%) or American Indian and Alaska Native (16.4%).
- There is substantial geographic heterogeneity in rates of HDP across the United States (Chart 11-4). In 2019, the highest rate of HDP was observed in Louisiana at 116 per 1000 live births.
- Rates of chronic hypertension before pregnancy increased significantly between 2007 and 2018.[19] Among 47 949 381 live births to females 15 to 44 years of age, the overall prevalence of prepregnancy hypertension increased from 10.9 to 20.5 per 1000 live births; significant disparities were observed with higher prevalence of prepregnancy hypertension in rural compared with urban areas (rate ratio in 2018, 1.18 [95% CI, 1.16–1.20]).

### *Risk Factors (Including Social Determinants)*

- Among 2304 female-newborn dyads in the multinational HAPO study, lower CVH (based on 5 metrics: BMI, BP, cholesterol, glucose, and smoking) at 28 weeks' gestation was associated with higher risk of preeclampsia; aRRs were 3.13 (95% CI, 1.39–7.06), 5.34 (95% CI, 2.44–11.70), and 9.30 (95% CI, 3.95–21.86) for females with ≥1 intermediate, 1 poor, or ≥2 poor (versus all ideal) CVH metrics during pregnancy, respectively.[20] Conversely, each 1-point higher (more favorable) CVH score was associated with 33% lower risk for preeclampsia (aRR, 0.67 [95% CI, 0.61–0.73]).
- Among 7633 pregnant females recruited between 12 and 20 weeks' gestation in the Ottawa and Kingston Birth Cohort from 2002 to 2009, risk factors for gestational hypertension and preeclampsia were studied and compared. Risk factors for gestational hypertension and preeclampsia were largely similar; aRRs for gestational hypertension and preeclampsia for overweight were 1.80 (95% CI, 1.35–2.41) and 1.93 (95% CI, 1.37–2.70), respectively; for obesity, 2.81 (95% CI, 2.07–3.81) and 3.38 (95% CI, 2.40–4.76); for nulliparity, 2.59 (95% CI, 1.90–3.52) and 2.78 (95% CI, 2.00–3.86); for preeclampsia in previous pregnancy, 14.09 (95% CI, 9.28–21.40) and 6.35 (95% CI, 3.69–10.94); for diabetes, 3.24 (95% CI, 1.17–8.97) and 3.76 (95% CI, 1.62–8.71); and for twin birth, 4.82 (95% CI, 1.47–15.83) and 10.25 (95% CI, 5.48–19.15).[21]
- In a meta-analysis of 25 356 688 pregnancies from 92 studies published between 2000 and 2015, the following factors at ≤16 weeks' gestation were associated with significantly elevated risks for preeclampsia (reported as pooled unadjusted RR): >35 years of age (versus <35 years of age; 1.2 [95% CI, 1.1–1.3]); prior preeclampsia (8.4 [95% CI, 7.1–9.9]); chronic hypertension (5.1 [95% CI, 4.0–6.5]); prepregnancy diabetes (3.7 [95% CI, 3.1–4.3]); prepregnancy obesity (BMI >30 kg/m$^2$ versus <30 kg/m$^2$; 2.8 [95% CI, 2.6–3.1]); prior stillbirth (2.4 [95% CI, 1.7–3.4]); multifetal pregnancy (2.9 [95% CI, 2.6–3.1]); nulliparity (2.1 [95% CI, 1.9–2.4]); CKD (1.8 [95% CI, 1.5–2.1]); systemic lupus erythematosus (2.5 [95% CI, 1.0–6.3]); antiphospholipid antibody syndrome (2.8 [95% CI, 1.8–4.3]); and conception by assisted reproductive techniques (1.8 [95% CI, 1.6–2.1]). PAF was highest for nulliparity (32.3% [95% CI, 27.4%–37.0%]), followed by prepregnancy BMI >25 kg/m$^2$ (23.8% [95% CI, 22.0%–25.6%]) and prior preeclampsia (22.8% [95% CI, 19.6%–26.3%]).[22]

### Weight Gain

- A review of 54 studies of >30 245 946 females in the obese weight category with singleton pregnancies showed that gestational weight gain less than recommended (by the current Institute of Medicine and the American College of Obstetricians and Gynecologists guidelines) compared with weight gain within the guidelines was associated with higher odds of having an SGA neonate (OR, 1.30 [95% CI, 1.17–1.45]) and lower odds for preeclampsia (OR, 0.71 [95% CI, 0.63–0.79]).[23] No significant differences were seen in gestational diabetes (OR, 1.56 [95% CI, 0.94–2.60]).
- In a meta-analysis of 13 studies including 156 170 singleton pregnancies in females who delivered at term, higher-than-recommended gestational weight gain per the 2009 National Academy of Medicine (Institute of Medicine) guidelines (12.5–18 kg for underweight [BMI <18.5 kg/m$^2$], 11.5–16 kg for normal weight [BMI, 18.5–24.9 kg/m$^2$], 7.0–11.5 kg for overweight [BMI, 25.0–29.9 kg/m$^2$], and 5.0–9.0 kg for obese [BMI >30.0 kg/m$^2$]) was associated with higher risks for overall HDP (OR, 1.79 [95% CI, 1.61–1.99]), gestational hypertension (OR, 1.67 [95% CI, 1.43–1.95]), and preeclampsia (OR, 1.92 [95% CI, 1.36–2.72]).[24]
- Among 8296 nulliparous females in the nuMoM2b study, higher HDP risks were observed for excess weight gain in midpregnancy (from 5–13 to 16–21 weeks' gestation; aIRR, 1.16 [95% CI, 1.01–1.35]) and late pregnancy (from 16–21 to 22–29 weeks' gestation; aIRR, 1.19 [95% CI, 1.02–1.40]) but not in early pregnancy (from prepregnancy to 5–13 weeks' gestation; aIRR, 0.95 [95% CI, 0.83–1.08]).[25]
- In a meta-analysis of 12 studies, interpregnancy weight gain was associated with increased HDP risk; each 1–kg/m$^2$ increase in BMI from the start of one pregnancy to the next was associated with 31% higher OR for HDP (0.31 [95% CI, 0.11–0.53]).[26]

### Blood Pressure

- Among 586 females with a mean age of 28.5 years (SD, 4.5 years) followed up from preconception through early pregnancy, each 2–mm Hg higher mean arterial pressure during preconception was associated with a higher risk of HDP (aRR, 1.08 [95% CI, 1.01–1.14]); in addition, each 2–mm Hg increase in mean arterial pressure from preconception to 4 weeks' gestation was associated with a higher risk of preeclampsia (aRR, 1.13 [95% CI, 1.02–1.25]), and each 2–mm Hg increase in mean arterial pressure from preconception to 20 weeks' gestation was associated with a higher risk of HDP (aRR, 1.14 [95% CI, 1.06–1.22]) and higher risk of preeclampsia (aRR, 1.20 [95% CI, 1.08–1.34]) after adjustment for age, parity, BMI, and aspirin use.[27]
- In a randomized clinical trial of 2408 pregnant females who had chronic hypertension before 23 weeks, a more intensive antihypertensive strategy targeting a BP of <140/90 mm Hg versus a strategy of no treatment unless BP was severely elevated (≥160/105 mm Hg) demonstrated an 18% reduction in the composite outcome of preeclampsia with severe features, PTB before 35 weeks, placental abruption, or fetal/neonatal death (aRR, 0.82 [95% CI, 0.74–0.92]).[28] In this same trial, targeting a BP of <140/90 mm Hg was also associated with reduced risk of developing any preeclampsia (RR, 0.79 [95% CI, 0.69–0.89]), with no increased risk in an SGA infant.

### Diet and Exercise

- In a meta-analysis of 23 trials (7236 participants), the joint effects of exercise and diet interventions on the development of preeclampsia were studied.[29] In females randomized to diet with or without exercise, compared with expectant management, there was no significant difference in the risk of preeclampsia (RR, 1.01 [95% CI, 0.80–1.27]) or HDP (RR, 0.87 [95% CI, 0.70–1.06]). In the intervention group, compared with expectant management, gestational weight gain was significantly lower (−1.47 kg, [95% CI, −1.97 to −0.97]). Meta-regression weighted by the size of the studies showed no significant association between gestational weight gain and the risk of PE or HDP ($P$=0.314 and $P$=0.124, respectively).
- Among 8507 females in the multiethnic Boston Birth Cohort, a greater adherence to a Mediterranean-style diet was associated with a 22% lower odds of preeclampsia (aOR, 0.78 [95% CI, 0.64–0.96] for the highest compared with lowest adherence of diet score).[30]
- Among 62 774 females with singleton pregnancies in the Danish National Birth Cohort, sodium intake during pregnancy (reported at 25 weeks' gestation) was associated with risk for HDP; females with >3.5 g/d sodium intake had 54% (95% CI, 16%–104%) higher risk for gestational hypertension and 20% (95% CI, 1%–42%) higher risk for preeclampsia compared with females with <2.8 g/d sodium intake.[31]
- Among 8259 pregnant females in the nuMoM2b cohort, periconceptional dietary quality was associated with HDP risk. The HDP rate was 25.9% for females in the lowest quartile (poorest quality) of the HEI-2010 compared with 20.3% for females in the highest quartile (aRR, 1.16 [95% CI, 1.02–1.31]).[32]

### Race and Ethnicity

- Among 9470 nulliparous pregnant females in nuMoM2b (60.4% NH White, 13.8% NH Black, 16.7% Hispanic, 4.0% Asian, 5.0% other), NH Black females were significantly more likely to

experience HDP compared with NH White females (16.7% versus 13.4%, respectively; OR, 1.30 [95% CI, 1.10–1.53]), whereas Hispanic females and Asian females were less likely to experience HDP (10.6%; OR, 0.77 [95% CI, 0.64–0.91]; and 8.5%; OR, 0.60 [95% CI, 0.41–0.87], respectively, versus NH White females).[33] These differences were largely attenuated after adjustment for age, BMI, smoking, and medical comorbidities.

- In meta-analysis, immigrant (versus nonimmigrant) status has been associated with lower risk of HDP (RR, 0.74 [95% CI, 0.67–0.82]).[34] Similarly, in the nuMoM2b study, greater acculturation (defined as born in the United States with high English proficiency versus born or not born in the United States with low proficiency in English or use of Spanish as the preferred language) was associated with higher risk of preeclampsia or eclampsia (aOR, 1.31 [95% CI, 1.03–1.67]) and gestational hypertension (aOR, 1.48 [95% CI, 1.22–1.79]).[35]
- In a nationwide sample spanning 15 years (2004–2019), among females with preeclampsia, Black females with high income still had worse maternal outcomes at delivery such as PPCM (aOR, 1.47 [95% CI, 1.16–1.86]), stroke (aOR, 2.05 [95% CI, 1.54–2.74]), HF (aOR, 1.63 [95% CI, 1.34–1.99]), cardiac arrhythmias (aOR, 1.43 [95% CI, 1.31–1.58]), and VTE (aOR, 2.37 [95% CI, 1.54–3.65]) compared with White females of low income.[36]

### Other

- Among 1964 females from the nuMoM2b-HHS, SDB (as reflected by an AHI ≥5) during pregnancy was associated with increased risk for hypertension 2 to 7 years after delivery (aRR, 2.02 [95% CI, 1.30–3.14]).[37] Risks of hypertension 2 to 7 years after delivery were greater for participants with an AHI ≥5 in pregnancy that persisted after delivery (aRR, 3.77 [95% CI, 1.84–7.73]).
- In a meta-analysis of 10 studies, air pollution (particulate matter [PM2.5]) exposure during pregnancy was associated with higher risk for HDP (OR, 1.52 [95% CI, 1.24–1.87] per 10 μg/m$^3$).[38]
- In an observational study, 12 715 Chinese females who had a singleton birth and underwent routine serum lipid screenings in early (9–13 weeks) and late (28–42 weeks) pregnancy were followed up for the development of APOs.[39] Elevated serum triglyceride levels during early pregnancy were associated with increased risks of preeclampsia (OR, 1.75 [95% CI, 1.29–2.36]). Persistently high triglyceride levels increased the risks of preeclampsia (OR, 2.53 [95% CI, 1.66–3.84]).
- In a study of 2148 pregnant females, the association between COVID-19 and APOs was studied.[40] Participants were enrolled in 43 institutions across 18 countries, and 725 (33.2%) had COVID-19. Pregnant females with COVID-19 were more likely to develop preeclampsia (8.1% versus 4.4%; aRR, 1.77 [95% CI, 1.25–2.52]) compared with pregnant females without COVID-19.
- In a nationwide analysis between 2016 and 2019, pregnant females from rural areas were at greater risk for maternal ICU admission (RR, 1.14 [95% CI, 1.04–1.20]) and maternal mortality (RR, 1.93 [1.71–2.17)] compared with their urban counterparts.[41]

### Genetics/Family History

- There is evidence of intergenerational transmission of HDP risk. According to multigenerational birth records for 17 302 nulliparous females in the Aberdeen Intergenerational Cohort, being born of a pregnancy complicated by preeclampsia or gestational hypertension was associated with higher risk for preeclampsia (aRR ratio, 2.55 [95% CI, 1.87–3.47] and 1.44 [95% CI, 1.23–1.69], respectively) and gestational hypertension (aRR ratio, 1.37 [95% CI, 1.09–1.71] and 1.36 [95% CI, 1.24–1.49], respectively).[25,42]
- Maternal, paternal, and fetal genomes may influence preeclampsia. Using the population-based Swedish Birth and Multi-Generation Registries of 244 564 sibling pairs, 1 study reported that ≈50% of the variance in preeclampsia was attributed to genetic factors and that maternal genomes contributed more to preeclampsia liability than fetal or paternal genomes.[43] Specifically, 35% of the variance in liability of preeclampsia was attributable to maternal genetic effects, 20% to fetal genetic effects (maternal and paternal genetic effects), 13% to the couple effect, and <1% to shared sibling environment.
- Many genetic risk factors for HDP may overlap with traditional CVD risk factors, most notably BP and anthropometry phenotypes. According to data from the UK Biobank, GRSs for SBP (aOR per 1 SD, 1.22 [95% CI, 1.17–1.27]), DBP (aOR per 1 SD, 1.22 [95% CI, 1.17–1.26]), and BMI (aOR per 1 SD, 1.06 [95% CI, 1.02–1.10]) were significantly associated with HDP risk, whereas GRSs for heart rate, type 2 diabetes, smoking, and LDL-C were not associated.[44]
- Analysis of genetic instruments related to BP-lowering pathways suggested that nitric oxide signaling might be particularly relevant for HDP risk (*GUCY1A3* SNP was associated with an aOR of 0.21 per 5–mm Hg lowering of SBP versus PRS for systolic BP; aOR, 0.65 per 5–mm Hg lowering of SBP; $P_{heterogeneity}$=0.037).[44]

### Genetic Variants

- A limited number of preeclampsia GWASs have been published; available GWASs have examined both the maternal and fetal genomes. One GWAS of preeclampsia analyzed 4380 offspring of females

with preeclampsia and 310 238 control subjects and identified a locus near the *FLT1* gene with strongest association in offspring from pregnancies in which preeclampsia developed during late gestation.[45] *FLT1* encodes a transmembrane tyrosine kinase receptor that mediates angiogenesis by binding placental growth factor.

- A second GWAS meta-analysis of 7219 European mothers with preeclampsia and 155 660 control subjects and 2296 Central Asian mothers with preeclampsia and 2059 control subjects identified the *FLT1* locus and variants at *ZNF831* and *FTO*.[46] *ZNF831* and *FTO* were previously associated with BP, among other cardiometabolic traits.[47] Furthermore, a GRS for hypertension was associated with preeclampsia ($P$=1.2×10$^{-12}$, effect [log OR]=0.18 [95% CI, 0.13–0.23], with effect corresponding to the increase in the risk of preeclampsia per 1 SD in GRS).[46]
- The most recent (and largest) GWAS combined summary statistics from the FinnGen cohort and UK Biobank for 24 self-reported pregnancy complications among European ancestry participants. Five loci were identified for hypertension complicating pregnancy, childbirth, and the puerperium (*MTHFR*, *FGF5*, *PLCE1*, *RGL3*, and *ZNF831*), and 1 locus was identified for gestational hypertension (*PREX1*). *MTHRF*, *FGF5*, and *ZNF831* were previously linked to pregnancy complications, whereas *PLCE1*, *RGL3*, and *PREX1* were novel.[48]
- The role of variants associated with preeclampsia risk factors (eg, hypertension and BMI) in preeclampsia is supported by a study of 498 preeclampsia cases. Specifically, both a hypertension GRS and a BMI GRS were associated with increased odds of preeclampsia.[49]
- *TTN* variants, present in DCM and PPCM, are enriched in patients with preeclampsia, suggesting a shared genetic architecture. In a study of 181 primarily White females with preeclampsia, the prevalence of loss-of-function variants in cardiomyopathy genes was higher in preeclampsia cases compared with controls (5.5% versus 2.5%; $P$=0.014), with most variants found in the *TTN* gene (see Chapter 22 [Cardiomyopathy and Heart Failure]).[50]
- Motivated by high disease heterogeneity and prior evidence suggesting increased risk in high-altitude regions, a study of N=883 families in the Peruvian Andes was performed. This study identified associations between preeclampsia and a fetal locus containing clotting factor genes *PROZ*, *F7*, and *F10*.[51]

## Prevention

### Breastfeeding

- Among 3598 participants from the Avon Longitudinal Study of Parents and Children cohort, after a mean follow-up of 18 years after delivery, breastfeeding for 6 to 9 months among females with HDP was associated with significant reductions in DBP (−4.87 mm Hg [95% CI, −7.86 to −1.88]), mean arterial pressure (−4.61 mm Hg [95% CI, −7.45 to −1.77]), and LDL-C (−0.40 mmol/L [95% CI, −0.62 to −0.17 mmol/L]).[52]

### Lifestyle Modifications

- PA is recommended for pregnant females without obstetric or medical complications.[53–55] Several reviews of the literature that supported these guidelines indicate that PA (600 MET-min/wk of moderate-intensity exercise) during pregnancy can decrease the odds of HDP by 25%.[56]
- Aerobic exercise for ≈30 to 60 minutes 2 to 7 times/wk during pregnancy was associated with a significantly lower risk of gestational hypertension in a systematic review from 17 trials including 5075 pregnant females (RR, 0.70 [95% CI, 0.53–0.83] for HDP).[57]

### Aspirin

- Low-dose aspirin started in early pregnancy reduces risk for some APOs among higher-risk females. A 2021 meta-analysis by the US Preventive Services Task Force reported a lower risk of preeclampsia (RR, 0.85 [95% CI, 0.75–0.95]), perinatal mortality (RR, 0.79 [95% CI, 0.66–0.96]), preterm birth <37 weeks (RR, 0.80 [95% CI, 0.67–0.95]), and fetal growth restriction (RR, 0.82 [95% CI, 0.68–0.99]) and no significant increase in bleeding-related harms.[58]
- Specific aspirin dose and preeclampsia prevention were studied in 23 randomized trials (32 370 females). Females assigned at random to 150 mg experienced a 62% reduction in risk of preterm preeclampsia (RR, 0.38 [95% CI, 0.20–0.72]).[59] Aspirin doses <150 mg produced no significant reductions. The number of pregnant females needed to treat with 150 mg aspirin in order to prevent 1 case of preeclampsia was 39 (95% CI, 23–100). There was a maximum 30% reduction in risk of all gestational age preeclampsia at all aspirin doses.

## Complications: Maternal CVD

- According to a meta-analysis of 9 studies, gestational hypertension was associated with a 67% (95% intrinsic CI, 1.28%–2.19%) higher risk of subsequent CVD, and preeclampsia was associated with a 75% (95% intrinsic CI, 1.46%–2.06%) higher risk of subsequent CVD-related mortality.[60]
- In an analysis of 65 286 425 females from the NIS from January 1, 1998, through December 31, 2014, females with HDP had a higher risk of stroke compared with those without HDP (34.5% versus 6.9%; $P$<0.0001).[61] A significant interaction with race and

ethnicity was observed with significantly higher risk of stroke in Black females (aRR, 2.07 [95% CI, 1.86–2.30]) and Hispanic females (aRR, 2.19 [95% CI, 1.98–2.43]) compared with NH White females.
- On the basis of data on 1.3 million females abstracted between 1997 and 2016 in the Clinical Practice Research Datalink in the United Kingdom, females with preeclampsia had an increased risk of hypertension (HR, 4.47 [95% CI, 4.3–4.62]) and various CVD subtypes (stroke: HR, 1.9 [95% CI, 1.53–2.35]; atherosclerotic CVD: HR, 1.67 [95% CI, 1.54–1.81]; HF: HR, 2.13 [95% CI, 1.64–2.76]; AF: HR, 1.73 [95% CI, 1.38–2.16]; and cardiovascular mortality: HR, 2.12 [95% CI, 1.49–2.99]).[62]
- In a 1980 to 2004 national cohort study from Norway, in 508 422 females 16 to 49 years of age at first birth, preeclampsia was associated with a significantly higher risk for HF (HR, 2.00 [95% CI, 1.50–2.68]) compared with normotension.[63]
- In an analysis from the Nurses' Health Study including >60 000 parous participants, history of HDP was associated with a 63% increased risk of incident CVD (HR, 1.63 [95% CI, 1.37–1.94]) with a greater risk for preeclampsia (HR, 1.72 [95% CI, 1.42–2.10]) than for gestational hypertension (HR, 1.41 [95% CI, 1.03–1.93]).[64] There was also a dose relationship, with HRs of 1.48 (95% CI, 1.23–1.78) and 2.28 (95% CI, 1.70–3.07) for history of 1 and ≥2 HDP, respectively, compared with parous individuals without a history of HDP. Mediation analysis suggested that 64% (95% CI, 39%–83%) of the increased risk of CVD conferred by HDP was explained by traditional CVD risk factors such as the subsequent development of chronic hypertension, hypercholesterolemia, diabetes, and changes in BMI.

### *Complications: Offspring Morbidity and Mortality*

- In a 2019 meta-analysis of studies reporting outcomes in childhood or young adulthood (up to 30 years of age), exposure to preeclampsia in utero was associated with higher SBP (pooled mean difference, 5.17 mm Hg [95% CI, 1.60–8.73]; 15 studies, 53 029 individuals, 1599 exposed), DBP (4.06 mm Hg [95% CI, 0.67–7.44]; 14 studies, 52 993 individuals, 1583 exposed), and BMI (0.36 kg/m$^2$ [95% CI, 0.04–0.68]; 13 studies, 53 293 individuals, 1752 exposed).[65] No significant pooled associations were found for offspring lipids, glucose, or insulin.
- A meta-analysis of 40 studies showed that offspring (at <10 years of age) of mothers with preeclampsia had increased SBP (mean difference, 2.2 mm Hg [95% CI, 1.28–3.12]) and DBP (mean difference, 1.41 mm Hg [95% CI, 0.3–2.52]) compared with control subjects.[66]

## Gestational Diabetes

### *Incidence, Prevalence, and Secular Trends*

### *(Charts 11-5 and 11-6)*

- The global prevalence of gestational diabetes was 13.4% in 2021.[67]
- The national prevalence of gestational diabetes was 7.8% in 2020, an increase of 30% from 2016 according to birth data from the NVSS.[68] There was a notably large annual percent change from 2019 to 2020 (13%) compared with the average annual percent change from 2016 to 2019 (5%) overall. In 2016, the prevalence of preexisting diabetes complicating pregnancies was 0.9%.[69]
  - The prevalence of gestational diabetes was highest in NH Asian females (14.9%), followed by NH American Indian or Alaska Native (11.8%), Native Hawaiian or other Pacific Islander (10.6%), Hispanic (8.5%), NH White (7.0%), and NH Black (6.5%) females.[58]
- The prevalence of gestational diabetes increases with each adiposity category ranges from 3.7% among underweight females to 12.6% among obese females (Chart 11-5).
- Temporal trends in gestational diabetes rates were estimated from a serial cross-sectional analysis of NCHS data for 12 610 235 females 15 to 44 years of age with singleton first live births from 2011 to 2019 in the United States (mean age, 26.3 years [SD, 5.8 years]).[70] Gestational diabetes rates increased across all races and ethnicities from 47.6 to 63.5 per 1000 live births from 2011 to 2019, a mean annual percent change of 3.7% (95% CI, 2.8%–4.6%) per year.
  - Of the participants, the following were race-specific gestational diabetes rates: Hispanic/Latina, 66.6 per 1000 live births (95% CI, 65.6–67.7; RR, 1.15 [95% CI, 1.13–1.18]); NH Asian/Pacific Islander, 102.7 per 1000 live births (95% CI, 100.7–104.7; RR, 1.78 [95% CI, 1.74–1.82]); NH Black, 55.7 per 1000 live births (95% CI, 54.5–57.0; RR, 0.97 [95% CI, 0.94–0.99]); and NH White, 57.7 per 1000 live births (95% CI, 57.2–58.3; referent group).
  - Gestational diabetes rates were highest in Asian Indian participants, 129.1 per 1000 live births (95% CI, 100.7–104.7; RR, 2.24 [95% CI, 2.15–2.33]). Among Hispanic/Latina participants, gestational diabetes rates were highest among Puerto Rican individuals at 75.8 per 1000 live births (95% CI, 71.8–79.9; RR, 1.31 [95% CI, 1.24–1.39]).

### *Risk Factors (Including Social Determinants)*

- In an individual participant data meta-analysis of 265 270 births from 39 cohorts in Europe, North

America, and Australia, higher prepregnancy BMI (OR per 1–kg/m$^2$ higher BMI, 1.12 [95% CI, 1.12–1.13]) and higher gestational weight gain (OR per 1-SD higher gestational weight gain, 1.14 [95% CI, 1.10–1.18]) were associated with higher risks of gestational diabetes.[6] Approximately 42.8% of gestational diabetes cases were estimated as attributable to prepregnancy overweight (OR, 2.22 [95% CI, 2.06–2.40]) or obesity (OR, 4.59 [95% CI, 4.22–4.99]).

- In the nuMoM2b study, among 782 nulliparous females in the early second trimester with objectively measured sleep for 5 to 7 nights, short sleep duration (<7 h/night average; present in 27.9%) and late sleep midpoint (>5 AM average; present in 18.9%) were significantly associated with risk for gestational diabetes (aOR, 2.06 [95% CI, 1.01–4.19] and 2.37 [95% CI, 1.13–4.97], respectively) independently of age, race and ethnicity, employment schedule, BMI, and snoring.[71]
- In a cohort of 595 pregnant females in 4 US areas (Chicago, IL; Schuylkill County, Pennsylvania; Pittsburgh, PA; and San Antonio, TX), perceived discrimination (self-reported as based on sex, race, income level or social status, age, and physical appearance) was associated with the development of gestational diabetes. Gestational diabetes occurred in 12.8% of females in the top quartile of a self-reported discrimination scale versus 7.0% in all others (aOR, 2.11 [95% CI, 1.03–4.22] adjusted for age, income, parity, race and ethnicity, and study site); 22.6% of this association was statistically mediated by obesity.[72]
- A systematic review of 17 studies demonstrated that individuals with gestational diabetes had statistically significant differences in the diversity of gut microbes.[73] Six prospective studies found that microbiota change during pregnancy is associated with risk of gestational diabetes.
- Among 8 574 264 females 15 to 44 years of age at first live singleton birth in the United States, 1 747 066 were born outside the United States.[74] In females born outside the United States, gestational diabetes rates were higher than in females born in the United States (70.3 versus 53.2 per 1000 live births; rate ratio,1.32 [95% CI, 1.31–1.33]). These findings were consistent in most racial and ethnic groups studied, with the exception of females born in Japan (who had lower rates than those born in the United States).

### Genetics/Family History

- Although gestational diabetes is thought to be heritable, heritability estimates for gestational diabetes from twin or familial clustering studies are not available. Korean females with gestational diabetes had a greater parental history of type 2 diabetes compared with pregnant females with normal glucose tolerance (13.2% versus 30.1%; $P<0.001$).[75]
- A GWAS of gestational diabetes in FinnGen cohort and UK Biobank participants of European ancestry identified 4 maternal loci: *GCKR*, *HLA*, *TCF7L2*, and *MTNR1B.* All maternal loci are known to affect type 2 diabetes.[48] Similarly, in a multiethnic GWAS of n=5485 females with gestational diabetes and n=347 856 females without gestational diabetes that also included UK Biobank participants, 5 gestational diabetes loci were identified: *MTNR1B*, *TCF7L2*, *CDKAL1*, *CDKN2A/2B*, and *HKDC1*. *HKDC1* was the only locus without evidence pointing to a shared pathophysiology between gestational diabetes and type 2 diabetes.[76]
- Reflecting the hypothesis that gestational diabetes and diabetes have a shared genetic architecture, the majority of gestational diabetes genetic studies have examined variants previously mapped for type 2 diabetes. For example, a meta-analysis of 23 studies examined the relevance of 100 type 2 diabetes variants that were reported by a minimum of 2 studies for gestational diabetes. This meta-analysis identified significant associations for gestational diabetes with 16 variants in 8 loci (in or near *IGF2BP2*, *CDKAL1*, *GLIS3*, *CDKN2A/2B*, *HHEX/IDE*, *TCF7L2*, *MTNR1B*, and *HNF1A*).[77]
- GRSs composed of diabetes loci predict gestational diabetes. In a case-control study of 2636 females with gestational diabetes and 6086 females without gestational diabetes from the US Nurses' Health Study II and the Danish National Birthday Cohort, a weighted GRS of 8 variants previously associated with diabetes was associated with gestational diabetes (OR for highest GRS quartile compared with lowest, 1.53 [95% CI, 1.34–1.74]).[78] Similarly, among the US-based nuMoM2b cohort, compared with the general population, participants with a high diabetes GRS and low PA levels had higher odds of a gestational diabetes diagnosis (OR, 3.4 [95% CI, 2.3–5.3]). In contrast, compared with the general population, participants with a low diabetes GRS and high PA levels had a lower odds of a gestational diabetes diagnosis (OR, 0.5 [95% CI, 0.3–0.9]).[79]
- Association of diabetes GRSs with gestational diabetes is consistent in other ancestries; in a study of 832 South Asian females from the START and UK Biobank cohorts, a diabetes GRS optimized to South Asian ancestry was associated with gestational diabetes (OR, 2.51 [95% CI, 1.82–3.47]; $P=1.75\times10^{-8}$; and OR, 2.66 [95% CI, 1.51–4.63]; $P=0.0006$, respectively, for the top 25% of GRSs compared with the bottom 75%).[80]
- Few GWASs of gestational diabetes have been published, and available GWASs have identified

known diabetes genetic variants only. For example, the largest published gestational diabetes GWAS included a discovery cohort of 468 Korean females with gestational diabetes and 1242 females without diabetes, with validation in a second cohort of 931 cases and 783 controls. This GWAS identified 2 loci at genome-wide significance levels.[81] Both loci, *CDKAL1* and *MTNR1B*, were previously identified by type 2 diabetes and fasting glucose GWASs.[82,83] It is interesting to note that lead variants at both loci also were associated with lower fasting insulin levels during pregnancy.

- A GWAS of diverse ancestry in 5485 females with gestational diabetes and 347 856 without gestational diabetes identified 5 loci with genome-wide significant association with gestational diabetes, mapping to or near *MTNR1B*, *TCF7L2*, *CDKAL1*, *CDKN2A/2B*, and *HKDC1*.[76] All loci except *HKDC1* have previously been reported at genome-wide significance for type 2 diabetes. Mendelian randomization analyses demonstrated significant causal association of higher BMI and increased gestational diabetes risk.

## Prevention

- A meta-analysis of 35 randomized trials showed that exercise interventions during pregnancy decrease the incidence of developing gestational diabetes (pooled OR, 0.61 [95% CI, 0.51–0.74]), particularly when they are supervised, have a low to moderate intensity level, and are initiated during the first trimester of pregnancy.[84]

### *Complications: Maternal Cardiovascular Risk Factors and CVD*

- In a meta-analysis of 20 studies that included 1 332 373 individuals, the RR for diabetes was estimated as 10 times higher (95% CI, 7.14–12.67) in females with a history of gestational diabetes compared with females without gestational diabetes.[85]

### *Complications: Offspring Morbidity and Mortality*

- In the multinational HAPO Follow-Up Study of 4832 children 10 to 14 years of age, in utero exposure to gestational diabetes, independently of maternal BMI during pregnancy, was associated with higher odds of obesity (aOR, 1.58 [95% CI, 1.24–2.01]; risk difference, 5.0% [95% CI, 2.0%–8.0%]) and excess adiposity (body fat percentage >85th percentile; aOR, 1.35 [95% CI, 1.08–1.68]; risk difference, 4.2% [95% CI, 0.9%–7.4%]) at 10 to 14 years of age.[86] Gestational diabetes exposure was also associated with greater odds for impaired glucose tolerance at 10 to 14 years of age independently of maternal BMI, child BMI, and family history of diabetes (aOR, 1.96 [95% CI, 1.41–2.73]).[87]
- Among 2 432 000 live-born children without congenital HD in the Danish national health registries during 1977 to 2016, in utero exposure to gestational diabetes was associated with higher risk for CVD during up to 40 years of follow-up (aOR, 1.19 [95% CI, 1.07–1.32]).[88] Findings were similar when a sibship design was used (ie, comparing exposed with unexposed siblings) and when controlling for maternal prepregnancy BMI and paternal diabetes status.

## Preterm Birth

### *Incidence, Prevalence, and Secular Trends*

#### *(See Chart 11-6)*

- In 2016, PTB accounted for 9.9% of all births with a similar proportion of PTBs (10.0%) reported in 2018 from a total of 3 791 712 live births (or a birth rate of 11.6 per 1000 population).[89,90]
  - PTB rates were higher among NH Black females (14.1%) compared with NH White (9.1%) and Hispanic (9.7%) females in 2018 (Chart 11-6).[90]
- Among all singleton deliveries at a single US tertiary care center, compared with the overall PTB rate before the COVID-19 pandemic (11.1% among 17 687 deliveries from January 1, 2018–January 31, 2020), the rate was significantly lower during the pandemic (10.1% among 5396 deliveries from April 1, 2020–October 27, 2020; *P*=0.039 for comparison); spontaneous PTB rates also decreased during the pandemic (from 5.7% to 5.0%; *P*=0.074). However, decreases in spontaneous PTB occurred only among females from more advantaged neighborhoods (compared with less advantaged neighborhoods; from 4.4% to 3.8% versus from 7.2% to 7.4%), White (versus Black) females (from 5.6% to 4.7% versus from 6.6% to 7.1%), and females receiving care from clinics that do not (versus do) provide prenatal care to those eligible for Medical Assistance (from 5.5% to 4.8% versus from 6.3% to 6.7%).[91]

### *Risk Factors*

- In a meta-analysis of studies reported between December 2019 and June 2020, maternal COVID-19 infection (versus no COVID-19 infection) was associated with higher prevalence and odds of PTB (10.8% versus 6.0%; OR, 3.0 [95% CI, 1.15–7.85]).[92] In another US study using a surveillance database, among 4442 pregnant females with COVID-19 from March to October 2020, the PTB rate was 12.9%; this was higher than the rate in the general population in 2019 (10.2%).[93]
- Among 1482 nulliparous low-risk females at <20 weeks' gestation (who received placebo in a trial of low-dose aspirin to prevent preeclampsia), risks for

indicated (but not spontaneous) PTB were elevated even with mild stage 1 hypertension (SBP from 130–135 mm Hg or DBP from 80–85 mm Hg; 4.2% versus 1.1%; RR, 3.79 [95% CI, 1.28–11.20]; adjusted for age, race, and prepregnancy BMI: RR, 3.98 [95% CI, 1.36–11.70]).[94]

- Among 8259 pregnant females in the nuMoM2b cohort, periconceptional dietary quality was associated with PTB risk. The PTB rate was 9.5% for females in the lowest quartile (poorest quality) of the HEI-2010 compared with 6.9% for females in the highest quartile (aRR, 1.27 [95% CI, 1.01–1.60]).[32]
- In a meta-analysis of 6 studies, objectively measured SDB (OSA) was associated with a higher risk of PTB, with an aOR of 1.6 (95% CI, 1.2–2.2).[95]
- In a study of 8026 births during the first wave of the COVID-19 pandemic in New York, no racial and ethnic differences were found in either preterm or very PTB (<32 weeks' gestational age) between Black and White females.[96]

### Environmental Exposures

- In a systematic review of studies examining air pollution, significant associations were found with PTB for 19 of 24 studies (examining a total of >7 million births). The risk was higher by a median of 11.5% (range, 2.0%–19.0%) for whole-pregnancy PM2.5 exposure per IQR higher exposure,[97] and risk was greater among NH Black females compared with NH White females. In a study of >14 000 mothers in California, the risk of PTB associated with increasing temperature was numerically but not statistically higher among Black (24.60% [95% CI, 1.00%–55.27%]) and Hispanic (17.35% [95% CI, 3.04%–34.98%]) mothers compared with Asian mothers (7.25% [95% CI, −11.31% to 30.99%]) or White mothers (7.25% [95% CI, −6.77% to 22.14%]; $P$=0.56, 0.64, and 1.0, respectively, with White mothers as reference group).[98]
- In a systematic review, 4 of 5 studies (>800 000 births) examining heat demonstrated that risk for PTB was higher by a median of 15.8% (range, 9.0%–22.0%) for whole-pregnancy heat exposure for each 5.6°C increase in weekly mean temperature.[97] Similarly, in a meta-analysis of 47 studies including international populations, the odds of PTB were 1.05 times higher (95% CI, 1.03–1.07) per 1°C increase in environmental temperature and were 1.16 times higher (95% CI, 1.10–1.23) during heat waves (defined in this analysis as ≥2 days with temperatures ≥90th percentile).[99]
- In a meta-analysis of 4 studies, more favorable environmental characteristics such as access to green space or greater environmental greenness (based on a standardized measure commonly used to indicate the presence and level of green space: the normalized difference vegetation index) within a 100-m buffer were associated with a lower risk for PTB (pooled standardized OR, 0.98 [95% CI, 0.97–0.99]).[100]

### Social Determinants of Health and Health Equity in PTB

- In a meta-analysis of 13 studies of 9299 females, racial discrimination was associated with an increased odds of preterm birth (pooled OR, 1.40 [95% CI, 1.17–1.68]).[101] When 3 low-quality studies (as determined by the Newcastle-Ottawa and Agency for Healthcare Research and Quality scales, eg, case-control study, selection bias, and publication bias) were excluded, the odds of preterm birth was attenuated but remained statistically significant (OR, 1.31 [95% CI, 1.08–1.59]).
- Among infants born to females who were evicted in Georgia from 2000 to 2016, eviction during gestation (versus infants born to females who experienced an eviction before they were pregnant) was associated with 1.14 (95% CI, 0.21–2.06) percentage points higher rate of PTB after covariate adjustment (crude rate, 15.28% versus 13.36%, respectively).[102]
- In a cohort of 3801 females with 9075 live singleton births, latent class analysis revealed a stress/anxiety/depression class that was associated with increased risk for PTB (OR, 1.87 [95% CI, 1.20–2.30]).[103]
- In a study from data from the California Office of Statewide Health Planning and Development, 2794 females with unstable housing were exactly propensity score matched with 2318 control subjects.[104] Females with unstable housing had higher odds of PTB (OR, 1.2 [95% CI, 1.0–1.4]; $P$<0.05) and preterm labor (OR, 1.4 [95% CI, 1.2–1.6]; $P$<0.001).

### Genetics/Family History

- There is evidence of intergenerational transmission of PTB risk.[105] For example, heritability estimates for maternal genetic effects on PTB have ranged from 15% to 40%, although these estimates also may include effects of the fetal genome. Fetal genetic factors were estimated to account for 0 to 13% of the variation in gestational age at delivery; similarly negligible to small genetic effects were estimated for the paternal contribution.[106]
- A maternal GWAS of gestational duration and PTB analyzed a discovery set of 43 568 females of European ancestry and found that variants at the *EBF1*, *EEFSEC*, *AGTR2*, *WNT4*, *ADCY5*, and *RAP2C* loci were associated with gestational duration and variants at the *EBF1*, *EEFSEC*, and *AGTR2* loci were associated with PTB.[107] These genes have previously established roles in uterine development, maternal nutrition, and vascular control. Another

GWAS in 84 689 infants found a locus on chromosome 2q13, which includes several interleukin-1 family member genes, that was associated with gestational duration.[108]
- A GWAS of gestational diabetes in FinnGen cohort and UK Biobank participants of European ancestry identified 1 maternal locus: *EBF1*.[76] This locus was previously implicated in an mRNA study of maternal blood and PTB.[109]
- An international study that evaluated haplotype genetic scores known to be associated with adult height, BMI, BP, blood glucose, and type 2 diabetes in 10 734 female-infant duos of European ancestry found that taller genetic maternal height was associated with longer gestational duration (0.14 d/cm [95% CI, 0.10–0.18]; $P=2.2\times10^{-12}$), lower PTB risk (OR, 0.7/cm [95% CI, 0.96–0.98]; $P=2.2\times10^{-9}$), and higher birth weight (15 g/cm [95% CI, 13.7–16.3]; $P=1.5\times10^{-111}$).[110] Genetically determined maternal BMI was associated with higher birth weight (15.6 g/[kg/m$^2$] [95% CI, 13.5–17.7]; $P=1.0\times10^{-47}$) but not gestational duration or PTB risk.

### Race and Ethnicity

- Among 9470 nulliparous pregnant females (60.4% NH White, 13.8% NH Black, 16.7% Hispanic, 4.0% Asian, 5.0% other), PTB occurred in 8.1% of NH White females, 12.3% of NH Black females (OR versus NH White females, 1.60 [95% CI, 1.32–1.93]), 8.1% of Hispanic females (OR, 1.00 [95% CI, 0.82–1.23]), and 6.3% of Asian females (OR, 0.77 [95% CI, 0.51–1.18]).[33] The higher risk among NH Black females was partly attenuated by adjustment for age, BMI, smoking, and medical comorbidities (aOR, 1.31 [95% CI, 1.06–1.63]) and, separately, for perceived social support (aOR, 1.35 [95% CI, 1.06–1.72]). The OR for the association of low perceived social support (lowest quartile of support) with PTB was 1.21 (95% CI, 1.01–1.44).
- Examination of state Medicaid expansion noted an association with improvement in relative disparities between Black people and White people in rates of PTB among states that expanded compared with those that did not. Difference-in-difference models between 2011 and 2016 estimated a decline of −0.43 percentage points (95% CI, −0.84 to −0.002) for PTB for Black infants compared with White infants.[111]
- Black race–White race disparities in PTB are also present among females of high SES; among 2 170 686 singleton live births in the United States from 2015 to 2017 to college-educated females with private insurance who were not receiving WIC benefits, PTB rates for females who identified as NH White, mixed NH White/Black, and NH Black were 5.5% versus 6.1% versus 9.9%, respectively, for PTB at <37 weeks' gestation and 0.2% versus 0.4% versus 1.2% for PTB at <28 weeks' gestation.[112]

### Complications: Maternal CVD and Mortality

- Among 57 904 females in the Nurses' Health Study II with at least 1 live birth, PTB was associated with increased risk of hypertension (HR, 1.11 [95% CI, 1.06–1.17]), type 2 diabetes (HR, 1.17 [95% CI, 1.03–1.33]), and hyperlipidemia (HR, 1.07 [95% CI, 1.03–1.11]).[113]
- Among 1049 Black and White females in the CARDIA study, 272 (26%) had a pregnancy with a PTB (<37 weeks). Females with PTB were more likely to have an increasing trajectory of SBP and CAC (39% versus 12%) over 25 years of follow-up.[114]
- In a separate study from the Swedish national birth registry among 2 189 190 females with singleton delivery from 1973 to 2015, the aHR for IHD for females who experienced PTB was 2.47 (95% CI, 2.16–2.82) in the 10 years after delivery, 1.86 (95% CI, 1.73–1.99) in the 10 to 19 years after delivery, 1.52 (95% CI, 1.45–1.59) in the 20 to 29 years after delivery, and 1.38 (95% CI, 1.32–1.45) in the 30 to 43 years after delivery.[115]
- In a meta-analysis of 14 studies, females with a history of PTB (<37 weeks' gestation) had a 63% (95% intrinsic CI, 1.39%–1.93%) higher risk of CVD compared with females with no history of PTB.[60]
- Among 2 189 477 females with a singleton delivery in 1973 to 2015, risk of all-cause mortality was higher among those with PTB (<37 weeks' gestational age) with an aHR of 1.73 (95% CI, 1.61–1.87) in the 10 years after delivery; a dose-dependent relationship was observed with higher risk based on delivery at earlier gestational ages (extremely preterm, 22–27 weeks: 2.20 [95% CI, 1.63–2.96]; very preterm, 28–33 weeks: 2.28 [95% CI, 2.01–2.58]; late preterm, 34–36 weeks: 1.52 [95% CI, 1.39–1.67]; early term, 37–38 weeks: 1.19 [95% CI, 1.12–1.27]) compared with full-term delivery between 39 and 41 weeks.[116]

### Complications: Offspring Morbidity and Mortality

- In a meta-analysis of 4 cohort studies, having been born preterm was associated with increased risk for MetS in children and adults (pooled OR, 1.72 [95% CI, 1.12–2.65]).[117]
- In analyses of Swedish national birth register data (>2 million–>4 million individuals), gestational age at birth was inversely associated with the risks for type 1 diabetes (aHR, 1.21 [95% CI, 1.14–1.28] at <18 years of age and 1.24 [95% CI, 1.13–1.37] at 18–43 years of age), type 2 diabetes (aHR, 1.26 [95% CI, 1.01–1.58] at <18 years of age and 1.49 [95% CI,

1.31–1.68] at 18–43 years of age), hypertension (aHR, 1.24 [95% CI, 1.15–1.34] at <18 years of age, 1.28 [95% CI, 1.21–1.36] at 18–29 years of age, and 1.25 [95% CI, 1.18–1.31] at 30–43 years of age), and lipid disorders (aHR, 1.23 [95% CI, 1.16–1.29] at 0–44 years of age) among individuals born preterm compared with those born term.
  - In cosibling analyses, associations remained significant for type 1 and 2 diabetes but were largely attenuated for hypertension and lipid disorders (suggesting that shared familial genetic and lifestyle risk factors for PTB and hypertension or lipid disorders accounted for much of their associations).[118–120]

### *Offspring Cardiac Remodeling and HF*

- In a 2020 meta-analysis of 32 studies, individuals born preterm had higher LV mass (increase compared with control subjects, 0.71 g/m$^2$ [95% CI, 0.20–1.22] per year from childhood), smaller LV diastolic dimension (percent WMD in young adulthood, −4.9%; $P$=0.006), lower LV stroke volume index (percent WMD in young adulthood, −8.2%; $P$<0.001), poorer LV diastolic function (e′ percent WMD in childhood/young adulthood, −5.9%; $P$<0.001), and poorer RV systolic function (longitudinal strain percent WMD, −14.3%; $P$<0.001) compared with term-born individuals.[121]
- In a study of 4 193 069 individuals born in Sweden during 1973 through 2014, PTB was associated with higher risk of HF at <1 year of age (aHR, 4.49 [95% CI, 3.86–5.22]), 1 to 17 years of age (aHR, 3.42, [95% CI, 2.75–4.27]), and 18 to 43 years of age (aHR, 1.42 [95% CI, 1.19–1.71]) compared with individuals born full term. A dose-dependent relationship with prematurity was observed with further stratification in the group 18 to 43 years of age with highest risk for HF among those born extremely preterm (22–27 weeks; HR, 4.72 [95% CI, 2.75–4.27]).[122]

### *Offspring CVD and Mortality*

- Among 2 141 709 live-born singletons in the Swedish Birth Registry from 1973 to 1994 followed up through 2015 (maximum, 43 years of age), gestational age at birth was inversely associated with risk for premature CHD (aHR at 30–43 years of age versus full-term [39–41 weeks] births: for preterm [<37 weeks], 1.53 [95% CI, 1.20–1.94]; for early term [37–38 weeks], 1.19 [95% CI, 1.01–1.40]).[123] Cosibling analyses supported an association that was independent of familial shared genetic and environmental factors.
- Among 4 296 814 singleton live births in Sweden during 1973 to 2015 with up to 45 years of follow-up, gestational age at birth was inversely associated with mortality at 0 to 45 years of age, with an aHR of 0.78 (95% CI, 0.78–0.78) per 1-week-longer gestation.[124] Relative to full-term birth (39–41 weeks), PTB (<37 weeks) and early-term birth (37–38 weeks) were associated with mortality (aHR, 5.01 [95% CI, 4.88–5.15] and 1.34 [95% CI, 1.30–1.37], respectively), and earlier gestations were associated with even higher risks (eg, <28 weeks; aHR, 66.14 [95% CI, 63.09–69.34]). The HRs for mortality were highest in infancy (aHR for preterm, 17.15 [95% CI, 16.50–17.82]) and weakened at subsequent age intervals but remained significantly elevated through 30 to 45 years of age (aHR for preterm, 1.28 [95% CI, 1.14–1.43]).

## LBW or SGA Delivery

### *Incidence, Prevalence, and Secular Trends*

***(See Chart 11-7)***

- The percentage of LBW (defined as delivered at <2500 g) deliveries was 8.3% for 2017 to 2018, which has increased slightly since 2014 (8.0%).[125] Prevalence of LBW by race is shown in Chart 11-7.

### *Risk Factors (Including Social Determinants)*

- Among 1482 nulliparous low-risk females at <20 weeks' gestation (who received placebo in a trial of low-dose aspirin to prevent preeclampsia), risks for SGA delivery were elevated even for mild stage 1 hypertension (SBP of 130–135 mm Hg or DBP of 80–85 mm Hg; 10.2% versus 5.6%; adjusted for age, race, and prepregnancy BMI: RR, 2.16 [95% CI, 1.12–4.16]) by the 2017 Hypertension Clinical Practice Guidelines.[94]
- In an individual participant data meta-analysis of 265 270 births from 39 cohorts in Europe, North America, and Australia, prepregnancy underweight BMI (BMI <18.5 kg/m$^2$; OR, 1.67 [95% CI, 1.58–1.76]) was associated with higher risks for SGA delivery.[6] Females with underweight prepregnancy BMI and low gestational weight gain had the highest odds for SGA delivery (3.12 [95% CI, 2.75–3.54]), but risks were elevated when gestational weight gain was low even for normal-weight (1.81 [95% CI, 1.73–1.89]) and overweight (1.23 [95% CI, 1.14–1.33]) females (but not females with obesity).
- Among 8259 pregnant females in the nuMoM2b cohort, periconceptional dietary quality was associated with risks for SGA (birth weight <10th percentile for gestational age) and LBW (<2500 g). The SGA and LBW rates were 12.8% and 7.7%, respectively, for females in the lowest quartile (poorest quality) of the HEI-2010 compared with 9.5% and 5.4% for females in the highest quartile (aRRs, 1.24 [95% CI, 1.02–1.51] and 1.32 [95% CI, 1.02–1.71], respectively).[32]

- Among 3435 females in a health system with routine urine toxicology screening at the first prenatal visit, cannabis exposure (detected in 8.2% of females) was associated with SGA delivery, with an aRR of 1.69 (95% CI, 1.22–2.34) after adjustment for maternal race and ethnicity, prepregnancy BMI, age, and cigarette smoking. In stratified analyses, the aRR for SGA associated with cannabis exposure was 1.42 (95% CI, 0.32–2.15) in females who did not also smoke cigarettes and 2.38 (95% CI, 1.35–4.19) in females who also smoked cigarettes during pregnancy.[126]
- In a study of 156 278 nulliparous females in Ontario, Canada, with singleton pregnancies between January 2011 and December 2018, the associations between prepregnancy HbA1c, glucose, lipids, and alanine aminotransferase and SGA were studied.[127] There were 19 367 with SGA infants. Females with SGA infants had lower pregravid fasting glucose, random glucose, and triglyceride levels than those without SGA infants. Therefore, prepregnancy cardiometabolic biomarkers were not associated with the development of SGA.

### Environmental Exposures

- In a systematic review of studies examining associations of air pollution, significant associations were found with LBW for 25 of 29 studies (examining a total of >18 million births) in the United States.[97]
- The median risk was 10.8% higher (range, 2.0%–36.0%) for whole-pregnancy PM2.5 exposure per IQR greater exposure, and in 1 study, risk was higher by 3% for each 5-km closer proximity to a solid waste plant.[97]
- In a systematic review examining heat, 3 of 3 studies (2.7 million births) demonstrated that the median risk for LBW was 31.0% higher (range, 13.0%–49.0%) for whole-pregnancy heat exposure per 5.6°C higher weekly mean temperature, and in 1 study, whole-pregnancy ambient local temperature >95th percentile was associated with an RR of 2.49 (95% CI, 2.20–2.83).[97]
- In a meta-analysis of 5 studies, more favorable environmental characteristics such as greater access to green space or greater environmental greenness (based on a standardized measure commonly used to indicate the presence and level of green space: the normalized difference vegetation index) within a 100- to 500-m buffer were associated with lower risk for LBW or SGA infants (pooled standardized OR, 0.94 [95% CI, 0.92–0.97]).[100]

### Social Determinants of Health/Health Equity

- In a meta-analysis of 3 studies of 1588 participants from the United States and Australia, racial discrimination was associated with increased odds of SGA (OR 1.23 [95% CI, 0.76–1.99]).[101]
- Among infants born to females who were evicted in Georgia from 2000 to 2016, eviction during gestation (versus infants born to females who experienced an eviction before they were pregnant) was associated with 0.88 (95% CI, 0.23–1.54) percentage points higher rate of LBW (<2500 g) after covariate adjustment (crude rate, 11.59% versus 10.24%, respectively).[102]
- Among 9470 nulliparous pregnant females in the nuMoM2b study (60.4% NH White, 13.8% NH Black, 16.7% Hispanic, 4.0% Asian, 5.0% other), NH White females were least likely to experience SGA delivery (8.6%), whereas higher rates were seen among Hispanic females (11.7%; OR, 1.41 [95% CI, 1.18–1.69]), Asian females (16.4%; OR, 2.08 [95% CI, 1.56–2.77]), and NH Black females (17.2%; OR, 2.21 [95% CI, 1.86–2.62]).[33] These differences remained essentially unchanged after adjustment for age, BMI, smoking, medical comorbidities, or psychosocial burden (including depression, anxiety, experienced racism, perceived stress, social support, or resilience), although lower social support was independently associated with SGA delivery (OR, 1.20 [95% CI, 1.03–1.40] for the lowest quartile of perceived social support compared with the upper 3 quartiles).
- Among >23 million singleton live births in the United States, the excess risks of intrauterine growth restriction and SGA related to race and ethnicity were partly mediated by the adequacy of prenatal care: 13%, 12%, and 10% for intrauterine growth restriction and 7%, 6%, and 5% for SGA among Black females, Hispanic females, and females of other race and ethnicity, respectively, compared with White females.[128]
- Examination of state Medicaid expansion noted an association with improvement in relative disparities between Black people and White people in rates of infants with LBW among states that expanded compared with those that did not. Difference-in-difference models between 2011 and 2016 estimated a decline of −0.53 percentage points (95% CI, −0.96 to −0.10) for LBW for Black infants compared with White infants.[111]

### Genetics/Family History

- Birth weight shows evidence of intergenerational transmission, which may extend across 3 generations.[129] For example, a study using population-based Swedish Multi-Generation and Medical Birth Registers that included 2 193 142 births reported that females whose full sisters had a child born SGA had an elevated risk of having a child born SGA (OR, 1.8 [95% CI, 1.7–1.9]). For brothers, the corresponding risk of SGA was 1.3 (95% CI, 1.2–1.4). This study also reported that 37% of the liability in

SGA was explained by fetal genetic effects, whereas maternal genetic effects explained only 9% of SGA liability.[130]

- Few SGA GWASs have been published. However, genetic risk factors for SGA share similarities in the genetic architecture of birth weight and maternal SBP.[131] In a study of N=11 951 infants and N=5182 mothers of European ancestry, each decile increase in the fetal PRS for higher birth weight was associated with a lower odds of SGA (OR, 0.75 [95% CI, 0.71–0.80]). This effect was similar in magnitude to the association for maternal PRS and SGA (OR, 0.81 [95% CI, 0.75–0.88]). Last, an SBP maternal PRS also was associated with increased SGA odds (OR, 1.15 [95% CI, 1.04–1.27]).

### *Complications: Maternal CVD*

- There is limited weak evidence for a relationship between infant birth weight and maternal CVD, which may be attributable in part to heterogeneity in definitions of LBW and SGA. In a meta-analysis examining 4 studies that defined LBW (<2500 g at term), females with a history of an infant with LBW had no difference in risk for CVD (OR, 1.29 [95% intrinsic CI, 0.91–1.83]). Across 7 studies (3 of which defined SGA as 1–2 SD from the mean and 4 defined it as <10th percentile of weight for gestational age), a trend was observed of higher risk of CVD (OR, 1.29 [95% intrinsic CI, 0.91–1.83]), but there was significant between-study heterogeneity.[60]
- In data from 11 110 females in the prospectively collected Västerbotten Intervention Program and population-based registries in Sweden, LBW was associated with 10-year risk of CVD (HR, 1.95 [95% CI, 1.38–2.75]) at 50 years of age. However, this association did not persist by 60 years of age, and the history of LBW did not improve risk reclassification for CVD in prediction models.[132]

### *Complications: Offspring Morbidity and Mortality*

- In a meta-analysis of 6 cohort studies, LBW was associated with higher risk for MetS in either childhood or adulthood (pooled OR, 1.79 [95% CI, 1.39–2.31]).[117]
- Among 4 193 069 individuals born in Sweden during 1973 to 2014, SGA birth (weight <10th percentile for gestational age) was associated with risk for type 2 diabetes; aHRs were 1.61 (95% CI, 1.38–1.89) at <18 years of age and 1.79 (95% CI, 1.65–1.93) at 18 to 43 years of age.[118]
- A 2018 meta-analysis of 49 studies with 4 053 367 participants found a J-shaped association between birth weight and adult type 2 diabetes.[133] The pooled HRs were 0.78 (95% CI, 0.70–0.87) per 1-kg-higher birth weight, 1.45 (95% CI, 1.33–1.59) for <2.5 kg (versus >2.5 kg), 0.94 (95% CI, 0.87–1.01) for >4.0 kg (versus <4.0 kg), and 1.08 (95% CI, 0.95–1.23) for >4.5 kg (versus <4.5 kg).
- For hypertension, among 53 studies with 4 335 149 participants, the association was inverse, with pooled HRs of 0.77 (95% CI, 0.68–0.88) per 1-kg-higher birth weight, 1.30 (95% CI, 1.16–1.46) for <2.5 kg, 0.88 (95% CI, 0.81–0.95) for >4.0 kg, and 1.05 (95% CI, 0.93–1.19) for >4.5 kg.
  - For CVD, among 33 studies with 5 949 477 participants, the association was also J shaped, with pooled HRs of 0.84 (95% CI, 0.81–0.86) per 1-kg-higher birth weight, 1.30 (95% CI, 1.01–1.67) for <2.5 kg, 0.99 (95% CI, 0.90–1.10) for >4.0 kg, and 1.28 (95% CI, 1.10–1.50) for >4.5 kg.
- In a pooled analysis from 22 389 men from the HPFS and 162 231 women from the Nurses' Health and Nurses Health II Studies, participant-reported LBW was associated with a greater risk of cardiovascular and respiratory disease mortality among women and high birth weight was associated with a greater cancer mortality risk in both men and women.[134] Compared with women with a birth weight of 3.16 to 3.82 kg, the pooled HRs for all-cause mortality were 1.13 (95% CI, 1.08–1.17), 0.99 (95% CI, 0.96–1.02), 1.04 (95% CI, 1.00–1.08), and 1.03 (95% CI, 0.96–1.10) for women with a birth weight of <2.5, 2.5 to 3.15, 3.83 to 4.5, and >4.5 kg, respectively. Women with a birth weight <2.5 kg had an elevated risk of mortality from CVDs (HR, 1.15 [95% CI, 1.05–1.25]) and respiratory diseases (HR, 1.35 [95% CI, 1.18–1.54]), whereas those with birth weight >4.5 kg had a higher risk of cancer mortality (HR, 1.15 [95% CI, 1.00–1.31]). Among men, birth weight was unrelated to all-cause mortality but was inversely associated with CVD mortality and positively associated with cancer mortality ($P_{\text{linear trend}}$=0.012 and 0.0039, respectively).

## Pregnancy Loss

### *Incidence, Prevalence, and Secular Trends*

- In 2020, the stillbirth (≥20 weeks' gestation) rate in the United States was 5.74 per 1000 live births and fetal deaths, which was stable from the prior year and 23% less than in 1990.[135]
  - Stillbirth rates per 1000 live births were highest among Native Hawaiian or other Pacific Islander females (10.59) and NH Black females (10.34), intermediate among American Indian or Alaska Native females (7.84), and lower among Hispanic (4.86), NH White (4.73), and Asian or Pacific Islander (3.93) females.
  - Stillbirth rates were highest for females <15 years of age (13.42) and ≥45 years of age (12.2) and were lowest among females 30 to 35 years of age (5.12).

– Geographic differences were observed in stillbirth rates (analyzed for ≥24 weeks' gestation), with the highest rates in Mississippi (6.57) and the lowest rates in New Mexico (2.47).

### Risk Factors (Including Social Determinants)

- Maternal cardiovascular risk factors, including diabetes (6–35 per 1000 live births and stillbirths), chronic hypertension (6–25 per 1000 live births and stillbirths), prepregnancy obesity (13–18 per 1000 live births and stillbirths), and smoking (10–15 per 1000 live births and stillbirths), as well as exposure to secondhand smoke, are associated with increased risk of stillbirth compared with total population rates (6.4 per 1000 live births and stillbirths).[136]
- Antiphospholipid syndrome was associated with higher risk for pregnancy loss (RR, 2.42 [95% CI, 1.46–4.01] for loss at <10 weeks; RR, 1.33 [95% CI, 1.00–1.76] for loss at ≥10 weeks) in a meta-analysis of 212 184 females (including 770 with antiphospholipid syndrome) from 8 studies.[137]
- In a systematic review of studies examining associations of air pollution in US populations, significant associations with stillbirth risk were found for 4 of 5 studies (examining a total of >5 million births) in which the median risk for stillbirth was 14.5% higher (range, 6.0%–23.0%) for whole-pregnancy PM2.5 exposure per IQR greater exposure, and risk was higher by 42% (95% CI, 6%–91%) with high third-trimester PM2.5 exposure.[97]
- In a systematic review of 2 US studies (>200 000 births) examining heat, the risk for stillbirth was 6% higher per 1°C higher ambient temperature the week before delivery during the warm season.[97] Similarly, in a separate meta-analysis of 8 studies (including international populations), the odds of stillbirth were 1.05 times higher (95% CI, 1.01–1.08) for each 1°C rise in environmental temperature.[99]
- Contrasting findings have been noted for rates of stillbirth before and during the COVID-19 pandemic. At 1 hospital in London, UK, that examined 1681 births before the pandemic and 1718 births during the pandemic, the incidence of stillbirth was 9.31 per 1000 births compared with 2.38 per 1000 births.[138] However, in a follow-up study from the National Health Service in England, there was no change in stillbirth deliveries (4.1 per 1000 live births [95% CI, 3.8–4.5] versus 4.0 per 1000 live births [95% CI, 3.7–4.4]) between April 1, 2020, and June 30, 2020, compared with the same period in 2019 (IRR, 1.02 [95% CI, 0.91–1.15]).[139]

### Genetics/Family History

- The heritability of any pregnancy loss has been reported at 29% (95% CI, 20%–38%) for any miscarriage.[140]
- Fetal genetic factors also play a role in recurrent pregnancy loss. Fetal aneuploidy is common in first-trimester spontaneous miscarriages but is also seen in recurrent pregnancy loss, increasing with maternal age (in 1 study accounting for 78% of miscarriages in females ≥35 years of age with recurrent pregnancy loss versus 70% in females with nonrecurrent pregnancy loss).[141]
- Fetal single-gene disorders may also play a role in recurrent pregnancy loss; for example, 1 study found that 3.3% of stillbirths carried pathogenic variants in LQTS genes compared with a prevalence of <0.05% in the general population.[142]
- A study to identify novel genetic risk factors for recurrent pregnancy loss analyzed rare variants using whole-exome sequencing in 75 females with either recurrent pregnancy loss or lack of achieving clinical pregnancy and identified the presence of rare variants in 13% of the females with recurrent pregnancy loss.[143]
- In a GWAS of 69 054 females with sporadic pregnancy loss, 750 females with recurrent pregnancy loss, and 359 469 control subjects, only 1 genome-wide significant variant was found for sporadic pregnancy loss (OR, 1.4 [95% CI, 1.2–1.6]; $P=3.2\times10^{-8}$), and 3 were found for recurrent pregnancy loss (OR, 1.7–3.8), including variants in *FGF9*, *TLE1*, and *TLE4*.[140]

### Prevention

- In a meta-analysis of 23 relatively homogeneous studies of 608 243 pregnant females, having been vaccinated with the COVID-19 mRNA vaccine was associated with a lower risk of stillbirth by 15% (pooled OR, 0.85 [95% CI, 0.73–0.99]).[144] COVID-19 mRNA vaccination in pregnancy was shown to be safe; there was no evidence of a higher risk of adverse outcomes, including miscarriage, earlier gestation at birth, placental abruption, PE, postpartum hemorrhage, maternal death, ICU admission, lower birthweight *z* score, or neonatal ICU admission ($P>0.05$ for all outcomes).

### Complications: Maternal CVD

- Among >95 000 ever-gravid females in the Nurses' Health Study II followed up for a mean of 23 years, a history of pregnancy loss was independently associated with a 21% greater risk for developing incident CVD (HR, 1.21 [95% CI, 1.10–1.33]), with similar associations for incident CHD (HR, 1.20 [95% CI, 1.07–1.35]) and stroke (HR, 1.23 [95% CI, 1.04–1.44]), compared with no pregnancy loss.[145] The risk was greater for females with ≥2 pregnancy losses (HR, 1.34 [95% CI, 1.21–1.62]) compared with 1 pregnancy loss (HR, 1.18 [95% CI, 1.04–1.44]). Mediation analysis suggested that traditional risk factors such as hypertension, hyperlipidemia, and

type 2 diabetes explained only <2% of the association between pregnancy loss and CVD.
- Data from the Nurses' Health Study II identified higher rates of type 2 diabetes (HR, 1.20 [95% CI, 1.07–1.34]), hypertension (HR, 1.05 [95% CI, 1.00–1.11]), and hyperlipidemia (HR, 1.06 [95% CI, 1.02–1.10]) with early miscarriage (<12 weeks) with similar findings for late miscarriage (12–19 weeks). Rates of type 2 diabetes (HR, 1.45 [95% CI, 1.13–1.87]) and hypertension (HR, 1.15 [95% CI, 1.01–1.30]) were higher in females with a history of stillbirth delivery.[146]
- In 79 121 postmenopausal females from the WHI, ≈35% experienced a history of pregnancy loss. This was associated with higher adjusted risk of incident CVD (HR, 1.11 [95% CI, 1.06–1.16]) over a mean follow-up of 16 years.[147]
- A systematic review of 84 studies (28 993 438 patients) with a median follow-up of 7.5 years postpartum evaluated the associations between APOs and CVD.[60] The risk of CVD was higher among females with stillbirth (OR, 1.5 [95% CI, 1.1–2.1]). In this meta-analysis, miscarriage was not associated with CVD.

## Placental Abruption

### *Incidence, Prevalence, and Secular Trends*

- The majority of studies have reported an incidence of 0.5% to 1% for placental abruption.[148] In the nuMoM2b study, placental abruption was identified in 62 of 9450 nulliparous females (0.66%): 35 (56%) were antepartum and 27 (44%) were intrapartum.[149]

### *Risk Factors (Including Social Determinants)*

- In the nuMoM2b study, risk factors for placental abruption were studied in 9450 females.[149] For females with abruption, the mean gestational age at delivery was 35.6±4.4 weeks; it was 38.8±2.2 weeks for females without abruption. Gravidity was associated with abruption (OR, 3.1 [95% CI, 1.6–6.0]).
- Several risk factors for placental abruption were identified in a case-crossover study in Finland, Malta, and Aberdeen.[150] Preeclampsia (194 [6.5%] versus 115 [3.8%]; aOR, 1.69 [95% CI, 1.23–2.33]), idiopathic antepartum hemorrhage (556 [18.6%] versus 69 [2.3%]; aOR, 27.05 [95% CI, 16.61–44.03]), placenta previa (80 [2.7%] versus 21 [0.7%]; aOR, 3.05 [95% CI, 1.74–5.36]), maternal age of 35 to 39 years compared with 20 to 25 years (365 [12.2%] versus 323 [10.8%]; aOR, 1.32 [95% CI, 1.01–1.73]), and single marital status (aOR, 1.36 [95% CI, 1.04–1.76]) were independently associated with placental abruption.

### *Genetics/Family History*

- A study from the medical birth register of Norway estimated the heritability of placental abruption between sisters of placental abruption to be 16% (95% CI, 8%–23%).[151]
- A GWAS in the PAGE study (507 placental abruption cases and 1090 controls) and a GWAS meta-analysis in 2512 participants (959 placental abruption cases and 1553 controls) that included PAGE and the previously reported PAPE study were undertaken.[151] Independent loci suggestively associated with placental abruption included rs4148646 and rs2074311 in *ABCC8*; rs7249210, rs7250184, rs7249100, and rs10401828 in *ZNF28*; rs11133659 in *CTNND2*; and rs2074314 and rs35271178 near *KCNJ11*. Independent loci suggestively associated with placental abruption in the GWAS meta-analysis included rs76258369 near *IRX1* and rs7094759 and rs12264492 in *ADAM12*. Functional analyses of these genes showed trophoblast-like cell interaction, endocrine system disorders, CVDs, and cellular function.[151]

### *Maternal CVD*

- A meta-analysis of 11 cohort studies of 6 325 152 pregnancies analyzed the association between placental abruption and CVD.[152] Risks of CVD morbidity/mortality among the abruption and nonabruption groups were 16.7 and 9.3 per 1000 births, respectively (RR, 1.76 [95% CI, 1.24–2.50]; $I^2$=94%).
- Among >1.5 million pregnancies from the HCUP in California, placental abruption occurred in 14 881 females (1%).[153] Median follow-up time from delivery to event or censoring was 4.87 years (IQR, 3.54–5.96 years). Placental abruption was associated with HF (aHR, 1.44 [95% CI, 1.09–1.90]). HDP and PTB modified and mediated, respectively, the association between placental abruption and HF.

## Health Care Use

- In 2016, there were 313 530 hospital discharges for HDP, 128 240 for preexisting diabetes and gestational diabetes, 362 955 for PTB, and 78 820 for SGA/LBW.
- In 2016, there were 73 485 visits to the ED for HDP, 19 903 for preexisting diabetes and gestational diabetes, 101 047 for PTB, and 5985 for SGA/LBW.
- According to a systematic review and meta-analysis that included 52 articles, late-preterm infants born at 34 to 36 weeks' gestation compared with term infants had a higher aOR of all-cause admissions in the neonatal period (OR, 2.34 [95% CI, 1.19–4.61]) and through adolescence (OR, 1.09 [95% CI, 1.05–1.13]).[154]

## Cost

- Pregnancy and postpartum care accounted for $71.3 billion ($64.9–$77.7 billion) in total health care spending in 2016. Complications related to HDP and PTB were estimated to account for $5.5 billion ($4.8–$6.3 billion) and $28.2 billion ($21.8–$37.6 billion), respectively.[155]
- The cost of the 9 common maternal morbidity conditions for all US births in 2019 was $32.3 billion from conception through the child's fifth birthday.[156] Two-thirds of these costs occurred within the first year postpartum, and the majority of the costs were due to child (compared with maternal outcomes; 74% versus 26%). The largest costs included maternal mental health conditions ($18.1 billion), hypertensive disorders ($7.5 billion), gestational diabetes ($4.8 billion), and PTB ($13.7 billion),

## Global Burden

## (See Charts 11-8 and 11-9)

- In 2015, an estimated 20.5 million infants were born with LBW worldwide.[157]
- The prevalence of LBW in 2015 was 14.6% compared with 17.6% in 2000.[157]
- Analysis of WHO and UNICEF data estimates that 23.4 million liveborn babies (17.4%) were born SGA in 2020 worldwide. There was marked regional variation in SGA, with more than a third (40.9%) of all newborns in southern Asia being SGA compared with 10.7% in sub-Saharan Africa and <10% in other regions.[158]
- In an analysis of data from the WHO Global Survey for Maternal and Perinatal Health (conducted in African, Latin American, and Asian countries), higher risks for gestational hypertension (aOR among nulliparous females, 1.56 [95% CI, 0.94–2.58]; aOR among multiparous females, 1.73 [95% CI, 1.25–2.39]) were observed for females with severe anemia (hemoglobin <7 mg/dL) at delivery compared with females with hemoglobin ≥7 mg/dL at delivery. The risk for preeclampsia/eclampsia was also higher with severe anemia (hemoglobin <7 mg/dL) at delivery compared with hemoglobin ≥7 mg/dL at delivery (aOR among nulliparous females, 3.74 [95% CI, 2.90–4.81]; aOR among multiparous females, 3.45 [95% CI, 2.79–4.25]).[159]
  - Sickle cell disease was associated with higher risk for gestational hypertension (7.2% versus 2.1%; aOR among nulliparous females, 2.41 [95% CI, 1.42–4.10]; aOR among multiparous females, 3.26 [95% CI, 2.32–4.58]) but not preeclampsia/eclampsia (4.2% versus 4.5%; *P*=0.629).
  - No significant associations were found between thalassemia and HDP.
- Globally, 2.5 million (uncertainty range, 2.4–3.0 million) third-trimester stillbirths (defined as ≥28 weeks' gestation or late fetal deaths) occurred annually with a PAF of 6.7% for maternal age >35 years, 8.2% for malaria, 14% for prolonged pregnancy (>42 weeks' gestation), and 10% for lifestyle factors and obesity.[160]
- Based on 204 countries and territories in 2021, the incidence of maternal hypertensive disorders was highest throughout sub-Saharan Africa and lowest in east Asia (Chart 11-8). In 2021, the incidence of maternal hypertensive disorders among females 15 to 49 years of age was 18.00 (95% UI, 15.25-21.16) million cases with an average rate of 923.45 (95% UI, 782.27-1085.61) per 100 000 female population 15 to 49 years of age.[161]
- Based on 204 countries and territories in 2021, the highest rates of neonatal PTB were found in South Asia, followed by the Caribbean and Oceania. Rates were the lowest in East Asia (Chart 11-9). The incidence of neonatal PTB was 21.33 (95% UI, 21.18-21.48) million cases with an average rate of 16 600.87 (95% UI, 16 482.85-16 718.36) per 100 000 births.[161]
- Rates of placental abruption varied across 7 countries.[162] Compared with births in 2000, births after 2000 in European countries had lower abruption rates. In the United States, there was an increase in placental abruption rates up to 2000 and a plateau thereafter. Changes in smoking prevalence may have partially explained the period effect in the United States (*P*=0.01).

| Pre-Pregnancy Body Mass Index Category | Gestational Weight Gain Category | | |
|---|---|---|---|
| | Low (≤ 1.1 SD) | Medium (-1.0 to 0.9 SD) | High ( ≥1.0 SD) |
| Underweight | 1.09 (0.94 – 1.26) | 1.04 (0.96 – 1.12) | 1.13 (0.98 – 1.30) |
| Normal weight | 1.04 (1.01 – 1.08) | Referent | 1.10 (1.06 – 1.14) |
| Overweight | 1.23 (1.16 – 1.32) | 1.38 (1.33 – 1.43) | 1.63 (1.54– 1.73) |
| Obese | 1.70 (1.56 – 1.85) | 2.06 (1.96 – 2.16) | 2.51 (2.31 – 2.74) |

**Chart 11-1. Adjusted odds ratios for any APO, by prepregnancy BMI and gestational weight gain categories.**
Estimates are based on a meta-analysis of individual participant data from 265 270 females from 39 European, North American, and Oceanic cohort studies. APOs include HDP (gestational hypertension or preeclampsia), gestational diabetes, PTB (<37 weeks' gestation), small (birth weight <10th percentile) or large (birth weight >90th percentile) size for sex, and gestational age at birth. Prepregnancy BMI categories are as follows: underweight, <18.5 kg/m$^2$; normal weight, 18.5 to 24.9 kg/m$^2$; overweight, 25.0 to 29.9 kg/m$^2$; and obesity, ≥30 kg/m$^2$. Gestational weight gain values corresponding to the SD cutoffs were not provided by the source, but the median gestational weight gain was 14.0 kg (95% CI, 3.9–27.0).
APO indicates adverse pregnancy outcome; BMI, body mass index; HDP, hypertensive disorders of pregnancy; and PTB, preterm birth.
Source: Data derived from Santos et al.[6]

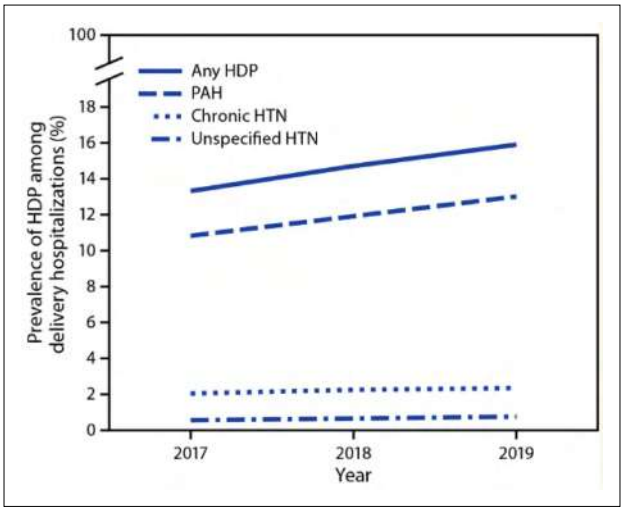



**Chart 11-3. Prevalence of hypertensive disorders in pregnancy* among delivery hospitalizations, by year, National Inpatient Sample, United States, 2017 to 2019.**
HDP indicates hypertensive disorder in pregnancy; HTN, hypertension; and PAH, pregnancy-associated hypertension.
*HDPs are defined as chronic hypertension, pregnancy-associated hypertension (ie, gestational hypertension, preeclampsia, eclampsia, and chronic hypertension with superimposed preeclampsia), and unspecified maternal hypertension.
Source: Reprinted from Ford et al.[163]

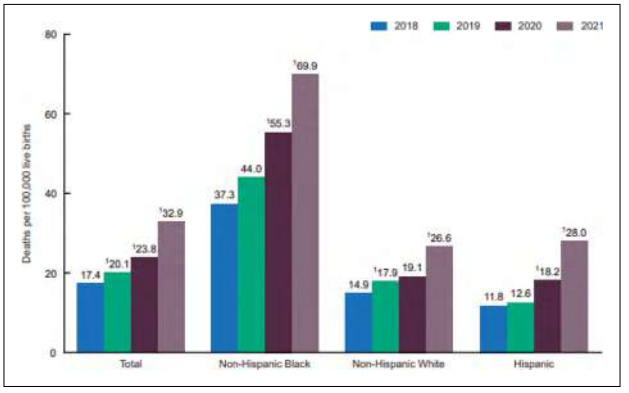



**Chart 11-2. Maternal mortality rates, by race and Hispanic origin: United States, 2018 to 2021. Race groups are single race.**
†Statistically significant increase from previous year ($P$<0.05).
Source: Reprinted from Hoyert.[10]

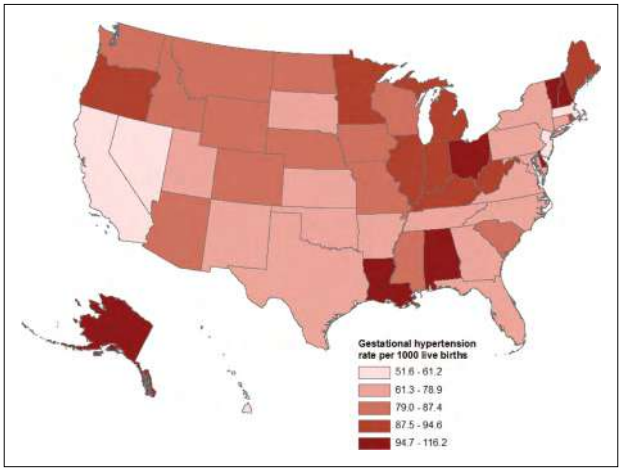



**Chart 11-4. State-level rates of de novo hypertension in pregnancy per 1000 live births, United States, 2019.**
Unadjusted rates are calculated for each state based on 3 736 144 females 15 to 44 years of age with a live birth.
Source: Unpublished map using Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research.[164]

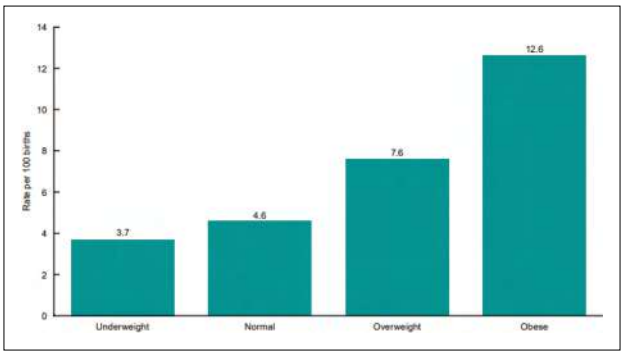



**Chart 11-5. Rate of gestational diabetes, by BMI: United States, 2020.**
Significant increasing trend ($P<0.05$).
BMI indicates body mass index.
Source: Reprinted from Gregory and Ely.[68]

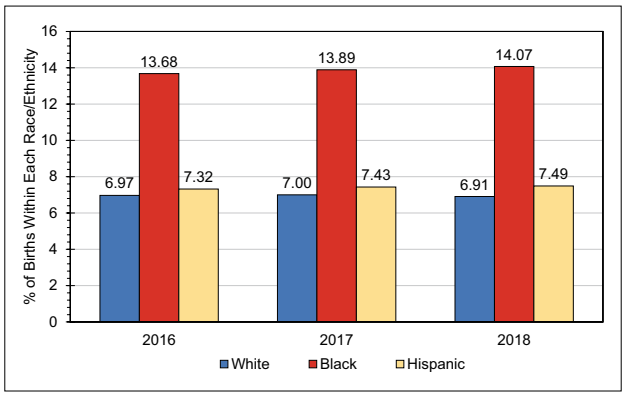



**Chart 11-7. Trends in the rates of infants with LBW (<2500 g) in the United States, by race and ethnicity of females with a live birth, 2016 to 2018.**
LBW indicates low birth weight.
Source: Data derived from Martin et al.[125]

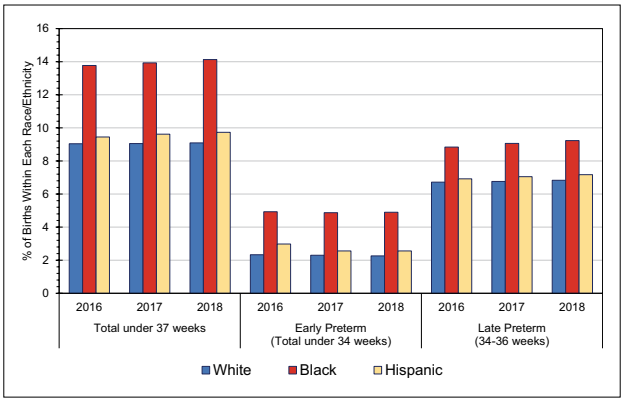



**Chart 11-6. Trends in the rates of PTB by gestational age (weeks) in the United States, by maternal race and ethnicity, 2016 to 2018.**
PTB indicates preterm birth.
Source: Data derived from Martin et al.[125]

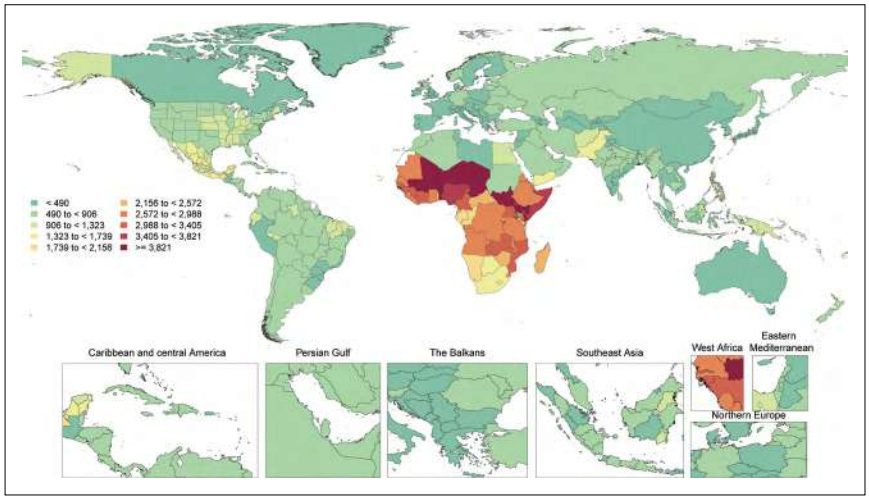



**Chart 11-8. Global incidence rates of maternal hypertensive disorders per 100 000 females, 15 to 49 years of age, 2021.**
During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.
GBD indicates Global Burden of Disease.
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[161]

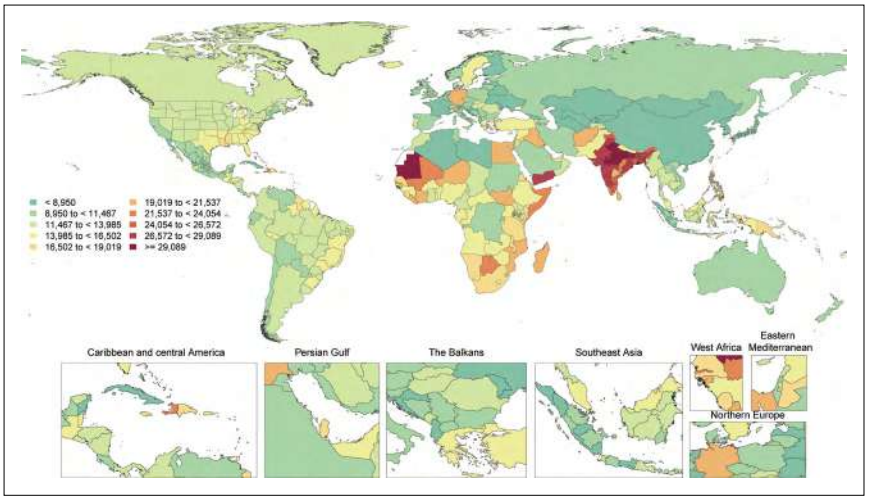



**Chart 11-9. Global incidence rates of neonatal PTB per 100 000, both sexes, at birth, 2021.**
During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.
GBD indicates Global Burden of Disease; and PTB, preterm birth.
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[161]

## REFERENCES


1. Parikh NI, Gonzalez JM, Anderson CAM, Judd SE, Rexrode KM, Hlatky MA, Gunderson EP, Stuart JJ, Vaidya D; on behalf of the American Heart Association Council on Epidemiology and Prevention; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular and Stroke Nursing; and the Stroke Council. Adverse pregnancy outcomes and cardiovascular disease risk: unique opportunities for cardiovascular disease prevention in women: a scientific statement from the American Heart Association. *Circulation*. 2021;143:e902–e916. doi: 10.1161/CIR.0000000000000961
2. Brown HL, Warner JJ, Gianos E, Gulati M, Hill AJ, Hollier LM, Rosen SE, Rosser ML, Wenger NK; on behalf of the American Heart Association and the American College of Obstetricians and Gynecologists. Promoting risk identification and reduction of cardiovascular disease in women through collaboration with obstetricians and gynecologists: a presidential advisory from the American Heart Association and the American College of Obstetricians and Gynecologists. *Circulation*. 2018;137:e843–e852. doi: 10.1161/CIR.0000000000000582
3. Khan SS, Brewer LC, Canobbio MM, Cipolla MJ, Grobman WA, Lewey J, Michos ED, Miller EC, Perak AM, Wei GS, et al; on behalf of the American Heart Association Council on Epidemiology and Prevention; Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Hypertension; Council on Lifestyle and Cardiometabolic Health; Council on Peripheral Vascular Disease; and Stroke Council. Optimizing prepregnancy cardiovascular health to improve outcomes in pregnant and postpartum individuals and offspring: a scientific statement from the American Heart Association. *Circulation*. 2023;147:e76–e91. doi: 10.1161/CIR.0000000000001124
4. Bello NA, Zhou H, Cheetham TC, Miller E, Getahun DT, Fassett MJ, Reynolds K. Prevalence of hypertension among pregnant women when using the 2017 American College of Cardiology/American Heart Association blood pressure guidelines and association with maternal and fetal outcomes. *JAMA Netw Open*. 2021;4:e213808. doi: 10.1001/jamanetworkopen.2021.3808
5. Lane-Cordova AD, Khan SS, Grobman WA, Greenland P, Shah SJ. Long-term cardiovascular risks associated with adverse pregnancy outcomes: JACC review topic of the week. *J Am Coll Cardiol*. 2019;73:2106–2116. doi: 10.1016/j.jacc.2018.12.092
6. Santos S, Voerman E, Amiano P, Barros H, Beilin LJ, Bergstrom A, Charles MA, Chatzi L, Chevrier C, Chrousos GP, et al. Impact of maternal body mass index and gestational weight gain on pregnancy complications: an individual participant data meta-analysis of European, North American and Australian cohorts. *BJOG*. 2019;126:984–995. doi: 10.1111/1471-0528.15661
7. LifeCycle Project-Maternal Obesity and Childhood Outcomes Study Group; Voerman E, Santos S, Inskip H, Amiano P, Barros H, Charles MA, Chatzi L, Chrousos GP, Corpeleijn E, Crozier S, et al. Association of gestational weight gain with adverse maternal and infant outcomes. *JAMA*. 2019;321:1702–1715. doi: 10.1001/jama.2019.3820
8. Sendeku FW, Beyene FY, Tesfu AA, Bante SA, Azeze GG. Preterm birth and its associated factors in Ethiopia: a systematic review and meta-analysis. *Afr Health Sci*. 2021;21:1321–1333. doi: 10.4314/ahs.v21i3.43
9. Hounkpatin OI, Amidou SA, Houehanou YC, Lacroix P, Preux PM, Houinato DS, Bezanahary H. Systematic review of observational studies of the impact of cardiovascular risk factors on preeclampsia in sub-Saharan Africa. *BMC Pregnancy Childbirth*. 2021;21:97. doi: 10.1186/s12884-021-03566-2
10. Hoyert DL. Maternal mortality rates in the United States, 2021. National Center for Health Statistics, Centers for Disease Control and Prevention. 2023. Accessed October 31, 2023. https://cdc.gov/nchs/data/hestat/maternal-mortality/2021/maternal-mortality-rates-2021.htm
11. Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion and Centers for Disease Control. Pregnancy-related mortality ratio by urban-rural classifications: 2016-2018. 2022.
12. Centers for Disease Control and Prevention and Reproductive Health. Pregnancy Mortality Surveillance System. Accessed July 20, 2023. https://www.cdc.gov/reproductivehealth/maternal-mortality/pregnancy-mortality-surveillance-system.htm#causes
13. Say L, Chou D, Gemmill A, Tuncalp O, Moller AB, Daniels J, Gulmezoglu AM, Temmerman M, Alkema L. Global causes of maternal death: a WHO systematic analysis. *Lancet Glob Health*. 2014;2:e323–e333. doi: 10.1016/S2214-109X(14)70227-X
14. Hinkle SN, Schisterman EF, Liu D, Pollack AZ, Yeung EH, Mumford SL, Grantz KL, Qiao Y, Perkins NJ, Mills JL, et al. Pregnancy complications and long-term mortality in a diverse cohort. *Circulation*. 2023;147:1014–1025. doi: 10.1161/CIRCULATIONAHA.122.062177
15. Crump C, Sundquist J, Sundquist K. Preterm delivery and long-term risk of hypertension in women. *JAMA Cardiol*. 2022;7:65–74. doi: 10.1001/jamacardio.2021.4127
16. Haas DM, Parker CB, Marsh DJ, Grobman WA, Ehrenthal DB, Greenland P, Bairey Merz CN, Pemberton VL, Silver RM, Barnes S, et al; NHLBI nuMoM2b Heart Health Study. Association of adverse pregnancy outcomes with hypertension 2 to 7 years postpartum. *J Am Heart Assoc*. 2019;8:e013092. doi: 10.1161/JAHA.119.013092
17. Sondergaard MM, Hlatky MA, Stefanick ML, Vittinghoff E, Nah G, Allison M, Gemmill A, Van Horn L, Park K, Salmoirago-Blotcher E, et al. Association of adverse pregnancy outcomes with risk of atherosclerotic cardiovascular disease in postmenopausal women. *JAMA Cardiol*. 2020;5:1390–1398. doi: 10.1001/jamacardio.2020.4097
18. Hansen AL, Sondergaard MM, Hlatky MA, Vittinghof E, Nah G, Stefanick ML, Manson JE, Farland LV, Wells GL, Mongraw-Chaffin M, et al. Adverse pregnancy outcomes and incident heart failure in the Women's Health Initiative. *JAMA Netw Open*. 2021;4:e2138071. doi: 10.1001/jamanetworkopen.2021.38071
19. Cameron NA, Molsberry R, Pierce JB, Perak AM, Grobman WA, Allen NB, Greenland P, Lloyd-Jones DM, Khan SS. Pre-pregnancy hypertension among women in rural and urban areas of the United States. *J Am Coll Cardiol*. 2020;76:2611–2619. doi: 10.1016/j.jacc.2020.09.601
20. Perak AM, Lancki N, Kuang A, Labarthe DR, Allen NB, Shah SH, Lowe LP, Grobman WA, Scholtens DM, Lloyd-Jones DM, et al; Hyperglycemia Adverse Pregnancy Outcome Study Cooperative Research Group. Associations of gestational cardiovascular health with pregnancy outcomes: the Hyperglycemia and Adverse Pregnancy Outcome study. *Am J Obstet Gynecol*. 2021;224:210.e1–210.e17. doi: 10.1016/j.ajog.2020.07.053

21. Pan H, Xian P, Yang D, Zhang C, Tang H, He X, Lin H, Wen X, Ma H, Lai M. Polycystic ovary syndrome is an independent risk factor for hypertensive disorders of pregnancy: a systematic review, meta-analysis, and meta-regression. *Endocrine*. 2021;74:518–529. doi: 10.1007/s12020-021-02886-9
22. Bartsch E, Medcalf KE, Park AL, Ray JG; High Risk of Pre-Eclampsia Identification Group. Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies. *BMJ*. 2016;353:i1753. doi: 10.1136/bmj.i1753
23. Mustafa HJ, Seif K, Javinani A, Aghajani F, Orlinsky R, Alvarez MV, Ryan A, Crimmins S. Gestational weight gain below instead of within the guidelines per class of maternal obesity: a systematic review and meta-analysis of obstetrical and neonatal outcomes. *Am J Obstet Gynecol MFM*. 2022;4:100682. doi: 10.1016/j.ajogmf.2022.100682
24. Ren M, Li H, Cai W, Niu X, Ji W, Zhang Z, Niu J, Zhou X, Li Y. Excessive gestational weight gain in accordance with the IOM criteria and the risk of hypertensive disorders of pregnancy: a meta-analysis. *BMC Pregnancy Childbirth*. 2018;18:281. doi: 10.1186/s12884-018-1922-y
25. Dude AM, Kominiarek MA, Haas DM, Iams J, Mercer BM, Parry S, Reddy UM, Saade G, Silver RM, Simhan H, et al. Weight gain in early, mid, and late pregnancy and hypertensive disorders of pregnancy. *Pregnancy Hypertens*. 2020;20:50–55. doi: 10.1016/j.preghy.2020.03.001
26. Martínez-Hortelano JA, Cavero-Redondo I, Álvarez-Bueno C, Sanabria-Martínez G, Poyatos-León R, Martínez-Vizcaíno V. Interpregnancy weight change and hypertension during pregnancy: a systematic review and meta-analysis. *Obstet Gynecol*. 2020;135:68–79. doi: 10.1097/AOG.0000000000003573
27. Nobles CJ, Mendola P, Mumford SL, Silver RM, Kim K, Andriessen VC, Connell M, Sjaarda L, Perkins NJ, Schisterman EF. Preconception blood pressure and its change into early pregnancy: early risk factors for preeclampsia and gestational hypertension. *Hypertension*. 2020;76:922–929. doi: 10.1161/HYPERTENSIONAHA.120.14875
28. Tita AT, Szychowski JM, Boggess K, Dugoff L, Sibai B, Lawrence K, Hughes BL, Bell J, Aagaard K, Edwards RK, et al; Chronic Hypertension and Pregnancy (CHAP) Trial Consortium. Treatment for mild chronic hypertension during pregnancy. *N Engl J Med*. 2022;386:1781–1792. doi: 10.1056/NEJMoa2201295
29. Syngelaki A, Sequeira Campos M, Roberge S, Andrade W, Nicolaides KH. Diet and exercise for preeclampsia prevention in overweight and obese pregnant women: systematic review and meta-analysis. *J Matern Fetal Neonatal Med*. 2019;32:3495–3501. doi: 10.1080/14767058.2018.1481037
30. Minhas AS, Hong X, Wang G, Rhee DK, Liu T, Zhang M, Michos ED, Wang X, Mueller NT. Mediterranean-style diet and risk of preeclampsia by race in the Boston Birth Cohort. *J Am Heart Assoc*. 2022;11:e022589. doi: 10.1161/JAHA.121.022589
31. Arvizu M, Bjerregaard AA, Madsen MTB, Granström C, Halldorsson TI, Olsen SF, Gaskins AJ, Rich-Edwards JW, Rosner BA, Chavarro JE. Sodium Intake during pregnancy, but not other diet recommendations aimed at preventing cardiovascular disease, is positively related to risk of hypertensive disorders of pregnancy. *J Nutr*. 2020;150:159–166. doi: 10.1093/jn/nxz197
32. Yee LM, Silver RM, Haas DM, Parry S, Mercer BM, Iams J, Wing D, Parker CB, Reddy UM, Wapner RJ, et al. Quality of periconceptional dietary intake and maternal and neonatal outcomes. *Am J Obstet Gynecol*. 2020;223:121.e1–121.e8. doi: 10.1016/j.ajog.2020.01.042
33. Grobman WA, Parker CB, Willinger M, Wing DA, Silver RM, Wapner RJ, Simhan HN, Parry S, Mercer BM, Haas DM, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-Be (nuMoM2b) Network. Racial disparities in adverse pregnancy outcomes and psychosocial stress. *Obstet Gynecol*. 2018;131:328–335. doi: 10.1097/AOG.0000000000002441
34. Mogos MF, Salinas-Miranda AA, Salemi JL, Medina IM, Salihu HM. Pregnancy-related hypertensive disorders and immigrant status: a systematic review and meta-analysis of epidemiological studies. *J Immigr Minor Health*. 2017;19:1488–1497. doi: 10.1007/s10903-016-0410-6
35. Premkumar A, Debbink MP, Silver RM, Haas DM, Simhan HN, Wing DA, Parry S, Mercer BM, Iams J, Reddy UM, et al. Association of acculturation with adverse pregnancy outcomes. *Obstet Gynecol*. 2020;135:301–309. doi: 10.1097/AOG.0000000000003659
36. Zahid S, Tanveer ud Din M, Minhas AS, Rai D, Kaur G, Carfagnini C, Khan MZ, Ullah W, Van Spall HGC, Hays AG, et al. Racial and socioeconomic disparities in cardiovascular outcomes of preeclampsia hospitalizations in the United States 2004-2019. *JACC Adv*. 2022;1:100062. doi: 10.1016/j.jacadv.2022.100062
37. Facco FL, Redline S, Hunter SM, Zee PC, Grobman WA, Silver RM, Louis JM, Pien GW, Mercer B, Chung JH, et al. Sleep-disordered breathing in pregnancy and after delivery: associations with cardiometabolic health. *Am J Respir Crit Care Med*. 2022;205:1202–1213. doi: 10.1164/rccm.202104-0971OC
38. Sun M, Yan W, Fang K, Chen D, Liu J, Chen Y, Duan J, Chen R, Sun Z, Wang X, et al. The correlation between PM(2.5) exposure and hypertensive disorders in pregnancy: a meta-analysis. *Sci Total Environ*. 2020;703:134985. doi: 10.1016/j.scitotenv.2019.134985
39. Xue R-H, Wu D-D, Zhou C-L, Chen L, Li J, Li Z-Z, Fan J-X, Liu X-M, Lin X-H, Huang H-F. Association of high maternal triglyceride levels early and late in pregnancy with adverse outcomes: a retrospective cohort study. *J Clin Lipidol*. 2021;15:162–172. doi: 10.1016/j.jacl.2020.10.001
40. Papageorghiou AT, Deruelle P, Gunier RB, Rauch S, García-May PK, Mhatre M, Usman MA, Abd-Elsalam S, Etuk S, Simmons LE, et al. Preeclampsia and COVID-19: results from the INTERCOVID prospective longitudinal study. *Am J Obstet Gynecol*. 2021;225:289.e1–289.e17. doi: 10.1016/j.ajog.2021.05.014
41. Harrington KA, Cameron NA, Culler K, Grobman WA, Khan SS. Rural-urban disparities in adverse maternal outcomes in the United States, 2016-2019. *Am J Public Health*. 2023;113:224–227. doi: 10.2105/AJPH.2022.307134
42. Ayorinde AA, Bhattacharya S. Inherited predisposition to preeclampsia: analysis of the Aberdeen intergenerational cohort. *Pregnancy Hypertens*. 2017;8:37–41. doi: 10.1016/j.preghy.2017.03.001
43. Cnattingius S, Reilly M, Pawitan Y, Lichtenstein P. Maternal and fetal genetic factors account for most of familial aggregation of preeclampsia: a population-based Swedish cohort study. *Am J Med Genet A*. 2004;130A:365–371. doi: 10.1002/ajmg.a.30257
44. Honigberg MC, Chaffin M, Aragam K, Bhatt DL, Wood MJ, Sarma AA, Scott NS, Peloso GM, Natarajan P. Genetic variation in cardiometabolic traits and medication targets and the risk of hypertensive disorders of pregnancy. *Circulation*. 2020;142:711–713. doi: 10.1161/CIRCULATIONAHA.120.047936
45. McGinnis R, Steinthorsdottir V, Williams NO, Thorleifsson G, Shooter S, Hjartardottir S, Bumpstead S, Stefansdottir L, Hildyard L, Sigurdsson JK, et al; FINNPEC Consortium. Variants in the fetal genome near FLT1 are associated with risk of preeclampsia. *Nat Genet*. 2017;49:1255–1260. doi: 10.1038/ng.3895
46. Steinthorsdottir V, McGinnis R, Williams NO, Stefansdottir L, Thorleifsson G, Shooter S, Fadista J, Sigurdsson JK, Auro KM, Berezina G, et al; FINNPEC Consortium. Genetic predisposition to hypertension is associated with preeclampsia in European and Central Asian women. *Nat Commun*. 2020;11:5976. doi: 10.1038/s41467-020-19733-6
47. Sung YJ, Winkler TW, de Las Fuentes L, Bentley AR, Brown MR, Kraja AT, Schwander K, Ntalla I, Guo X, Franceschini N, et al; CHARGE Neurology Working Group. A large-scale multi-ancestry genome-wide study accounting for smoking behavior identifies multiple significant loci for blood pressure. *Am J Hum Genet*. 2018;102:375–400. doi: 10.1016/j.ajhg.2018.01.015
48. Changalidis AI, Maksiutenko EM, Barbitoff YA, Tkachenko AA, Vashukova ES, Pachuliia OV, Nasykhova YA, Glotov AS. Aggregation of genome-wide association data from FinnGen and UK Biobank replicates multiple risk loci for pregnancy complications. *Genes (Basel)*. 2022;13:2255. doi: 10.3390/genes13122255
49. Gray KJ, Kovacheva VP, Mirzakhani H, Bjonnes AC, Almoguera B, Wilson ML, Ingles SA, Lockwood CJ, Hakonarson H, McElrath TF, et al. Risk of pre-eclampsia in patients with a maternal genetic predisposition to common medical conditions: a case-control study. *BJOG*. 2021;128:55–65. doi: 10.1111/1471-0528.16441
50. Gammill HS, Chettier R, Brewer A, Roberts JM, Shree R, Tsigas E, Ward K. Cardiomyopathy and Preeclampsia. *Circulation*. 2018;138:2359–2366. doi: 10.1161/CIRCULATIONAHA.117.031527
51. Nieves-Colon MA, Badillo Rivera KM, Sandoval K, Villanueva Davalos V, Enriquez Lencinas LE, Mendoza-Revilla J, Adhikari K, Gonzalez-Buenfil R, Chen JW, Zhang ET, et al. Clotting factor genes are associated with preeclampsia in high-altitude pregnant women in the Peruvian Andes. *Am J Hum Genet*. 2022;109:1117–1139. doi: 10.1016/j.ajhg.2022.04.014
52. Magnus MC, Wallace MK, Demirci JR, Catov JM, Schmella MJ, Fraser A. Breastfeeding and later-life cardiometabolic health in women with and without hypertensive disorders of pregnancy. *J Am Heart Assoc*. 2023;12:e026696. doi: 10.1161/JAHA.122.026696
53. Bull FC, Al-Ansari SS, Biddle S, Borodulin K, Buman MP, Cardon G, Carty C, Chaput JP, Chastin S, Chou R, et al. World Health Organization 2020

guidelines on physical activity and sedentary behaviour. *Br J Sports Med*. 2020;54:1451–1462. doi: 10.1136/bjsports-2020-102955
54. Mottola MF, Davenport MH, Ruchat SM, Davies GA, Poitras VJ, Gray CE, Jaramillo Garcia A, Barrowman N, Adamo KB, Duggan M, et al. 2019 Canadian guideline for physical activity throughout pregnancy. *Br J Sports Med*. 2018;52:1339–1346. doi: 10.1136/bjsports-2018-100056
55. US Department of Health and Human Services. Physical Activity Guidelines for Americans. 2nd ed. 2018. Accessed March 15, 2023. https://health.gov/sites/default/files/2019-09/Physical_Activity_Guidelines_2nd_edition.pdf
56. Davenport MH, Ruchat SM, Poitras VJ, Jaramillo Garcia A, Gray CE, Barrowman N, Skow RJ, Meah VL, Riske L, Sobierajski F, et al. Prenatal exercise for the prevention of gestational diabetes mellitus and hypertensive disorders of pregnancy: a systematic review and meta-analysis. *Br J Sports Med*. 2018;52:1367–1375. doi: 10.1136/bjsports-2018-099355
57. Magro-Malosso ER, Saccone G, Di Tommaso M, Roman A, Berghella V. Exercise during pregnancy and risk of gestational hypertensive disorders: a systematic review and meta-analysis. *Acta Obstet Gynecol Scand*. 2017;96:921–931. doi: 10.1111/aogs.13151
58. Henderson JT, Vesco KK, Senger CA, Thomas RG, Redmond N. Aspirin use to prevent preeclampsia and related morbidity and mortality: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2021;326:1192–1206. doi: 10.1001/jama.2021.8551
59. Van Doorn R, Mukhtarova N, Flyke IP, Lasarev M, Kim K, Hennekens CH, Hoppe KK. Dose of aspirin to prevent preterm preeclampsia in women with moderate or high-risk factors: a systematic review and meta-analysis. *PLoS One*. 2021;16:e0247782. doi: 10.1371/journal.pone.0247782
60. Grandi SM, Filion KB, Yoon S, Ayele HT, Doyle CM, Hutcheon JA, Smith GN, Gore GC, Ray JG, Nerenberg K, et al. Cardiovascular disease-related morbidity and mortality in women with a history of pregnancy complications. *Circulation*. 2019;139:1069–1079. doi: 10.1161/CIRCULATIONAHA.118.036748
61. Miller EC, Zambrano Espinoza MD, Huang Y, Friedman AM, Boehme AK, Bello NA, Cleary KL, Wright JD, D'Alton ME. Maternal race/ethnicity, hypertension, and risk for stroke during delivery admission. *J Am Heart Assoc*. 2020;9:e014775. doi: 10.1161/JAHA.119.014775
62. Leon LJ, McCarthy FP, Direk K, Gonzalez-Izquierdo A, Prieto-Merino D, Casas JP, Chappell L. Preeclampsia and cardiovascular disease in a large UK pregnancy cohort of linked electronic health records: a CALIBER study. *Circulation*. 2019;140:1050–1060. doi: 10.1161/CIRCULATIONAHA.118.038080
63. Honigberg MC, Riise HKR, Daltveit AK, Tell GS, Sulo G, Igland J, Klungsoyr K, Scott NS, Wood MJ, Natarajan P, et al. Heart failure in women with hypertensive disorders of pregnancy: insights from the Cardiovascular Disease in Norway Project. *Hypertension*. 2020;76:1506–1513. doi: 10.1161/HYPERTENSIONAHA.120.15654
64. Stuart JJ, Tanz LJ, Rimm EB, Spiegelman D, Missmer SA, Mukamal KJ, Rexrode KM, Rich-Edwards JW. Cardiovascular risk factors mediate the long-term maternal risk associated with hypertensive disorders of pregnancy. *J Am Coll Cardiol*. 2022;79:1901–1913. doi: 10.1016/j.jacc.2022.03.335
65. Andraweera PH, Lassi ZS. Cardiovascular risk factors in offspring of preeclamptic pregnancies: systematic review and meta-analysis. *J Pediatr*. 2019;208:104–113.e6. doi: 10.1016/j.jpeds.2018.12.008
66. Hoodbhoy Z, Mohammed N, Nathani KR, Sattar S, Chowdhury D, Maskatia S, Tierney S, Hasan B, Das JK. The impact of maternal preeclampsia and hyperglycemia on the cardiovascular health of the offspring: a systematic review and meta-analysis. *Am J Perinatol*. 2021;40:363–374. doi: 10.1055/s-0041-1728823
67. Kleinwechter HJ, Weber KS, Mingers N, Ramsauer B, Schaefer-Graf UM, Groten T, Kuschel B, Backes C, Banz-Jansen C, Berghaeuser MA, et al. Gestational diabetes mellitus and COVID-19: results from the COVID-19-Related Obstetric and Neonatal Outcome Study (CRONOS). *Am J Obstet Gynecol*. 2022;227:631.e1–631.e19. doi: 10.1016/j.ajog.2022.05.027
68. Gregory ECW, Ely DM. Trends and characteristics in gestational diabetes: United States, 2016–2020. 2022. Accessed May 22, 2023. https://cdc.gov/nchs/data/nvsr/nvsr71/nvsr71-03.pdf
69. Deputy NP, Kim SY, Conrey EJ, Bullard KM. Prevalence and changes in preexisting diabetes and gestational diabetes among women who had a live birth–United States, 2012-2016. *MMWR Morb Mortal Wkly Rep*. 2018;67:1201–1207. doi: 10.15585/mmwr.mm6743a2
70. Shah NS, Wang MC, Freaney PM, Perak AM, Carnethon MR, Kandula NR, Gunderson EP, Bullard KM, Grobman WA, O'Brien MJ, et al. Trends in gestational diabetes at first live birth by race and ethnicity in the US, 2011-2019. *JAMA*. 2021;326:660–669. doi: 10.1001/jama.2021.7217
71. Facco FL, Grobman WA, Reid KJ, Parker CB, Hunter SM, Silver RM, Basner RC, Saade GR, Pien GW, Manchanda S, et al. Objectively measured short sleep duration and later sleep midpoint in pregnancy are associated with a higher risk of gestational diabetes. *Am J Obstet Gynecol*. 2017;217:447.e1–447.e13. doi: 10.1016/j.ajog.2017.05.066
72. MacGregor C, Freedman A, Keenan-Devlin L, Grobman W, Wadhwa P, Simhan HN, Buss C, Borders A. Maternal perceived discrimination and association with gestational diabetes. *Am J Obst Gynecol MFM*. 2020;2:100222. doi: 10.1016/j.ajogmf.2020.100222
73. Medici Dualib P, Ogassavara J, Mattar R, Mariko Koga da Silva E, Atala Dib S, de Almeida Pititto B. Gut microbiota and gestational diabetes mellitus: a systematic review. *Diabetes Res Clin Pract*. 2021;180:109078. doi: 10.1016/j.diabres.2021.109078
74. Shah NS, Wang MC, Kandula NR, Carnethon MR, Gunderson EP, Grobman WA, Khan SS. Gestational diabetes and hypertensive disorders of pregnancy by maternal birthplace. *Am J Prev Med*. 2021;62:e223–e231. doi: 10.1016/j.amepre.2021.10.007
75. Jang HC, Min HK, Lee HK, Cho NH, Metzger BE. Short stature in Korean women: a contribution to the multifactorial predisposition to gestational diabetes mellitus. *Diabetologia*. 1998;41:778–783. doi: 10.1007/s001250050987
76. Pervjakova N, Moen GH, Borges MC, Ferreira T, Cook JP, Allard C, Beaumont RN, Canouil M, Hatem G, Heiskala A, et al. Multi-ancestry genome-wide association study of gestational diabetes mellitus highlights genetic links with type 2 diabetes. *Hum Mol Genet*. 2022;31:3377–3391. doi: 10.1093/hmg/ddac050
77. Powe CE, Kwak SH. Genetic studies of gestational diabetes and glucose metabolism in pregnancy. *Curr Diab Rep*. 2020;20:69. doi: 10.1007/s11892-020-01355-3
78. Ding M, Chavarro J, Olsen S, Lin Y, Ley SH, Bao W, Rawal S, Grunnet LG, Thuesen ACB, Mills JL, et al. Genetic variants of gestational diabetes mellitus: a study of 112 SNPs among 8722 women in two independent populations. *Diabetologia*. 2018;61:1758–1768. doi: 10.1007/s00125-018-4637-8
79. Pagel KA, Chu H, Ramola R, Guerrero RF, Chung JH, Parry S, Reddy UM, Silver RM, Steller JG, Yee LM, et al. Association of genetic predisposition and physical activity with risk of gestational diabetes in nulliparous women. *JAMA Netw Open*. 2022;5:e2229158. doi: 10.1001/jamanetworkopen.2022.29158
80. Lamri A, Mao S, Desai D, Gupta M, Pare G, Anand SS. Fine-tuning of genome-wide polygenic risk scores and prediction of gestational diabetes in South Asian women. *Sci Rep*. 2020;10:8941. doi: 10.1038/s41598-020-65360-y
81. Kwak SH, Kim SH, Cho YM, Go MJ, Cho YS, Choi SH, Moon MK, Jung HS, Shin HD, Kang HM, et al. A genome-wide association study of gestational diabetes mellitus in Korean women. *Diabetes*. 2012;61:531–541. doi: 10.2337/db11-1034
82. Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature*. 2007;447:661–678. doi: 10.1038/nature05911
83. Prokopenko I, Langenberg C, Florez JC, Saxena R, Soranzo N, Thorleifsson G, Loos RJ, Manning AK, Jackson AU, Aulchenko Y, et al. Variants in *MTNR1B* influence fasting glucose levels. *Nat Genet*. 2009;41:77–81. doi: 10.1038/ng.290
84. Martínez-Vizcaíno V, Sanabria-Martínez G, Fernández-Rodríguez R, Cavero-Redondo I, Pascual-Morena C, Álvarez-Bueno C, Martínez-Hortelano JA. Exercise during pregnancy for preventing gestational diabetes mellitus and hypertensive disorders: an umbrella review of randomised controlled trials and an updated meta-analysis. *BJOG*. 2023;130:264–275. doi: 10.1111/1471-0528.17304
85. Vounzoulaki E, Khunti K, Abner SC, Tan BK, Davies MJ, Gillies CL. Progression to type 2 diabetes in women with a known history of gestational diabetes: systematic review and meta-analysis. *BMJ*. 2020;369:m1361. doi: 10.1136/bmj.m1361
86. Lowe WL Jr, Scholtens DM, Lowe LP, Kuang A, Nodzenski M, Talbot O, Catalano PM, Linder B, Brickman WJ, Clayton P, et al; HAPO Follow-up Study Cooperative Research Group. Association of gestational diabetes with maternal disorders of glucose metabolism and childhood adiposity. *JAMA*. 2018;320:1005–1016. doi: 10.1001/jama.2018.11628
87. Lowe WL Jr, Scholtens DM, Kuang A, Linder B, Lawrence JM, Lebenthal Y, McCance D, Hamilton J, Nodzenski M, Talbot O, et al; HAPO Follow-up Study Cooperative Research Group. Hyperglycemia and Adverse Pregnancy Outcome Follow-up Study (HAPO FUS): maternal gestational diabetes mellitus and childhood glucose metabolism. *Diabetes Care*. 2019;42:372–380. doi: 10.2337/dc18-1646

88. Yu Y, Arah OA, Liew Z, Cnattingius S, Olsen J, Sorensen HT, Qin G, Li J. Maternal diabetes during pregnancy and early onset of cardiovascular disease in offspring: population based cohort study with 40 years of follow-up. *BMJ*. 2019;367:l6398. doi: 10.1136/bmj.l6398
89. Martin JA, Hamilton BE, Osterman MJK. Births in the United States, 2018. *NCHS Data Brief*. 2019:1–8.
90. Martin JA, Osterman MJK. Describing the increase in preterm births in the United States, 2014-2016. *NCHS Data Brief*. 2018:1–8.
91. Lemon L, Edwards RP, Simhan HN. What is driving the decreased incidence of preterm birth during the COVID-19 pandemic? *Am J Obstet Gynecol MFM*. 2021;3:100330. doi: 10.1016/j.ajogmf.2021.100330
92. Allotey J, Stallings E, Bonet M, Yap M, Chatterjee S, Kew T, Debenham L, Llavall AC, Dixit A, Zhou D, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. *BMJ*. 2020;370:m3320. doi: 10.1136/bmj.m3320
93. Woodworth KR, Olsen EO, Neelam V, Lewis EL, Galang RR, Oduyebo T, Aveni K, Yazdy MM, Harvey E, Longcore ND, et al; CDC COVID-19 Response Pregnancy and Infant Linked Outcomes Team. Birth and infant outcomes following laboratory-confirmed SARS-CoV-2 infection in pregnancy: SET-NET, 16 jurisdictions, March 29-October 14, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69:1635–1640. doi: 10.15585/mmwr.mm6944e2
94. Sutton EF, Hauspurg A, Caritis SN, Powers RW, Catov JM. Maternal outcomes associated with lower range stage 1 hypertension. *Obstet Gynecol*. 2018;132:843–849. doi: 10.1097/AOG.0000000000002870
95. Warland J, Dorrian J, Morrison JL, O'Brien LM. Maternal sleep during pregnancy and poor fetal outcomes: a scoping review of the literature with meta-analysis. *Sleep Med Rev*. 2018;41:197–219. doi: 10.1016/j.smrv.2018.03.004
96. Janevic T, Glazer KB, Vieira L, Weber E, Stone J, Stern T, Bianco A, Wagner B, Dolan SM, Howell EA. Racial/ethnic disparities in very preterm birth and preterm birth before and during the COVID-19 pandemic. *JAMA Network Open*. 2021;4:e211816. doi: 10.1001/jamanetworkopen.2021.1816
97. Bekkar B, Pacheco S, Basu R, DeNicola N. Association of air pollution and heat exposure with preterm birth, low birth weight, and stillbirth in the US: a systematic review. *JAMA Netw Open*. 2020;3:e208243. doi: 10.1001/jamanetworkopen.2020.8243
98. Basu R, Chen H, Li DK, Avalos LA. The impact of maternal factors on the association between temperature and preterm delivery. *Environ Res*. 2017;154:109–114. doi: 10.1016/j.envres.2016.12.017
99. Chersich MF, Pham MD, Areal A, Haghighi MM, Manyuchi A, Swift CP, Wernecke B, Robinson M, Hetem R, Boeckmann M, et al; Climate Change and Heat-Health Study Group. Associations between high temperatures in pregnancy and risk of preterm birth, low birth weight, and stillbirths: systematic review and meta-analysis. *BMJ*. 2020;371:m3811. doi: 10.1136/bmj.m3811
100. Lee KJ, Moon H, Yun HR, Park EL, Park AR, Choi H, Hong K, Lee J. Greenness, civil environment, and pregnancy outcomes: perspectives with a systematic review and meta-analysis. *Environ Health*. 2020;19:91. doi: 10.1186/s12940-020-00649-z
101. van Daalen KR, Kaiser J, Kebede S, Cipriano G, Maimouni H, Olumese E, Chui A, Kuhn I, Oliver-Williams C. Racial discrimination and adverse pregnancy outcomes: a systematic review and meta-analysis. *BMJ Glob Health*. 2022;7:e009227. doi: 10.1136/bmjgh-2022-009227
102. Himmelstein G, Desmond M. Association of eviction with adverse birth outcomes among women in Georgia, 2000 to 2016. *JAMA Pediatr*. 2021;175:494. doi: 10.1001/jamapediatrics.2020.6550
103. Hendryx M, Chojenta C, Byles JE. Latent class analysis of low birth weight and preterm delivery among Australian women. *J Pediatr*. 2020;218:42–48.e1. doi: 10.1016/j.jpeds.2019.11.007
104. Pantell MS, Baer RJ, Torres JM, Felder JN, Gomez AM, Chambers BD, Dunn J, Parikh NI, Pacheco-Werner T, Rogers EE, et al. Associations between unstable housing, obstetric outcomes, and perinatal health care utilization. *Am J Obstet Gynecol MFM*. 2019;1:100053. doi: 10.1016/j.ajogmf.2019.100053
105. Urquia ML, Wall-Wieler E, Ruth CA, Liu X, Roos LL. Revisiting the association between maternal and offspring preterm birth using a sibling design. *BMC Pregnancy Childbirth*. 2019;19:157. doi: 10.1186/s12884-019-2304-9
106. Wadon M, Modi N, Wong HS, Thapar A, O'Donovan MC. Recent advances in the genetics of preterm birth. *Ann Hum Genet*. 2020;84:205–213. doi: 10.1111/ahg.12373
107. Zhang G, Feenstra B, Bacelis J, Liu X, Muglia LM, Juodakis J, Miller DE, Litterman N, Jiang PP, Russell L, et al. Genetic associations with gestational duration and spontaneous preterm birth. *N Engl J Med*. 2017;377:1156–1167. doi: 10.1056/NEJMoa1612665
108. Liu X, Helenius D, Skotte L, Beaumont RN, Wielscher M, Geller F, Juodakis J, Mahajan A, Bradfield JP, Lin FTJ, et al. Variants in the fetal genome near pro-inflammatory cytokine genes on 2q13 associate with gestational duration. *Nat Commun*. 2019;10:3927. doi: 10.1038/s41467-019-11881-8
109. Zhou G, Holzman C, Heng YJ, Kibschull M, Lye SJ, Vazquez A. EBF1 gene mRNA levels in maternal blood and spontaneous preterm birth. *Reprod Sci*. 2020;27:316–324. doi: 10.1007/s43032-019-00027-2
110. Chen J, Bacelis J, Sole-Navais P, Srivastava A, Juodakis J, Rouse A, Hallman M, Teramo K, Melbye M, Feenstra B, et al. Dissecting maternal and fetal genetic effects underlying the associations between maternal phenotypes, birth outcomes, and adult phenotypes: a mendelian-randomization and haplotype-based genetic score analysis in 10,734 mother-infant pairs. *PLoS Med*. 2020;17:e1003305. doi: 10.1371/journal.pmed.1003305
111. Brown CC, Moore JE, Felix HC, Stewart MK, Bird TM, Lowery CL, Tilford JM. Association of state Medicaid expansion status with low birth weight and preterm birth. *JAMA*. 2019;321:1598–1609. doi: 10.1001/jama.2019.3678
112. Johnson JD, Green CA, Vladutiu CJ, Manuck TA. Racial disparities in prematurity persist among women of high socioeconomic status. *Am J Obstet Gynecol MFM*. 2020;2:100104. doi: 10.1016/j.ajogmf.2020.100104
113. Tanz LJ, Stuart JJ, Williams PL, Missmer SA, Rimm EB, James-Todd TM, Rich-Edwards JW. Preterm delivery and maternal cardiovascular disease risk factors: the Nurses' Health Study II. *J Womens Health (Larchmt)*. 2019;28:677–685. doi: 10.1089/jwh.2018.7150
114. Catov JM, Snyder GG, Fraser A, Lewis CE, Liu K, Althouse AD, Bertolet M, Gunderson EP. Blood pressure patterns and subsequent coronary artery calcification in women who delivered preterm births. *Hypertension*. 2018;72:159–166. doi: 10.1161/HYPERTENSIONAHA.117.10693
115. Crump C, Sundquist J, Howell EA, McLaughlin MA, Stroustrup A, Sundquist K. Pre-term delivery and risk of ischemic heart disease in women. *J Am Coll Cardiol*. 2020;76:57–67. doi: 10.1016/j.jacc.2020.04.072
116. Crump C, Sundquist J, Sundquist K. Preterm delivery and long term mortality in women: national cohort and co-sibling study. *BMJ*. 2020;370:m2533. doi: 10.1136/bmj.m2533
117. Liao L, Deng Y, Zhao D. Association of low birth weight and premature birth with the risk of metabolic syndrome: a meta-analysis. *Front Pediatr*. 2020;8:405. doi: 10.3389/fped.2020.00405
118. Crump C, Sundquist J, Sundquist K. Preterm birth and risk of type 1 and type 2 diabetes: a national cohort study. *Diabetologia*. 2020;63:508–518. doi: 10.1007/s00125-019-05044-z
119. Crump C, Sundquist J, Sundquist K. Risk of hypertension into adulthood in persons born prematurely: a national cohort study. *Eur Heart J*. 2020;41:1542–1550. doi: 10.1093/eurheartj/ehz904
120. Crump C, Sundquist J, Sundquist K. Association of preterm birth with lipid disorders in early adulthood: a Swedish cohort study. *PLoS Med*. 2019;16:e1002947. doi: 10.1371/journal.pmed.1002947
121. Telles F, McNamara N, Nanayakkara S, Doyle MP, Williams M, Yaeger L, Marwick TH, Leeson P, Levy PT, Lewandowski AJ. Changes in the preterm heart from birth to young adulthood: a meta-analysis. *Pediatrics*. 2020;146:e20200146. doi: 10.1542/peds.2020-0146
122. Crump C, Groves A, Sundquist J, Sundquist K. Association of preterm birth with long-term risk of heart failure into adulthood. *JAMA Pediatr*. 2021;175:689–697. doi: 10.1001/jamapediatrics.2021.0131
123. Crump C, Howell EA, Stroustrup A, McLaughlin MA, Sundquist J, Sundquist K. Association of preterm birth with risk of ischemic heart disease in adulthood. *JAMA Pediatr*. 2019;173:736–743. doi: 10.1001/jamapediatrics.2019.1327
124. Crump C, Sundquist J, Winkleby MA, Sundquist K. Gestational age at birth and mortality from infancy into mid-adulthood: a national cohort study. *Lancet Child Adolesc Health*. 2019;3:408–417. doi: 10.1016/S2352-4642(19)30108-7
125. Martin JA, Hamilton BE, Osterman MJK, Driscoll AK. Births: Final Data for 2018. National Vital Statistics Reports, Vol. 68. November 27, 2019. Accessed April 15, 2023. https://www.cdc.gov/nchs/data/nvsr/nvsr68/nvsr68_13-508.pdf
126. Kharbanda EO, Vazquez-Benitez G, Kunin-Batson A, Nordin JD, Olsen A, Romitti PA. Birth and early developmental screening outcomes associated with cannabis exposure during pregnancy. *J Perinatol*. 2020;40:473–480. doi: 10.1038/s41372-019-0576-6
127. Retnakaran R, Shah BR. Patterns of cardiovascular risk factors in the years before pregnancy in nulliparous women with and without preterm birth and small-for-gestational-age delivery. *J Am Heart Assoc*. 2021;10:e021321. doi: 10.1161/JAHA.121.021321
128. Nasiri K, Moodie EEM, Abenhaim HA. To what extent is the association between race/ethnicity and fetal growth restriction explained by adequacy

of prenatal care? A mediation analysis of a retrospectively selected cohort. *Am J Epidemiol*. 2020;189:1360–1368. doi: 10.1093/aje/kwaa054
129. Lahti-Pulkkinen M, Bhattacharya S, Raikkonen K, Osmond C, Norman JE, Reynolds RM. Intergenerational transmission of birth weight across 3 generations. *Am J Epidemiol*. 2018;187:1165–1173. doi: 10.1093/aje/kwx340
130. Svensson AC, Pawitan Y, Cnattingius S, Reilly M, Lichtenstein P. Familial aggregation of small-for-gestational-age births: the importance of fetal genetic effects. *Am J Obstet Gynecol*. 2006;194:475–479. doi: 10.1016/j.ajog.2005.08.019
131. Beaumont RN, Kotecha SJ, Wood AR, Knight BA, Sebert S, McCarthy MI, Hattersley AT, Jarvelin MR, Timpson NJ, Freathy RM, et al. Common maternal and fetal genetic variants show expected polygenic effects on risk of small- or large-for-gestational-age (SGA or LGA), except in the smallest 3% of babies. *PLoS Genet*. 2020;16:e1009191. doi: 10.1371/journal.pgen.1009191
132. Timpka S, Fraser A, Schyman T, Stuart JJ, Asvold BO, Mogren I, Franks PW, Rich-Edwards JW. The value of pregnancy complication history for 10-year cardiovascular disease risk prediction in middle-aged women. *Eur J Epidemiol*. 2018;33:1003–1010. doi: 10.1007/s10654-018-0429-1
133. Knop MR, Geng TT, Gorny AW, Ding R, Li C, Ley SH, Huang T. Birth weight and risk of type 2 diabetes mellitus, cardiovascular disease, and hypertension in adults: a meta-analysis of 7 646 267 participants from 135 studies. *J Am Heart Assoc*. 2018;7:e008870. doi: 10.1161/JAHA.118.008870
134. Wang YX, Ding M, Li Y, Wang L, Rich-Edwards JW, Florio AA, Manson JE, Chavarro JE. Birth weight and long-term risk of mortality among US men and women: results from three prospective cohort studies. *Lancet Reg Health Am*. 2022;15:100344. doi: 10.1016/j.lana.2022.100344
135. Gregory EC, Valenzuela CP, Hoyert DL. Fetal mortality: United States, 2020. *Natl Vital Stat Rep*. 2022;71:1–20.
136. Management of Stillbirth: Obstetric Care Consensus No, 10. *Obstet Gynecol*. 2020;135:e110–e132. doi: 10.1097/AOG.0000000000003719
137. Liu L, Sun D. Pregnancy outcomes in patients with primary antiphospholipid syndrome: a systematic review and meta-analysis. *Medicine (Baltimore)*. 2019;98:e15733. doi: 10.1097/MD.0000000000015733
138. Khalil A, von Dadelszen P, Draycott T, Ugwumadu A, O'Brien P, Magee L. Change in the incidence of stillbirth and preterm delivery during the COVID-19 pandemic. *JAMA*. 2020;324:705–706. doi: 10.1001/jama.2020.12746
139. Stowe J, Smith H, Thurland K, Ramsay ME, Andrews N, Ladhani SN. Stillbirths during the COVID-19 pandemic in England, April-June 2020. *JAMA*. 2021;325:86–87. doi: 10.1001/jama.2020.21369
140. Laisk T, Soares ALG, Ferreira T, Painter JN, Censin JC, Laber S, Bacelis J, Chen CY, Lepamets M, Lin K, et al. The genetic architecture of sporadic and multiple consecutive miscarriage. *Nat Commun*. 2020;11:5980. doi: 10.1038/s41467-020-19742-5
141. Marquard K, Westphal LM, Milki AA, Lathi RB. Etiology of recurrent pregnancy loss in women over the age of 35 years. *Fertil Steril*. 2010;94:1473–1477. doi: 10.1016/j.fertnstert.2009.06.041
142. Crotti L, Tester DJ, White WM, Bartos DC, Insolia R, Besana A, Kunic JD, Will ML, Velasco EJ, Bair JJ, et al. Long QT syndrome-associated mutations in intrauterine fetal death. *JAMA*. 2013;309:1473–1482. doi: 10.1001/jama.2013.3219
143. Maddirevula S, Awartani K, Coskun S, AlNaim LF, Ibrahim N, Abdulwahab F, Hashem M, Alhassan S, Alkuraya FS. A genomics approach to females with infertility and recurrent pregnancy loss. *Hum Genet*. 2020;139:605–613. doi: 10.1007/s00439-020-02143-5
144. Prasad S, Kalafat E, Blakeway H, Townsend R, O'Brien P, Morris E, Draycott T, Thangaratinam S, Le Doare K, Ladhani S, et al. Systematic review and meta-analysis of the effectiveness and perinatal outcomes of COVID-19 vaccination in pregnancy. *Nat Commun*. 2022;13:2414. doi: 10.1038/s41467-022-30052-w
145. Wang YX, Minguez-Alarcon L, Gaskins AJ, Wang L, Ding M, Missmer SA, Rich-Edwards JW, Manson JE, Chavarro JE. Pregnancy loss and risk of cardiovascular disease: the Nurses' Health Study II. *Eur Heart J*. 2022;43:190–199. doi: 10.1093/eurheartj/ehab737
146. Horn J, Tanz LJ, Stuart JJ, Markovitz AR, Skurnik G, Rimm EB, Missmer SA, Rich-Edwards JW. Early or late pregnancy loss and development of clinical cardiovascular disease risk factors: a prospective cohort study. *BJOG*. 2019;126:33–42. doi: 10.1111/1471-0528.15452
147. Hall PS, Nah G, Vittinghoff E, Parker DR, Manson JE, Howard BV, Sarto GE, Gass ML, Sealy-Jefferson SM, Salmoirago-Blotcher E, et al. Relation of pregnancy loss to risk of cardiovascular disease in parous postmenopausal women (from the Women's Health Initiative). *Am J Cardiol*. 2019;123:1620–1625. doi: 10.1016/j.amjcard.2019.02.012
148. Downes KL, Grantz KL, Shenassa ED. Maternal, labor, delivery, and perinatal outcomes associated with placental abruption: a systematic review. *Am J Perinatol*. 2017;34:935–957. doi: 10.1055/s-0037-1599149
149. Lueth A, Blue N, Silver RM, Allshouse A, Hoffman M, Grobman WA, Simhan HN, Reddy U, Haas DM. Prospective evaluation of placental abruption in nulliparous women. *J Matern Fetal Neonatal Med*. 2021;35:8603–8610. doi: 10.1080/14767058.2021.1989405
150. Anderson E, Raja EA, Shetty A, Gissler M, Gatt M, Bhattacharya S, Bhattacharya S. Changing risk factors for placental abruption: a case crossover study using routinely collected data from Finland, Malta and Aberdeen. *PLoS One*. 2020;15:e0233641. doi: 10.1371/journal.pone.0233641
151. Rasmussen S, Irgens LM. Occurrence of placental abruption in relatives. *BJOG*. 2009;116:693–699. doi: 10.1111/j.1471-0528.2008.02064.x
152. Ananth CV, Patrick HS, Ananth S, Zhang Y, Kostis WJ, Schuster M. Maternal cardiovascular and cerebrovascular health after placental abruption: a systematic review and meta-analysis (CHAP-SR). *Am J Epidemiol*. 2021;190:2718–2729. doi: 10.1093/aje/kwab206
153. DesJardin JT, Healy MJ, Nah G, Vittinghoff E, Agarwal A, Marcus GM, Velez JMG, Tseng ZH, Parikh NI. Placental abruption as a risk factor for heart failure. *Am J Cardiol*. 2020;131:17–22. doi: 10.1016/j.amjcard.2020.06.034
154. Isayama T, Lewis-Mikhael AM, O'Reilly D, Beyene J, McDonald SD. Health services use by late preterm and term infants from infancy to adulthood: a meta-analysis. *Pediatrics*. 2017;140:e20170266. doi: 10.1542/peds.2017-0266
155. Dieleman JL, Cao J, Chapin A, Chen C, Li Z, Liu A, Horst C, Kaldjian A, Matyasz T, Scott KW, et al. US health care spending by payer and health condition, 1996-2016. *JAMA*. 2020;323:863–884. doi: 10.1001/jama.2020.0734
156. O'Neil S, Platt I, Vohra D, Pendl-Robinson E, Dehus E, Zephyrin L, Zivin K. The high costs of maternal morbidity show why we need greater investment in maternal health. The Commonwealth Fund. 2021. Accessed August 6, 2023. https://commonwealthfund.org/publications/issue-briefs/2021/nov/high-costs-maternal-morbidity-need-investment-maternal-health
157. Blencowe H, Krasevec J, de Onis M, Black RE, An X, Stevens GA, Borghi E, Hayashi C, Estevez D, Cegolon L, et al. National, regional, and worldwide estimates of low birthweight in 2015, with trends from 2000: a systematic analysis. *Lancet Glob Health*. 2019;7:e849–e860. doi: 10.1016/S2214-109X(18)30565-5
158. Lawn JE, Ohuma EO, Bradley E, Idueta LS, Hazel E, Okwaraji YB, Erchick DJ, Yargawa J, Katz J, Lee ACC, et al; Lancet Small Vulnerable Newborn Steering Committee. Small babies, big risks: global estimates of prevalence and mortality for vulnerable newborns to accelerate change and improve counting. *Lancet*. 2023;401:1707–1719. doi: 10.1016/S0140-6736(23)00522-6
159. Chen C, Grewal J, Betran AP, Vogel JP, Souza JP, Zhang J. Severe anemia, sickle cell disease, and thalassemia as risk factors for hypertensive disorders in pregnancy in developing countries. *Pregnancy Hypertens*. 2018;13:141–147. doi: 10.1016/j.preghy.2018.06.001
160. Lawn JE, Blencowe H, Waiswa P, Amouzou A, Mathers C, Hogan D, Flenady V, Froen JF, Qureshi ZU, Calderwood C, et al; Lancet Ending Preventable Stillbirths Series Study Group. Stillbirths: rates, risk factors, and acceleration towards 2030. *Lancet*. 2016;387:587–603. doi: 10.1016/S0140-6736(15)00837-5
161. Global Burden of Disease Study and Institute for Health Metrics and Evaluation. University of Washington. Accessed August 2, 2023. http://ghdx.healthdata.org/
162. Ananth CV, Keyes KM, Hamilton A, Gissler M, Wu C, Liu S, Luque-Fernandez MA, Skjaerven R, Williams MA, Tikkanen M, et al. An international contrast of rates of placental abruption: an age-period-cohort analysis. *PLoS One*. 2015;10:e0125246. doi: 10.1371/journal.pone.0125246
163. Ford ND, Cox S, Ko JY, Ouyang L, Romero L, Colarusso T, Ferre CD, Kroelinger CD, Hayes DK, Barfield WD. Hypertensive disorders in pregnancy and mortality at delivery hospitalization: United States, 2017-2019. *MMWR Morb Mortal Wkly Rep*. 2022;71:585–591. doi: 10.15585/mmwr.mm7117a1
164. Centers for Disease Control and Prevention and National Center for Health Statistics. Multiple cause of death, CDC WONDER online database. Accessed April 1, 2023. https://wonder.cdc.gov/mcd-icd10.html

# 12. KIDNEY DISEASE

*ICD-10 N18.0. See Charts 12-1 through 12-13*

Click here to return to the Table of Contents
Click here to return to the Abbreviations

## Definition

## (See Chart 12-1)

CKD, defined as reduced eGFR (<60 mL·min$^{-1}$·1.73 m$^{-2}$), excess urinary albumin excretion (ACR ≥30 mg/g), or both, is a serious health condition and a worldwide public health problem that is associated with poor outcomes and a high cost to the US health care system.[1]

- eGFR is usually determined from serum creatinine level with equations that account for age, sex, and race. Given that race is a social construct and its inclusion in eGFR equations may perpetuate bias by wrongly ascribing biological differences to race, a task force from the American Society of Nephrology and the National Kidney Foundation recommended using the eGFR equation without the race variable and to facilitate increased and timely use of cystatin C, which is a filtration marker not affected by race.[2–5] Newer versions of the eGFR equations, which do not incorporate race, have been developed and validated and were used for calculating CKD estimates in the 2022 USRDS report.[6]
- The spot (random) urine ACR is recommended as a measure of urine albumin excretion.
- CKD is characterized by eGFR category (G1–G5) and albuminuria category (A1–A3), as well as cause of CKD (Chart 12-1).[7,8]
- ESRD is defined as severe CKD requiring long-term kidney replacement therapy such as hemodialysis, peritoneal dialysis, or kidney transplantation.[8] Individuals with ESRD are an extremely high-risk population for CVD morbidity and mortality.

The 2024 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2024. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

## Prevalence

## (See Charts 12-1 through 12-3)

- Using data from NHANES 2017 to 2020, the USRDS has estimated the prevalence of CKD by eGFR and albuminuria categories as shown in Chart 12-1. The overall prevalence of CKD (eGFR <60 mL·min$^{-1}$·1.73 m$^{-2}$ or ACR ≥30 mg/g; shown in yellow, orange, and red in Chart 12-1) in 2017 to 2020 was 14.0%.[1]
- The overall prevalence of CKD increases substantially with age, with 9% of adults <65 years of age and 33.2% of adults ≥65 years of age having CKD in 2017 to 2020.[1]
- According to NHANES 2017 to 2020, the prevalence of ACR ≥30 mg/g was 13.5% for NH Black adults, 10.9% for Hispanic adults, and 9% for NH White adults. In contrast, the prevalence of eGFR <60 mL·min$^{-1}$·1.73 m$^{-2}$, calculated with the newer eGFR equations without the race coefficient, was lowest among Hispanic adults (2.2%), followed by NH White adults (6.3%), and highest for NH Black adults (9.1%).[1]
- In the Framingham Offspring Study, the prevalence of mildly reduced eGFR (60–89 mL·min$^{-1}$·1.73 m$^{-2}$) was reported in 62% of participants, higher than reported in the NHANES data, possibly related to the higher age of the cohort.[9]
- In 2020, the age-, race-, and sex-adjusted prevalence of ESRD in the United States was 2271 per million people, a decrease of 1.49 from 2019.[1] The overall prevalence count remained flat, or decreased slightly, from 808 330 in 2019 to 807 920 in 2020.
- ESRD prevalence varied by race and ethnicity (Chart 12-2). In 2020, ESRD prevalence was highest in Black adults, followed by Native American adults, Asian adults, and White adults. ESRD prevalence also was higher among Hispanic people than among NH people.
- Among those with prevalent ESRD, in 2020 compared with 2019, the use of in-center hemodialysis remained the most common modality but decreased from 61.3% to 59.8% (Chart 12-3). All other modalities increased: transplantation from 29.7% to 30.6%, peritoneal dialysis from 7.7% to 8.1%, and home hemodialysis from 1.3% to 1.5%.[1]

## Incidence

## (See Chart 12-4)

- According to 2019 data from the Veterans Affairs Health System, the CKD incidence rate (categories 3–5) increased with age. The incidence rate per 1000 patient-years was 1.2 (20–29 years of age), 3.2 (30–39 years of age), 11.4 (40–49 years

of age), 26.7 (50–59 years of age), 59.8 (60–69 years of age), and 113.5 (≥70 years of age).[10]
- The incidence of ESRD in 2020, adjusted for age, sex, and race and ethnicity, was 363 per million people, which is the lowest it has been since 2000. The incidence count also decreased from 134 862 in 2019 to 130 522 in 2020.[1] The incidence of ESRD was highest among Black individuals and lowest among White individuals (Chart 12-4).
- By modality, the initiation of in-center hemodialysis decreased from 85.2% to 83.9%, whereas peritoneal dialysis increased from 11.5% to 12.7% and home hemodialysis remained at 0.3%.[1]

## Secular Trends

## (See Charts 12-5 and 12-6)

- Among Medicare beneficiaries, the prevalence of CKD (based on coded diagnosis) increased from 1.8% in 1999 to 13.5% in 2018 (Chart 12-5).
- According to NHANES data, the overall prevalence of reduced eGFR and excess ACR across categories was generally similar from 2005 to 2020 (Chart 12-6).
- Between 2013 to 2016 and 2017 to 2020, the prevalence of CKD stage 3 decreased among individuals <65 years of age, from 1.6% to 1.3%, but was unchanged among those ≥65 years of age.[1]
- By race and ethnicity, the prevalence of stage 3 and 4 CKD increased from 7.9% to 8.8% in NH Black individuals, was unchanged at 6.3% among NH White individuals, and decreased slightly from 2.6% to 2.0 % in Hispanic individuals.[1] However, the prevalence of stage 5 CKD remained unchanged at 0.1% in NH White individuals, decreased from 0.5% to 0.3% among NH Black individuals, but increased slightly from 0.1% to 0.2% in Hispanic individuals.
- From 2000 to 2019, the prevalence count of ESRD had been increasing (389 592 in 2000 to 808 330 in 2019) despite a slowly decreasing adjusted incidence rate, attributable primarily to a combination of an aging population and improved survival with ESRD. In the year 2020, the 6.2% decline in adjusted incidence rate was accompanied by a 1.9% decline in the adjusted prevalence rate and an accompanying flattening or slight decline in prevalence count.[1] This decline is explained mostly by the effects of COVID-19 in the ESRD population. From January 2020 until the end of June 2021, >10% of patients with CKD, 13% of patients with a kidney transplantation, and 20% of patients receiving dialysis were diagnosed with COVID-19.[11] Mortality 90 days after COVID-19 diagnosis was 40.5% for patients receiving dialysis and 44.1% among kidney transplant recipients.

## Risk Factors

- In a pooled analysis of >5.5 million adults, higher BMI, WC, and waist-to-height ratio were independently associated with eGFR decline and death in individuals who had normal or reduced levels of eGFR.[12]
- In the ARIC study, incident hospitalization with any major CVD event (HF, AF, CHD, or stroke) was associated with an increased risk of ESRD (HR, 6.63 [95% CI, 4.88–9.00]). In analyses by CVD event type, the association with ESRD risk was more pronounced for HF (HR, 9.92 [95% CI, 7.14–13.79]) than CHD (HR, 1.80 [95% CI, 1.22–2.66]), AF (HR, 1.10 [95% CI, 0.76–1.60]), and stroke (HR, 1.09 [95% CI, 0.65–1.85]).[13]
- In the Framingham Offspring Study, maintaining Life's Simple 7 factors in the intermediate or ideal levels for 5 years was associated with lower risk of incident CKD during a median follow-up of 16 years (HR, 0.75 [95% CI, 0.63–0.89]).[14]
- In the ARIC study, higher scores for HEI (HR per 1 SD, 0.94 [95% CI, 0.90–0.98]), AHEI (HR per 1 SD, 0.93 [95% CI, 0.89–0.96]), and alternative Mediterranean diet (HR per 1 SD, 0.93 [95% CI, 0.89–0.97]) were associated with a lower risk of incident CKD during a median follow-up of 24 years.[15]
- In the CRIC study, with the use of unsupervised consensus clustering, a higher rate of progression of kidney function was reported in patients with less favorable levels of bone mineral density, poor cardiac and kidney function markers, and inflammation (HR, 1.63 [95% CI, 1.27–2.09]), followed by patients with a higher prevalence of diabetes and obesity and who used more medications (HR, 1.3 [95% CI, 1.05–1.67]), compared with the referent cluster.[16]
- In a meta-analysis of 23 studies, preeclampsia was associated with increased risk of ESRD (RR, 4.90 [95% CI, 3.56–6.74]) and CKD (RR, 2.11 [95% CI, 1.72–2.59]).[17]
- In a meta-analysis of 31 studies, living kidney donation was associated with a greater decline in GFR in older donors (>60 years of age), female donors, and donors with obesity with a BMI >30 kg/m$^2$.[18,19]
- In a meta-analysis of 20 studies, lithium treatment was associated with a prevalence rate of 25.5% for impaired kidney function (eGFR <60 mL·min$^{-1}$·1.73 m$^{-2}$). In a comparison of 14 187 patients on lithium and 722 529 on nonlithium treatment, lithium treatment was associated with higher risk of subsequent CKD (eGFR <60 mL·min$^{-1}$·1.73 m$^{-2}$) with a pooled OR of 2.09 (95% CI, 1.24–3.51).[20]

## Social Determinants of CKDs/Health Equity

- According to NHANES 2015 to 2018, the prevalence of CKD was 19.5% for adults with less than a high school education, 17.2% for those with a high school degree or equivalent, and 13.1% for those with some college or more.[21]
- In the CKiD study, Black children with CKD were more likely than White children to have public insurance, lower household income, and greater food insecurity (41% versus 14%; $P<0.001$).[22]
- A meta-analysis of 43 studies reported that lower SES, particularly income, was associated with a higher prevalence of CKD (OR, 1.34 [95% CI, 1.18–1.53]; $P<0.001$) and faster progression to ESRD (RR 1.24, [95% CI, 1.12–1.37]; $P<0.001$).[23] This association was observed in higher- versus lower- or middle-income countries and was more pronounced in the United States relative to Europe.
- In the HCHS/SOL, lower language acculturation was associated with CKD among older adults (>65 years of age; OR, 1.29 [95% CI, 1.03–1.63]); however, among those with CKD, acculturation measures were not associated with hypertension or diabetes control.[24]

## Genetics/Family History

- It is estimated that ≈30% of early-onset CKD is caused by single-gene variants, and several hundred loci have been implicated in monogenic CKD.[25,26]
- GWASs in >1 million individuals revealed >260 candidate loci for CKD phenotypes, including eGFR and serum urate.[27–30] GWAS meta-analysis in individuals of European ancestry identified 424 genetic loci (201 novel loci) associated with eGFR (estimated with creatinine). Among these, 348 loci were validated in association with eGFR estimation with the use of cystatin or blood urea nitrogen.[31] A multiancestry meta-analysis of GWASs including >1 500 000 individuals for creatinine-based eGFR led to the identification of 126 novel loci.[32] Heritability analysis showed that DNA methylation variations mediated about half of the heritability of kidney disease.[32] Multiple lines of evidence established the causal role of *SLC47A1* in the development of kidney disease.[32]
- Whole-genome sequencing–based GWASs, which provided a more granular understanding of the genetic architecture, in >23 000 multiethnic populations identified 3 novel loci associated with eGFR that are more commonly observed in individuals from non-European ancestry.[33] Rare and low-frequency genetic variants are likely to be population specific, and greater inclusion of individuals of non-European ancestry in future genomic discovery efforts may aid in understanding the comprehensive genetic architecture of renal function and CKD.[33]
- Refinement in discovery and validation efforts combining multiomics data has identified 182 likely causal genes for kidney function.[34] These data may be leveraged for drug repurposing, therapeutic pathway prioritization, and identification of potential drug interactions.
- A transcriptome-wide association study combined with functional validation has identified *DACH1* as a CKD risk gene that contributes to tubular damage and kidney fibrosis.[35] Racial differences in CKD prevalence might be attributable partially to differences in ancestry and genetic risk. The *APOL1* gene has been well studied as a kidney disease locus in individuals of African ancestry.[36] Specific SNPs in *APOL1* are present in individuals of African ancestry but absent in other racial groups. This might have been subjected to positive selection, conferring protection against trypanosome infection but leading to increased risk of renal disease, potentially through disruption of mitochondrial function.[37]
- Although certain variants of *APOL1* increase risk, this explains only a portion of the racial disparity in ESRD risk.[36] For example, eGFR decline was faster even for Black adults with low-risk *APOL1* status (0 or 1 allele) than for White adults in CARDIA; this difference was attenuated by adjustment for SES and traditional risk factors.[38]
- In a large, 2-stage individual-participant data meta-analysis, *APOL1* kidney-risk variants were not associated with incident CVD or death independently of kidney measures.[39]
- Use of PRSs based on 35 blood and urine biomarkers measured in >363 000 UK Biobank participants, including renal biomarkers, was found to improve genetic risk stratification for CKD.[40] Individuals belonging to the highest 2% of the multiancestry genome-wide CKD PRS distribution had an ≈3-fold higher risk of CKD across ancestries.[41]

## Awareness, Treatment, and Control

- Despite improvements in CKD awareness from 7.2% in NHANES 2003 to 2006 to 12.1% in 2015 to 2018, the vast majority of individuals with kidney disease remain unaware of underlying kidney disease.[21]
- Treatment and control of BP among those with CKD and hypertension improved from 31.1% in 2003 to 2006 to 37.5% in 2015 to 2018.[21]
- In 2015 to 2018, 69% of those with CKD and diabetes had HbA1c <8%, and 11% of them had fasting LDL-C levels <70 mg/dL.[21]
- Among patients with CKD with hypertension, an intensive SBP treatment goal of <130 mm Hg

versus a standard goal of <140 mm Hg decreased the risk of all-cause mortality (HR, 0.79 [95% CI, 0.63–1.00]) in a pooled analysis of 4 randomized clinical trials.[42]

## Complications

- DALYs for CKD were 457.25 per 100 000 in 2002 versus 536.85 per 100 000 in 2019.[43]

## Cost

- In 2020, Medicare spent >$85.4 billion caring for people with CKD and $50.8 billion caring for people with ESRD.[1] The ESRD population accounted for ≈6.1% of total Medicare expenditures in 2020.
- In inflation-adjusted dollars, Medicare spending per person per year for beneficiaries with ESRD decreased from $96 451 in 2010 to $79 439 in 2020: $116 383 to $95 932 for hemodialysis, $89 962 to $81 525 for beneficiaries receiving peritoneal dialysis, and $42 917 to $39 264 for beneficiaries with a kidney transplantation.[1] After adjustment for inflation, total spending among Medicare fee-for-service beneficiaries with CKD decreased for the first time in 2020 with expenditures $2 billion lower than in 2019.[1]
- Total hospitalization expenditure in Medicare fee-for-service beneficiaries with ESRD was $12.1 billion in 2020.[1]

## Global Burden of Kidney Disease (See Charts 12-7 and 12-8)

- Based on 204 countries and territories in 2021:
  - The total prevalence of CKD was 676.39 (95% UI, 629.36–718.63) million people, a 27.43% (95% UI, 26.38%–28.51%) increase since 2010.
  - The age-standardized prevalence of CKD was highest in Central, Southeast, and South Asia and Eastern Europe. Prevalence was lowest in Western Europe (Chart 12-7).
  - There were 1.56 (95% UI, 1.42–1.66) million deaths attributable to CKD.
  - Central sub-Saharan Africa, central Latin America, and eastern sub-Saharan Africa had the highest age-standardized mortality rates estimated for CKD. Rates were the lowest in Eastern Europe (Chart 12-8).

## Kidney Disease and CVD

### *CKD and CVD Outcomes*

- The association of reduced eGFR with CVD risk is generally similar across age, race, and sex subgroups,[44] although albuminuria tends to be a stronger risk factor for females than for males and for older (>65 years of age) than for younger people.[45]
- The addition of eGFR or albuminuria improves CVD prediction beyond traditional risk factors used in risk equations.[45]
- In a mendelian randomization analysis of 4 population data sources (Emerging Risk Factors Collaboration, European Prospective Investigation Into Cancer and Nutrition-Cardiovascular Disease Study, Million Veteran Program, and UK Biobank), in those with eGFR 60 mL·min$^{-1}$·1.73 m$^{-2}$, each 5–mL·min$^{-1}$·1.73 m$^{-2}$ lower eGFR was associated with a 14% (95% CI, 3%–27%) higher risk of CHD.[46]
- A meta-analysis of 21 cohort studies of 27 465 individuals with CKD found that nontraditional risk factors such as serum albumin, phosphate, urate, and hemoglobin are associated with CVD risk in this population.[47] In the CRIC study of 2399 participants without a history of CVD at baseline, a composite inflammation score (interleukin-6, tumor necrosis factor-α, fibrinogen, and serum albumin) was associated with increased CVD risk (ie, MI, PAD, stroke, or death; standardized HR, 1.47 [95% CI, 1.32–1.65]).[48]
- In a secondary analysis of the STABILITY trial, elevated interleukin-6 level (≥2.0 ng/L versus <2.0 ng/L) was associated with increased risk of major atherosclerotic cardiovascular events across kidney function strata: normal kidney function (HR, 1.35 [95% CI, 1.02–1.78]), mild CKD (HR, 1.57 [95% CI, 1.35–1.83]), and moderate to severe CKD (HR, 1.60 [95% CI, 1.28–1.99]).[49]
- In a randomized clinical trial of adults with PAD, CKD was associated with increased risk of MACEs (HR, 1.45 [95% CI, 1.30–1.63]) but not major amputation (HR, 0.92 [95% CI, 0.66–1.28]).[50]
- In a post hoc analysis of patients with hypertension in SPRINT, albuminuria was associated with increased stroke risk overall (HR, 2.24 [95% CI, 1.55–3.23]), with this association being present for those in the standard BP treatment arm (HR, 2.71 [95% CI, 1.61–4.55]) but not the intensive BP treatment arm (HR, 0.93 [95% CI, 0.48–1.78]).[51]
- In Framingham Offspring Study participants without CVD, participants with even mildly reduced kidney function (eGFR, 60–69 mL·min$^{-1}$·1.73 m$^{-2}$) experienced higher incidence of CVD (HR, 1.40 [95% CI, 1.02–1.93]).[9]

### *Prevalence of CVD Among People With CKD (See Charts 12-9 through 12-12)*

- People with CKD, as well as those with ESRD, have an extremely high prevalence of comorbid CVDs, ranging from IHD and HF to arrhythmias and VTE (Charts 12-9 and 12-10).

- In 2018, CVD was present in 37.5% of patients without CKD, but a higher prevalence was noted in the CKD population. CVD was present in 63.4% of patients with stage 1 to 2 CKD, 66.6% in those with stage 3 CKD, and 75.3% in those with stage 4 to 5 CKD.[21]
- The prevalence of CVD in patients with ESRD differs by treatment modality. Approximately 77.3% of patients with ESRD on hemodialysis have any CVD, whereas 66.4% of patients on peritoneal dialysis and 54.8% of patients receiving transplantation have any CVD (Chart 12-10).
- Among 2257 community-dwelling adults with CKD (ARIC study) monitored with an ECG for 2 weeks, nonsustained VT was the most frequent major arrhythmia, occurring at a rate of 4.2 episodes per person per month.[52] Albuminuria was associated with higher prevalence of AF and percent time in AF and nonsustained VT.
- Rates of hospitalizations for cardiovascular causes were stable from 2013 to 2019 and then decreased substantially in 2020 (Chart 12-11).
- During 2018 to 2020, the 2-year adjusted survival probability after a first hospitalization for various cardiovascular conditions was lower among beneficiaries with CKD than for those without CKD and worse among those with more advanced CKD (Chart 12-12).

### *Incidence of CVD Events Among People With CKD*

- In 3 community-based cohort studies (JHS, CHS, and MESA), absolute incidence rates for HF, CHD, and stroke for participants with versus without CKD were 22 versus 6.2 (per 1000 person-years) for HF, 24.5 versus 8.4 for CHD, and 13.4 versus 4.8 for stroke.[53]
- Both eGFR and albuminuria appear to predict HF events (improvement in C statistic of 0.0258) more strongly than CHD or stroke events.[45]
- In CRIC study participants with CKD, increases in NT-proBNP (the top quartile of NT-proBNP change) were significantly associated with greater risk of incident HF (HR, 1.79 [95% CI, 1.06–3.04]) and AF (HR, 2.32 [95% CI, 1.37–3.93]), and increases in soluble ST2 (the top quartile of soluble ST2 change) were associated with HF (HR, 1.89 [95% CI, 1.13–3.16]).[54]
- In a meta-analysis of patients with CKD, the prevalence of PH was 23% and was associated with increased risk of CVD (RR, 1.67 [95% CI, 1.07–2.60]) and mortality (RR, 1.44 [95% CI, 1.17–1.76]).[55]
- Among Medicare beneficiaries with CKD, presence of PH was associated with an increased risk of mortality after 1 (HR, 2.87 [95% CI, 2.79–2.95]), 2 to 3 (HR, 1.56 [95% CI, 1.51–1.61]), and 4 to 5 (HR, 1.47 [95% CI, 1.40–1.53]) years of follow-up and a higher risk of all-cause, cardiovascular, and noncardiovascular hospitalization during the same period.
- Despite having higher overall event rates than NH White people, NH Black people with CKD have similar (or possibly lower) rates of ASCVD events (HR, 1.08 [95% CI, 0.87–1.34]), HF events (HR, 1.05 [95% CI, 0.83–1.32]), or composite of HF or death (HR, 0.96 [95% CI, 0.80–1.14] after adjustment for demographic factors, baseline kidney function, and cardiovascular risk factors.[56] However, the risk of HF associated with CKD might be greater for Black people (HR, 1.59 [95% CI, 1.29–1.95]) than for White people.[53]
- Clinically significant bradyarrhythmias (event rate, 3.90 [95% CI, 1.04–14.63] per patient-month) appear to be more common than ventricular arrhythmias (event rate, 0.00 [95% CI, 0.00–0.02] per patient-month) among patients on hemodialysis and are highest in the immediate hours before dialysis sessions.[57]
- In a prospective study of 7916 patients on hemodialysis and peritoneal dialysis, risk for ischemic stroke/systemic embolism (subdistribution HR, 0.87 [95% CI, 0.79–0.96]) and major bleeding (subdistribution HR, 0.79 [95% CI, 0.64–0.97]) was lower in those undergoing peritoneal dialysis compared with those undergoing hemodialysis.[58]
- In the German diabetes dialysis (4D) study, patients in the highest oxalate quartile had an increased risk of cardiovascular events (HR, 1.40 [95% CI, 1.08–1.81]) and SCD (HR, 1.62 [95% CI, 1.03–2.56]).[59]

### *Prevention and Treatment of CVD in People With CKD*

#### *Medication Use*

- According to NHANES data, the percentage of adults with CKD taking statins increased from 17.6% in 1999 to 2002 to 35.7% in 2011 to 2014. However, there was no difference in statin use for those with versus without CKD (RR, 1.01 [95% CI, 0.96–1.08]).[60]
- Among veterans with diabetes and CKD, the proportion receiving an ACE inhibitor/ARB was 66% (95% CI, 62%–69%) in 2013 to 2014.[61,62]
- In NHANES 1999 to 2014, 34.9% of adults with CKD used an ACE inhibitor/ARB. The use of ACE inhibitors/ARBs increased in the early 2000s among adults with CKD but plateaued subsequently.[61]
- Among Medicare beneficiaries with CKD, in 2019, 54.4% of patients with CKD were on β-blockers and 64.3% were on lipid-powering agents.[21]
- Among 22739 Medicare beneficiaries with stage 3 to 5 CKD, apixaban compared with warfarin was associated with decreased risk of stroke (HR, 0.70 [95% CI, 0.51–0.96]) and major bleeding (HR, 0.47

[95% CI, 0.37–0.59]), but these risks did not differ with the use of rivaroxaban and dabigatran.[63]

- A secondary analysis of the ASPREE clinical trial comparing 100 mg enteric-coated aspirin daily with matching placebo did not demonstrate cardiovascular benefit but showed increased risk of bleeding in those with CKD.[64]
- Low eGFR is an indication for reduced dosing of non–vitamin K antagonist oral anticoagulant drugs. Among nearly 15 000 US Air Force patients prescribed non–vitamin K antagonist oral anticoagulant drugs in an administrative database, 1473 had a renal indication for reduced dosing, and 43% of these were potentially overdosed. Potential overdosing was associated with increased risk of major bleeding (HR, 2.9 [95% CI, 1.07–4.46]).[65]
- In the Valkyrie study, among patients on hemodialysis with AF (n=132), a reduced dose of rivaroxaban significantly decreased the composite outcome of fatal and nonfatal cardiovascular events (HR, 0.41[95% CI, 0.25–0.68]).[66]
- SGLT-2 inhibitor (dapagliflozin) use reduced the risk of a composite of a sustained decline in eGFR of at least 50%, ESRD, or death attributable to renal and cardiovascular causes among those with diabetes and nondiabetic CKD.[67] These benefits were independent of the presence of concomitant CVD (HR, 0.61 [95% CI, 0.48–0.78] in the primary prevention group versus 0.61 [95% CI, 0.47–0.79] in the secondary prevention group).
- Similarly, another trial examining another SGLT-2 inhibitor (empagliflozin) enrolled both individuals with CKD with diabetes and those with CKD without diabetes (n=6609) and reported a 28% reduction (HR, 0.72 [95% CI, 0.64–0.82]) in the progression of kidney disease or death resulting from cardiovascular causes compared with placebo.[68]
- In an individual patient-level meta-analysis of 6 trials including 49 875 participants that studied 4 different SGLT-2 inhibitors, there was a 16% reduced risk of serious hyperkalemia (HR, 0.84 [95% CI, 0.76–0.93]).[69]
- In an RCT of 7437 individuals with stage 3 to 4 CKD and type 2 diabetes, a novel mineralocorticoid receptor antagonist (finerenone) reduced the incidence of composite outcome of death resulting from cardiovascular causes, nonfatal MI, nonfatal stroke, or hospitalization for HF (HR, 0.87 [95% CI, 076–0.98]).[70]
- In a secondary analysis of the FIDELIO-DKD trial enrolling patients with CKD and type 2 diabetes, finerenone use was associated with lower incidence of new-onset AF (HR, 0.71 [95% CI, 0.53–0.94]).[71]
- In a systematic review of clinical trials of interventions to attenuate vascular calcification in people with CKD, magnesium and sodium thiosulfate consistently showed attenuation of vascular calcification. Studies examining intestinal phosphate binders, alterations in dialysate calcium concentration, vitamin K therapy, calcimimetics, and antiresorptive agents had conflicting or inconclusive outcomes. On the other hand, trials involving vitamin D therapy and HMG-CoA reductase inhibitors did not demonstrate attenuation of vascular calcification.[72]

### *Cardiovascular Procedures in CKD*

- In a study of 17 910 patients undergoing angiography for stable IHD in Alberta, Canada, those with ESRD (OR, 0.52 [95% CI, 0.35–0.79]) or mild to moderate CKD (OR, 0.80 [95% CI, 0.71–0.89]) were less likely to be revascularized for angiographically significant (>70%) coronary stenoses compared with those without CKD.[73]
- Among patients who underwent TAVR in the PARTNER trial, CKD stage either improved or was unchanged after the procedure.[74]
- In intermediate-risk patients with aortic stenosis and CKD, SAPIEN 3 TAVR and SAVR were associated with similar risk of reaching the composite primary outcome of death, stroke, rehospitalization, and new hemodialysis after a 5-year follow-up.[75]
- Among patients who underwent lower-extremity bypass surgery in the USRDS 2006 to 2011, females with ESRD were less likely than males with ESRD to receive an autogenous vein graft (55% versus 61%; $P<0.001$). Among those who received a prosthetic graft, acute graft failure was higher for females (HR, 1.23 [95% CI, 1.03–1.46]).[76]
- In a pooled analysis of patients with stable IHD, diabetes, and CKD from 3 clinical trials, CABG plus optimal medical therapy was associated with lower risk of subsequent revascularization (HR, 0.25 [95% CI, 0.15–0.41]) and MACEs (HR, 0.77 [95% CI, 0.55–1.06]) compared with PCI plus optimal medical therapy.[77]
- A randomized clinical trial comparing an initial invasive strategy (coronary angiography and revascularization added to medical therapy) with an initial conservative strategy (medical therapy alone and angiography if medical therapy fails) among those with advanced kidney disease (eGFR <30 $mL{\cdot}min^{-1}{\cdot}1.73\ m^{-2}$ or receiving dialysis) and moderate or severe myocardial ischemia reported similar rates of death or nonfatal MI (estimated 3-year event rate, 36.4% versus 36.7%; aHR, 1.01 [95% CI, 0.79–1.29]).[78]

## Lifestyle Interventions

- In a pooled analysis of data from the ARIC, MESA, and CHS studies, healthy lifestyle behaviors (no smoking, moderate to vigorous PA, no alcohol intake, adherence to healthy diet using diet score,

and BMI <30 kg/m$^2$) were associated with lower all-cause mortality, major coronary events, ischemic stroke, and HF.[79]
- A randomized clinical trial enrolling 160 patients with stage 3 or 4 CKD noted that both $Vo_2$peak and METs increased significantly in the lifestyle intervention group by 9.7% and 30%, respectively, without change in the usual care group during a 3-year lifestyle intervention program.[80]

## Cardiovascular Hospitalization and Mortality Attributable to CVD Among People With CKD (See Chart 12-13)

- CVD is a leading cause of death for people with CKD. Mortality risk depends not only on eGFR but also on the category of albuminuria. The aRR of all-cause mortality and cardiovascular mortality is highest in those with eGFR of 15 to 30 mL·min$^{-1}$·1.73 m$^{-2}$ and those with ACR >300 mg/g.
- Data from CARES and the Centers for Medicare & Medicaid Services dialysis facility database indicate that dialysis staff initiated CPR in 81.4% of events and applied defibrillators before EMS arrival in 52.3%. Staff-initiated CPR was associated with a 3-fold increase in the odds of hospital discharge and better neurological status at the time of discharge.[81]
- Data from the prospective CRIC study demonstrated that the crude rate of HF admissions was 5.8 per 100 person-years among those with CKD. The rates of both HF hospitalizations and rehospitalization were even higher across categories of lower eGFR and higher urine ACR (Chart 12-13).[82]
- Elevated levels of the alternative glomerular filtration marker cystatin C have been associated with increased risk for CVD and all-cause mortality in studies from a broad range of cohorts.
  - Cystatin C levels predicted ASCVD (HR, 1.21 [95% CI, 1.08–1.36]), HF (HR, 1.43 [95% CI, 1.22–1.67]), all-cause mortality (HR, 1.23 [95% CI, 1.13–1.34]), and cardiovascular death (HR, 1.55 [95% CI, 1.29–1.87]) in the FHS after accounting for clinical cardiovascular risk factors.[83]
  - The stronger associations observed with outcomes (relative to creatinine or creatinine-based eGFR) might be explained in part by non–glomerular filtration rate determinants of cystatin C such as chronic inflammation.[84]

## Footnote

A portion of the data reported here have been supplied by the USRDS.[1] The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the US government.

| eGFR Categories | A1: Normal to mildly increased (ACR <30 mg/g) | A2: Moderately increased (ACR 30-299 mg/g) | A3: Severely increased (ACR ≥300 mg/g) | Total |
|---|---|---|---|---|
| G1: Normal or high (eGFR ≥90ml/min/1.73m²) | 59.8 | 5.0 | 0.68 | 65.5 |
| G2: Mildly decreased (eGFR 60-89 ml/min/1.73m²) | 26.2 | 2.4 | 0.35 | 28.9 |
| G3a: Mildly to moderately decreased (eGFR 45-59 ml/min/1.73m²) | 3.1 | 0.79 | 0.12 | 4.0 |
| G3b: Moderately to severely decreased (eGFR 30-44 ml/min/1.73m²) | 0.61 | 0.32 | 0.18 | 1.1 |
| G4: Severely decreased (eGFR 15-29 ml/min/1.73m²) | 0.07 | 0.08 | 0.18 | 0.34 |
| G5: Kidney failure (eGFR <15 ml/min/1.73m²) | 0.00 | 0.02 | 0.13 | 0.15 |
| Total | 89.8 | 8.6 | 1.6 | 100 |

**Chart 12-1. Percentage of NHANES participants within the KDIGO CKD risk categories defined by eGFR and ACR, United States, 2017 to 2020.**
Green indicates low risk; yellow, moderately high risk; orange, high risk; and red, very high risk.
ACR indicates urinary albumin-to-creatinine ratio; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; and NHANES, National Health and Nutrition Examination Survey.
Source: Reprinted from 2022 United States Renal Data System Annual Data Report, volume 1, Table 1.1, [1] using NHANES.[85]

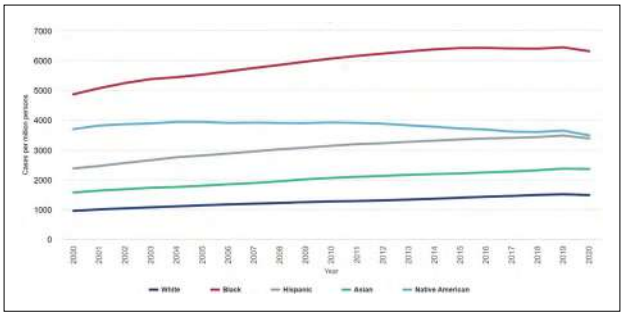



**Chart 12-2. ESRD prevalence, by racial group, United States, 2000 to 2020.**
Prevalence estimates are presented as cases per million people and are adjusted for age, sex, and ethnicity.
ESRD indicates end-stage renal disease.
Source: Reprinted from 2022 United States Renal Data System Annual Data Report, volume 2, Figure 1.8.[1]

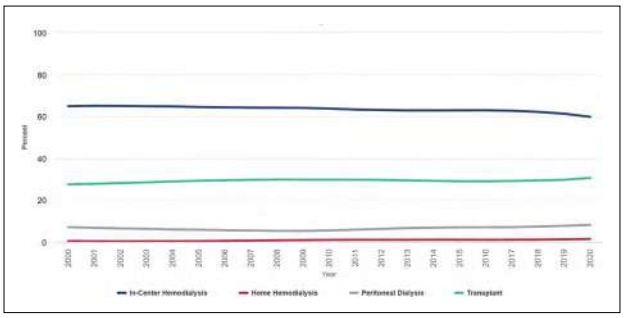


**Chart 12-3. Prevalent ESRD, by modality, United States, 2000 to 2020.**
ESRD indicates end-stage renal disease.
Source: Reprinted from 2022 United States Renal Data System Annual Data Report, volume 2, Figure 1.6.[1]

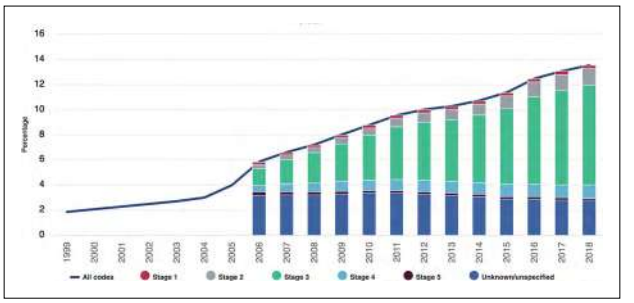


**Chart 12-5. Prevalence of CKD, overall and by CKD category, among Medicare beneficiaries ≥66 years of age, United States, 1999 to 2018.**
CKD indicates chronic kidney disease.
Source: Reprinted from 2020 United States Renal Data System Annual Data Report, volume 1, Figure 2.1.[21]

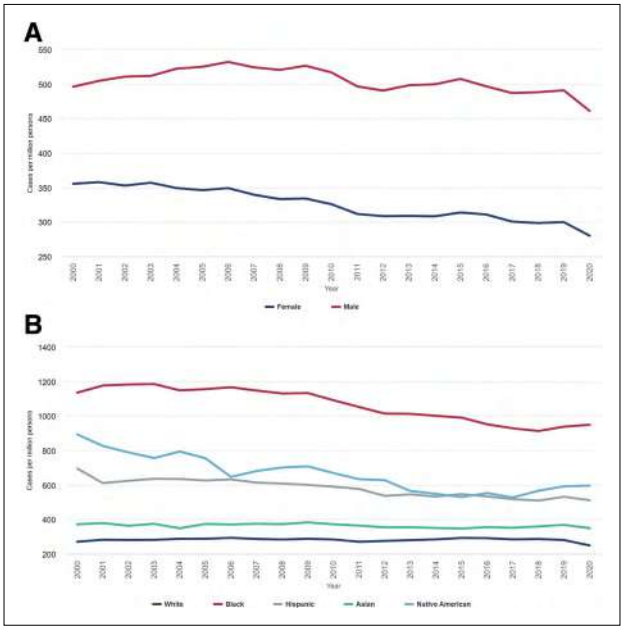


**Chart 12-4. ESRD incidence, by sex, United States, 2000 to 2020.**
**A**, Incidence by sex. **B**, Incidence by race and ethnicity. Incidence estimates are presented as cases per million people and are adjusted for age, sex, race, and ethnicity.
ESRD indicates end-stage renal disease.
Source: Reprinted from 2022 United States Renal Data System Annual Data Report, volume 2, Figure 1.4.[1]

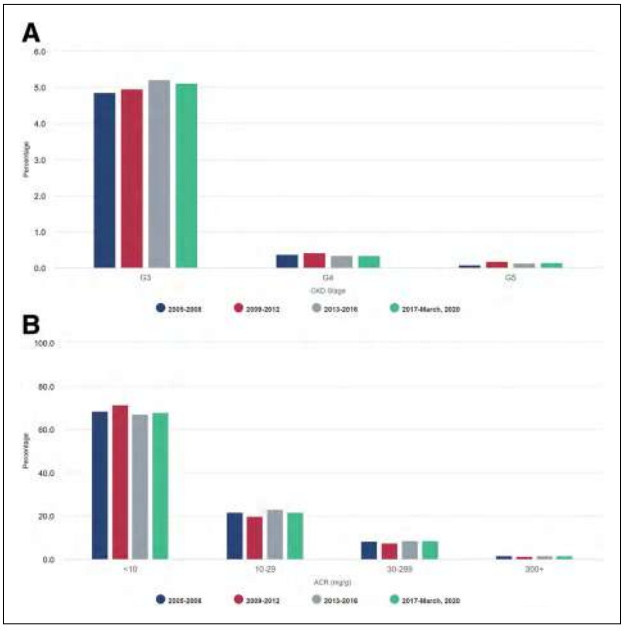


**Chart 12-6. Prevalence of reduced eGFR by stage, United States, 2005 to 2020.**
**A**, Prevalence of eGFR by stage. **B**, Prevalence of ACR by category. eGFR stages 1 through 5. Adjusted for age, sex, and race; single-sample calibrated estimates of ACR; eGFR calculated with the Chronic Kidney Disease Epidemiology Collaboration equation.
ACR indicates albumin-to-creatinine ration; CKD, chronic kidney disease; and eGFR, glomerular filtration rate.
Source: Reprinted from 2022 United States Renal Data System Annual Data Report, volume 1, Figures 1.2 and 1.3,[1] using National Health and Nutrition Examination Survey.[85]

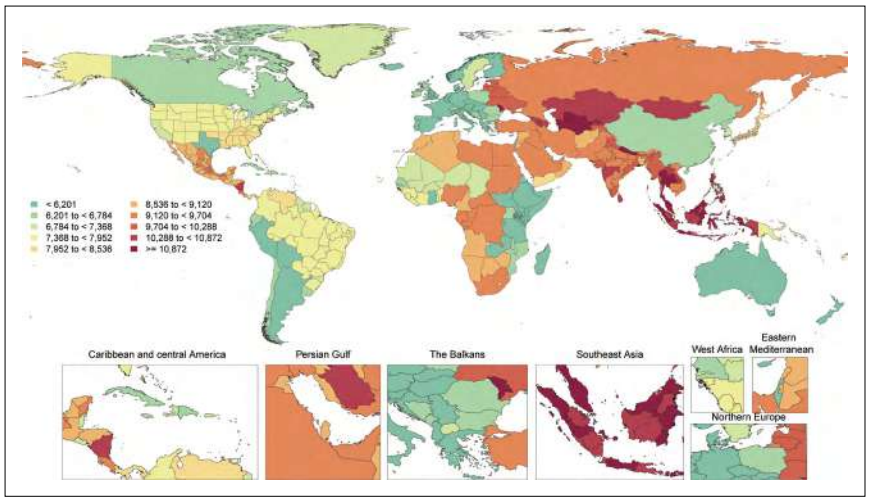



**Chart 12-7. Age-standardized global prevalence rates for CKD per 100 000, both sexes, 2021.**
During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.
CKD indicates chronic kidney disease; and GBD, Global Burden of Disease.
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[43]

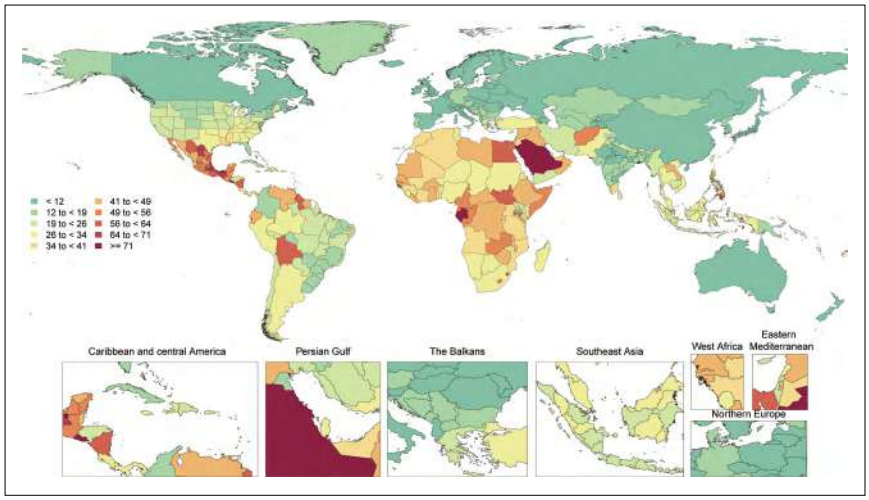



**Chart 12-8. Age-standardized global mortality rates for CKD per 100 000, both sexes, 2021.**
During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.
CKD indicates chronic kidney disease; and GBD, Global Burden of Disease.
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[43]

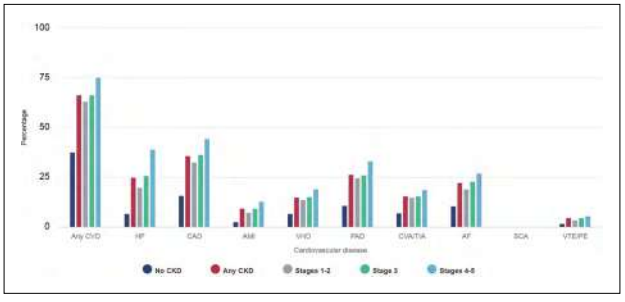



**Chart 12-9. Adjusted prevalence of common CVDs in Medicare beneficiaries ≥66 years of age, by CKD status and stage, United States, 2018.**
Special analyses, Medicare 5% sample.
AF indicates atrial fibrillation; AMI, acute myocardial infarction; CAD, coronary artery disease; CKD, chronic kidney disease; CVA, cerebrovascular accident; CVD, cardiovascular disease; HF, heart failure; PAD, peripheral artery disease; PE, pulmonary embolism; SCA, sudden cardiac arrest; TIA, transient ischemic attack; VHD, valvular heart disease; and VTE, venous thromboembolism.
Source: Reprinted from 2020 United States Renal Data System Annual Data Report, volume 1, Figure 4.2.[21]

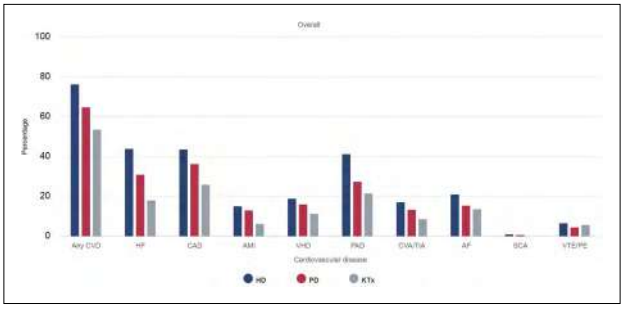



**Chart 12-10. Unadjusted prevalence of common CVDs in adult patients with ESRD, by treatment modality, United States, 2018.**
AF indicates atrial fibrillation; AMI, acute myocardial infarction; CAD, coronary artery disease; CVA, cerebrovascular accident; CVD, cardiovascular disease; ESRD, end-stage renal disease; HD, hemodialysis; HF, heart failure; KTx, kidney transplant recipients; PAD, peripheral artery disease; PD, peritoneal dialysis; PE, pulmonary embolism; SCA, sudden cardiac arrest; TIA, transient ischemic attack; VHD, valvular heart disease; and VTE, venous thromboembolism.
Source: Reprinted from 2020 United States Renal Data System Annual Data Report, volume 2, Figure 8.1.[21]

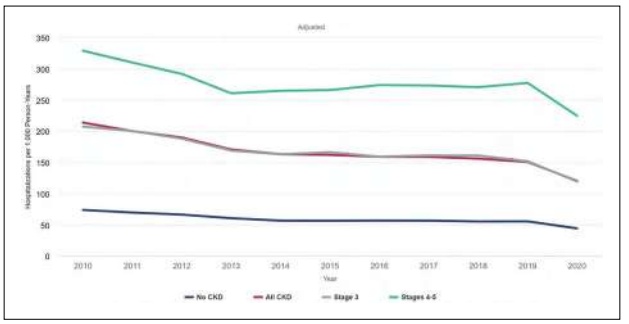



**Chart 12-11. Rate of hospitalization for CVD in older US adults, 2010 to 2020.**
CKD indicates chronic kidney disease; and CVD, cardiovascular disease.
Source: Reprinted from 2022 United States Renal Data System Annual Data Report, volume 2, Figure 3.9.[1]

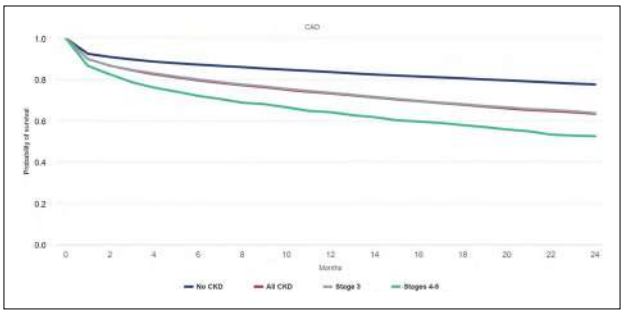



**Chart 12-12. Survival probability in older US adults after hospital admission for a CVD, by CKD status and stage, 2018 to 2020.**
Older adults: ≥66 years of age.
CAD indicates coronary artery disease; CKD, chronic kidney disease; and CVD, cardiovascular disease.
Source: Reprinted from 2022 United States Renal Data System Annual Data Report, volume 2, Figure 3.10.[1]

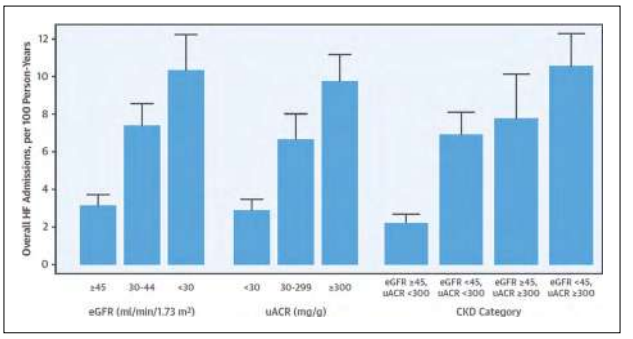



**Chart 12-13. US HF hospitalization rates among those with CKD based on eGFR and albuminuria.**
Unadjusted rates of HF admissions across by level of kidney function among participants with CKD.
CKD indicates chronic kidney disease; eGFR, estimated glomerular filtration rate; HF, heart failure; and uACR, urine albumin-to-creatinine ratio.
Source: Reprinted from Bansal et al,[82] Central Illustration, with permission from the American College of Cardiology Foundation. Copyright © 2019 American College of Cardiology Foundation.

## REFERENCES


1. United States Renal Data System, National Institutes of Health and Institute of Diabetes and Digestive and Kidney Diseases. 2022 USRDS annual data report: epidemiology of kidney disease in the United States. 2022. Accessed March 15, 2023. https://usrds-adr.niddk.nih.gov/2022
2. Grubbs V. Precision in GFR reporting: let's stop playing the race card. *Clin J Am Soc Nephrol.* 2020;15:1201–1202. doi: 10.2215/CJN.00690120
3. Mohottige D, Diamantidis CJ, Norris KC, Boulware LE. Time to repair the effects of racism on kidney health inequity. *Am J Kidney Dis.* 2021;77:951–962. doi: 10.1053/j.ajkd.2021.01.010
4. Levey AS, Titan SM, Powe NR, Coresh J, Inker LA. Kidney disease, race, and GFR estimation. *Clin J Am Soc Nephrol.* 2020;15:1203–1212. doi: 10.2215/CJN.12791019
5. Delgado C, Baweja M, Crews DC, Eneanya ND, Gadegbeku CA, Inker LA, Mendu ML, Miller WG, Moxey-Mims MM, Roberts GV, et al. A unifying approach for GFR estimation: recommendations of the NKF-ASN Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Disease. *J Am Soc Nephrol.* 2021;32:2994–3015. doi: 10.1681/asn.2021070988
6. Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y, Crews DC, Doria A, Estrella MM, Froissart M, et al; Chronic Kidney Disease Epidemiology Collaboration. New creatinine- and cystatin C-based equations to estimate GFR without race. *N Engl J Med.* 2021;385:1737–1749. doi: 10.1056/NEJMoa2102953
7. Levey AS, de Jong PE, Coresh J, El Nahas M, Astor BC, Matsushita K, Gansevoort RT, Kasiske BL, Eckardt KU. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. *Kidney Int.* 2011;80:17–28. doi: 10.1038/ki.2010.483
8. Levey AS, Eckardt KU, Dorman NM, Christiansen SL, Hoorn EJ, Ingelfinger JR, Inker LA, Levin A, Mehrotra R, Palevsky PM, et al. Nomenclature for kidney function and disease: report of a Kidney Disease: Improving Global Outcomes (KDIGO) Consensus Conference. *Kidney Int.* 2020;97:1117–1129. doi: 10.1016/j.kint.2020.02.010
9. Ataklte F, Song RJ, Upadhyay A, Musa Yola I, Vasan RS, Xanthakis V. Association of mildly reduced kidney function with cardiovascular disease: the Framingham Heart Study. *J Am Heart Assoc.* 2021;10:e020301. doi: 10.1161/JAHA.120.020301
10. Centers for Disease Control and Prevention. Chronic Kidney Disease Surveillance System–United States. Accessed October 23, 2023. https://nccd.cdc.gov/ckd/detail.aspx?Qnum=Q636&Strat=Year%2c+Age#refreshPosition
11. Johansen KL, Chertow GM, Gilbertson DT, Ishani A, Israni A, Ku E, Li S, Li S, Liu J, Obrador GT, et al. US Renal Data System 2022 annual data report: epidemiology of kidney disease in the United States. *Am J Kidney Dis.* 2023;81:A8–A11. doi: 10.1053/j.ajkd.2022.12.001
12. Chang AR, Grams ME, Ballew SH, Bilo H, Correa A, Evans M, Gutierrez OM, Hosseinpanah F, Iseki K, Kenealy T, et al; CKD Prognosis Consortium (CKD-PC). Adiposity and risk of decline in glomerular filtration rate: meta-analysis of individual participant data in a global consortium. *BMJ.* 2019;364:k5301. doi: 10.1136/bmj.k5301
13. Ishigami J, Cowan LT, Demmer RT, Grams ME, Lutsey PL, Carrero JJ, Coresh J, Matsushita K. Incident hospitalization with major cardiovascular diseases and subsequent risk of ESKD: implications for cardiorenal syndrome. *J Am Soc Nephrol.* 2020;31:405–414. doi: 10.1681/ASN.2019060574
14. Corlin L, Short MI, Vasan RS, Xanthakis V. Association of the duration of ideal cardiovascular health through adulthood with cardiometabolic

outcomes and mortality in the Framingham Offspring Study. *JAMA Cardiol*. 2020;5:549–556. doi: 10.1001/jamacardio.2020.0109
15. Hu EA, Steffen LM, Grams ME, Crews DC, Coresh J, Appel LJ, Rebholz CM. Dietary patterns and risk of incident chronic kidney disease: the Atherosclerosis Risk in Communities study. *Am J Clin Nutr*. 2019;110:713–721. doi: 10.1093/ajcn/nqz146
16. Zheng Z, Waikar SS, Schmidt IM, Landis JR, Hsu CY, Shafi T, Feldman HI, Anderson AH, Wilson FP, Chen J, et al; CRIC Study Investigators. Subtyping CKD patients by consensus clustering: the Chronic Renal Insufficiency Cohort (CRIC) Study. *J Am Soc Nephrol*. 2021;32:639–653. doi: 10.1681/ASN.2020030239
17. Barrett PM, McCarthy FP, Kublickiene K, Cormican S, Judge C, Evans M, Kublickas M, Perry IJ, Stenvinkel P, Khashan AS. Adverse pregnancy outcomes and long-term maternal kidney disease: a systematic review and meta-analysis. *JAMA Netw Open*. 2020;3:e1920964. doi: 10.1001/jamanetworkopen.2019.20964
18. Bellini MI, Nozdrin M, Pengel L, Knight S, Papalois V. Risks for donors associated with living kidney donation: meta-analysis. *Br J Surg*. 2022;109:671–678. doi: 10.1093/bjs/znac114
19. Hirano K, Komatsu Y, Shimbo T, Nakata H, Kobayashi D. Longitudinal relationship between long sleep duration and future kidney function decline. *Clin Kidney J*. 2022;15:1763–1769. doi: 10.1093/ckj/sfac107
20. Schoretsanitis G, de Filippis R, Brady BM, Homan P, Suppes T, Kane JM. Prevalence of impaired kidney function in patients with long-term lithium treatment: a systematic review and meta-analysis. *Bipolar Disord*. 2022;24:264–274. doi: 10.1111/bdi.13154
21. United States Renal Data System and National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. 2020 United States Renal Data System (USRDS) annual data report: epidemiology of kidney disease in the United States. 2020. Accessed March 15, 2023. https://adr.usrds.org/2020
22. Sgambat K, Roem J, Brady TM, Flynn JT, Mitsnefes M, Samuels JA, Warady BA, Furth SL, Moudgil A. Social determinants of cardiovascular health in African American children with CKD: an analysis of the Chronic Kidney Disease in Children (CKiD) study. *Am J Kidney Dis*. 2021;78:66–74. doi: 10.1053/j.ajkd.2020.11.013
23. Zeng X, Liu J, Tao S, Hong HG, Li Y, Fu P. Associations between socioeconomic status and chronic kidney disease: a meta-analysis. *J Epidemiol Community Health*. 2018;72:270–279. doi: 10.1136/jech-2017-209815
24. Lora CM, Ricardo AC, Chen J, Cai J, Flessner M, Moncrieft A, Peralta C, Raij L, Rosas SE, Talavera GA, et al. Acculturation and chronic kidney disease in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). *Prev Med Rep*. 2018;10:285–291. doi: 10.1016/j.pmedr.2018.04.001
25. Connaughton DM, Kennedy C, Shril S, Mann N, Murray SL, Williams PA, Conlon E, Nakayama M, van der Ven AT, Ityel H, et al. Monogenic causes of chronic kidney disease in adults. *Kidney Int*. 2019;95:914–928. doi: 10.1016/j.kint.2018.10.031
26. Mann N, Braun DA, Amann K, Tan W, Shril S, Connaughton DM, Nakayama M, Schneider R, Kitzler TM, van der Ven AT, et al. Whole-exome sequencing enables a precision medicine approach for kidney transplant recipients. *J Am Soc Nephrol*. 2019;30:201–215. doi: 10.1681/ASN.2018060575
27. Schmitz B, Kleber ME, Lenders M, Delgado GE, Engelbertz C, Huang J, Pavenstadt H, Breithardt G, Brand SM, Marz W, et al. Genome-wide association study suggests impact of chromosome 10 rs139401390 on kidney function in patients with coronary artery disease. *Sci Rep*. 2019;9:2750. doi: 10.1038/s41598-019-39055-y
28. Graham SE, Nielsen JB, Zawistowski M, Zhou W, Fritsche LG, Gabrielsen ME, Skogholt AH, Surakka I, Hornsby WE, Fermin D, et al. Sex-specific and pleiotropic effects underlying kidney function identified from GWAS meta-analysis. *Nat Commun*. 2019;10:1847. doi: 10.1038/s41467-019-09861-z
29. Wuttke M, Li Y, Li M, Sieber KB, Feitosa MF, Gorski M, Tin A, Wang L, Chu AY, Hoppmann A, et al. A catalog of genetic loci associated with kidney function from analyses of a million individuals. *Nat Genet*. 2019;51:957–972. doi: 10.1038/s41588-019-0407-x
30. Tin A, Marten J, Halperin Kuhns VL, Li Y, Wuttke M, Kirsten H, Sieber KB, Qiu C, Gorski M, Yu Z, et al; German Chronic Kidney Disease Study. Target genes, variants, tissues and transcriptional pathways influencing human serum urate levels. *Nat Genet*. 2019;51:1459–1474. doi: 10.1038/s41588-019-0504-x
31. Stanzick KJ, Li Y, Schlosser P, Gorski M, Wuttke M, Thomas LF, Rasheed H, Rowan BX, Graham SE, Vanderweff BR, et al; VA Million Veteran Program. Discovery and prioritization of variants and genes for kidney function in >1.2 million individuals. *Nat Commun*. 2021;12:4350. doi: 10.1038/s41467-021-24491-0
32. Liu H, Doke T, Guo D, Sheng X, Ma Z, Park J, Vy HMT, Nadkarni GN, Abedini A, Miao Z, et al. Epigenomic and transcriptomic analyses define core cell types, genes and targetable mechanisms for kidney disease. *Nat Genet*. 2022;54:950–962. doi: 10.1038/s41588-022-01097-w
33. Lin BM, Grinde KE, Brody JA, Breeze CE, Raffield LM, Mychaleckyj JC, Thornton TA, Perry JA, Baier LJ, de Las Fuentes L, et al; NHLBI Trans-Omics for Precision Medicine TOPMed Consortium, TOPMed Kidney Working Group. Whole genome sequence analyses of eGFR in 23,732 people representing multiple ancestries in the NHLBI Trans-Omics for Precision Medicine (TOPMed) Consortium. *EBioMedicine*. 2021;63:103157. doi: 10.1016/j.ebiom.2020.103157
34. Sheng X, Guan Y, Ma Z, Wu J, Liu H, Qiu C, Vitale S, Miao Z, Seasock MJ, Palmer M, et al. Mapping the genetic architecture of human traits to cell types in the kidney identifies mechanisms of disease and potential treatments. *Nat Genet*. 2021;53:1322–1333. doi: 10.1038/s41588-021-00909-9
35. Doke T, Huang S, Qiu C, Liu H, Guan Y, Hu H, Ma Z, Wu J, Miao Z, Sheng X, et al. Transcriptome-wide association analysis identifies *DACH1* as a kidney disease risk gene that contributes to fibrosis. *J Clin Invest*. 2021;131:e141801. doi: 10.1172/JCI141801
36. Grams ME, Rebholz CM, Chen Y, Rawlings AM, Estrella MM, Selvin E, Appel LJ, Tin A, Coresh J. Race, *APOL1* risk, and eGFR decline in the general population. *J Am Soc Nephrol*. 2016;27:2842–2850. doi: 10.1681/ASN.2015070763
37. Ma L, Chou JW, Snipes JA, Bharadwaj MS, Craddock AL, Cheng D, Weckerle A, Petrovic S, Hicks PJ, Hemal AK, et al. *APOL1* renal-risk variants induce mitochondrial dysfunction. *J Am Soc Nephrol*. 2017;28:1093–1105. doi: 10.1681/ASN.2016050567
38. Peralta CA, Bibbins-Domingo K, Vittinghoff E, Lin F, Fornage M, Kopp JB, Winkler CA. *APOL1* genotype and race differences in incident albuminuria and renal function decline. *J Am Soc Nephrol*. 2016;27:887–893. doi: 10.1681/ASN.2015020124
39. Grams ME, Surapaneni A, Ballew SH, Appel LJ, Boerwinkle E, Boulware LE, Chen TK, Coresh J, Cushman M, Divers J, et al. *APOL1* kidney risk variants and cardiovascular disease: an individual participant data meta-analysis. *J Am Soc Nephrol*. 2019;30:2027–2036. doi: 10.1681/ASN.2019030240
40. Sinnott-Armstrong N, Tanigawa Y, Amar D, Mars N, Benner C, Aguirre M, Venkataraman GR, Wainberg M, Ollila HM, Kiiskinen T, et al. Genetics of 35 blood and urine biomarkers in the UK Biobank. *Nat Genet*. 2021;53:185–194. doi: 10.1038/s41588-020-00757-z
41. Khan A, Turchin MC, Patki A, Srinivasasainagendra V, Shang N, Nadukuru R, Jones AC, Malolepsza E, Dikilitas O, Kullo IJ, et al. Genome-wide polygenic score to predict chronic kidney disease across ancestries. *Nat Med*. 2022;28:1412–1420. doi: 10.1038/s41591-022-01869-1
42. Aggarwal R, Petrie B, Bala W, Chiu N. Mortality outcomes with intensive blood pressure targets in chronic kidney disease patients. *Hypertension*. 2019;73:1275–1282. doi: 10.1161/HYPERTENSIONAHA.119.12697
43. Global Burden of Disease Study and Institute for Health Metrics and Evaluation. University of Washington. Accessed August 2, 2023. http://ghdx.healthdata.org/
44. Gregg LP, Hedayati SS. Management of traditional cardiovascular risk factors in CKD: what are the data? *Am J Kidney Dis*. 2018;72:728–744. doi: 10.1053/j.ajkd.2017.12.007
45. Matsushita K, Coresh J, Sang Y, Chalmers J, Fox C, Guallar E, Jafar T, Jassal SK, Landman GW, Muntner P, et al; CKD Prognosis Consortium. Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data. *Lancet Diabetes Endocrinol*. 2015;3:514–525. doi: 10.1016/S2213-8587(15)00040-6
46. Gaziano L, Sun L, Arnold M, Bell S, Cho K, Kaptoge SK, Song RJ, Burgess S, Posner DC, Mosconi K, et al; Emerging Risk Factors Collaboration/EPIC-CVD/Million Veteran Program. Mild-to-moderate kidney dysfunction and cardiovascular disease: observational and mendelian randomization analyses. *Circulation*. 2022;146:1507–1517. doi: 10.1161/CIRCULATIONAHA.122.060700
47. Major RW, Cheng MRI, Grant RA, Shantikumar S, Xu G, Oozeerally I, Brunskill NJ, Gray LJ. Cardiovascular disease risk factors in chronic kidney disease: a systematic review and meta-analysis. *PLoS One*. 2018;13:e0192895. doi: 10.1371/journal.pone.0192895
48. Amdur RL, Feldman HI, Dominic EA, Anderson AH, Beddhu S, Rahman M, Wolf M, Reilly M, Ojo A, Townsend RR, et al; CRIC Study Investigators. Use of measures of inflammation and kidney function for prediction of atherosclerotic vascular disease events and death in

patients with CKD: findings from the CRIC study. *Am J Kidney Dis*. 2019;73:344–353. doi: 10.1053/j.ajkd.2018.09.012
49. Batra G, Ghukasyan Lakic T, Lindback J, Held C, White HD, Stewart RAH, Koenig W, Cannon CP, Budaj A, Hagstrom E, et al; STABILITY Investigators. Interleukin 6 and cardiovascular outcomes in patients with chronic kidney disease and chronic coronary syndrome. *JAMA Cardiol*. 2021;6:1440–1445. doi: 10.1001/jamacardio.2021.3079
50. Hopley CW, Kavanagh S, Patel MR, Ostrom C, Baumgartner I, Berger JS, Blomster JI, Fowkes FGR, Jones WS, Katona BG, et al. Chronic kidney disease and risk for cardiovascular and limb outcomes in patients with symptomatic peripheral artery disease: the EUCLID trial. *Vasc Med*. 2019;24:422–430. doi: 10.1177/1358863X19864172
51. Leitao L, Soares-Dos-Reis R, Neves JS, Baptista RB, Bigotte Vieira M, Mc Causland FR. Intensive blood pressure treatment reduced stroke risk in patients with albuminuria in the SPRINT trial. *Stroke*. 2019;50:3639–3642. doi: 10.1161/STROKEAHA.119.026316
52. Kim ED, Soliman EZ, Coresh J, Matsushita K, Chen LY. Two-week burden of arrhythmias across CKD severity in a large community-based cohort: the ARIC study. *J Am Soc Nephrol*. 2021;32:629–638. doi: 10.1681/ASN.2020030301
53. Bansal N, Katz R, Robinson-Cohen C, Odden MC, Dalrymple L, Shlipak MG, Sarnak MJ, Siscovick DS, Zelnick L, Psaty BM, et al. Absolute rates of heart failure, coronary heart disease, and stroke in chronic kidney disease: an analysis of 3 community-based cohort studies. *JAMA Cardiol*. 2017;2:314–318. doi: 10.1001/jamacardio.2016.4652
54. Bansal N, Zelnick LR, Soliman EZ, Anderson A, Christenson R, DeFilippi C, Deo R, Feldman HI, He J, Ky B, et al; CRIC Study Investigators. Change in cardiac biomarkers and risk of incident heart failure and atrial fibrillation in CKD: the Chronic Renal Insufficiency Cohort (CRIC) study. *Am J Kidney Dis*. 2021;77:907–919. doi: 10.1053/j.ajkd.2020.09.021
55. Tang M, Batty JA, Lin C, Fan X, Chan KE, Kalim S. Pulmonary hypertension, mortality, and cardiovascular disease in CKD and ESRD patients: a systematic review and meta-analysis. *Am J Kidney Dis*. 2018;72:75–83. doi: 10.1053/j.ajkd.2017.11.018
56. Lash JP, Ricardo AC, Roy J, Deo R, Fischer M, Flack J, He J, Keane M, Lora C, Ojo A, et al; CRIC Study Investigators. Race/ethnicity and cardiovascular outcomes in adults with CKD: findings from the CRIC (Chronic Renal Insufficiency Cohort) and Hispanic CRIC studies. *Am J Kidney Dis*. 2016;68:545–553. doi: 10.1053/j.ajkd.2016.03.429
57. Roy-Chaudhury P, Tumlin JA, Koplan BA, Costea AI, Kher V, Williamson D, Pokhariyal S, Charytan DM; MiD Investigators and Committees. Primary outcomes of the Monitoring in Dialysis Study indicate that clinically significant arrhythmias are common in hemodialysis patients and related to dialytic cycle. *Kidney Int*. 2018;93:941–951. doi: 10.1016/j.kint.2017.11.019
58. Chang CH, Fan PC, Lin YS, Chen SW, Wu M, Lin MS, Lu CH, Chang PC, Hsieh MJ, Wang CY, et al. Dialysis mode and associated outcomes in patients with end-stage renal disease and atrial fibrillation: a 14-year nationwide cohort study. *J Am Heart Assoc*. 2021;10:e019596. doi: 10.1161/JAHA.120.019596
59. Pfau A, Ermer T, Coca SG, Tio MC, Genser B, Reichel M, Finkelstein FO, Marz W, Wanner C, Waikar SS, et al. High oxalate concentrations correlate with increased risk for sudden cardiac death in dialysis patients. *J Am Soc Nephrol*. 2021;32:2375–2385. doi: 10.1681/ASN.2020121793
60. Mefford MT, Rosenson RS, Deng L, Tanner RM, Bittner V, Safford MM, Coll B, Mues KE, Monda KL, Muntner P. Trends in statin use among US adults with chronic kidney disease, 1999-2014. *J Am Heart Assoc*. 2019;8:e010640. doi: 10.1161/JAHA.118.010640
61. Murphy DP, Drawz PE, Foley RN. Trends in angiotensin-converting enzyme inhibitor and angiotensin ii receptor blocker use among those with impaired kidney function in the United States. *J Am Soc Nephrol*. 2019;30:1314–1321. doi: 10.1681/ASN.2018100971
62. Navaneethan SD, Akeroyd JM, Ramsey D, Ahmed ST, Mishra SR, Petersen LA, Muntner P, Ballantyne C, Winkelmayer WC, Ramanathan V, et al. Facility-level variations in kidney disease care among veterans with diabetes and CKD. *Clin J Am Soc Nephrol*. 2018;13:1842–1850. doi: 10.2215/CJN.03830318
63. Wetmore JB, Roetker NS, Yan H, Reyes JL, Herzog CA. Direct-acting oral anticoagulants versus warfarin in Medicare patients with chronic kidney disease and atrial fibrillation. *Stroke*. 2020;51:2364–2373. doi: 10.1161/STROKEAHA.120.028934
64. Wolfe R, Wetmore JB, Woods RL, McNeil JJ, Gallagher H, Roderick P, Walker R, Nelson MR, Reid CM, Shah RC, et al. Subgroup analysis of the ASPirin in Reducing Events in the Elderly randomized clinical trial suggests aspirin did not improve outcomes in older adults with chronic kidney disease. *Kidney Int*. 2021;99:466–474. doi: 10.1016/j.kint.2020.08.011
65. Yao X, Shah ND, Sangaralingham LR, Gersh BJ, Noseworthy PA. Non-vitamin K antagonist oral anticoagulant dosing in patients with atrial fibrillation and renal dysfunction. *J Am Coll Cardiol*. 2017;69:2779–2790. doi: 10.1016/j.jacc.2017.03.600
66. De Vriese AS, Caluwe R, Van Der Meersch H, De Boeck K, De Bacquer D. Safety and efficacy of vitamin K antagonists versus rivaroxaban in hemodialysis patients with atrial fibrillation: a multicenter randomized controlled trial. *J Am Soc Nephrol*. 2021;32:1474–1483. doi: 10.1681/ASN.2020111566
67. McMurray JJV, Wheeler DC, Stefansson BV, Jongs N, Postmus D, Correa-Rotter R, Chertow GM, Greene T, Held C, Hou FF, et al; DAPA-CKD Trial Committees and Investigators. Effect of dapagliflozin on clinical outcomes in patients with chronic kidney disease, with and without cardiovascular disease. *Circulation*. 2021;143:438–448. doi: 10.1161/CIRCULATIONAHA.120.051675
68. Herrington WG, Staplin N, Wanner C, Green JB, Hauske SJ, Emberson JR, Preiss D, Judge P, Mayne KJ, Ng SYA, et al; EMPA-KIDNEY Collaborative Group. Empagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2023;388:117–127. doi: 10.1056/NEJMoa2204233
69. Neuen BL, Oshima M, Agarwal R, Arnott C, Cherney DZ, Edwards R, Langkilde AM, Mahaffey KW, McGuire DK, Neal B, et al. Sodium-glucose cotransporter 2 inhibitors and risk of hyperkalemia in people with type 2 diabetes: a meta-analysis of individual participant data from randomized, controlled trials. *Circulation*. 2022;145:1460–1470. doi: 10.1161/CIRCULATIONAHA.121.057736
70. Pitt B, Filippatos G, Agarwal R, Anker SD, Bakris GL, Rossing P, Joseph A, Kolkhof P, Nowack C, Schloemer P, et al; FIGARO-DKD Investigators. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. *N Engl J Med*. 2021;385:2252–2263. doi: 10.1056/NEJMoa2110956
71. Filippatos G, Bakris GL, Pitt B, Agarwal R, Rossing P, Ruilope LM, Butler J, Lam CSP, Kolkhof P, Roberts L, et al; FIDELIO-DKD Investigators. Finerenone reduces new-onset atrial fibrillation in patients with chronic kidney disease and type 2 diabetes. *J Am Coll Cardiol*. 2021;78:142–152. doi: 10.1016/j.jacc.2021.04.079
72. Xu C, Smith ER, Tiong MK, Ruderman I, Toussaint ND. Interventions to attenuate vascular calcification progression in chronic kidney disease: a systematic review of clinical trials. *J Am Soc Nephrol*. 2022;33:1011–1032. doi: 10.1681/ASN.2021101327
73. Shavadia JS, Southern DA, James MT, Welsh RC, Bainey KR. Kidney function modifies the selection of treatment strategies and long-term survival in stable ischaemic heart disease: insights from the Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH) registry. *Eur Heart J Qual Care Clin Outcomes*. 2018;4:274–282. doi: 10.1093/ehjqcco/qcx042
74. Cubeddu RJ, Asher CR, Lowry AM, Blackstone EH, Kapadia SR, Alu MC, Thourani VH, Mack MJ, Kodali SK, Herrmann HC, et al; PARTNER Trial Investigators. Impact of transcatheter aortic valve replacement on severity of chronic kidney disease. *J Am Coll Cardiol*. 2020;76:1410–1421. doi: 10.1016/j.jacc.2020.07.048
75. Garcia S, Cubeddu RJ, Hahn RT, Ternacle J, Kapadia SR, Kodali SK, Thourani VH, Jaber WA, Asher CR, Elmariah S, et al. 5-Year outcomes comparing surgical versus transcatheter aortic valve replacement in patients with chronic kidney disease. *JACC Cardiovasc Interv*. 2021;14:1995–2005. doi: 10.1016/j.jcin.2021.07.004
76. Arhuidese I, Kernodle A, Nejim B, Locham S, Hicks C, Malas MB. Sex-based outcomes of lower extremity bypass surgery in hemodialysis patients. *J Vasc Surg*. 2018;68:153–160. doi: 10.1016/j.jvs.2017.10.063
77. Farkouh ME, Sidhu MS, Brooks MM, Vlachos H, Boden WE, Frye RL, Hartigan P, Siami FS, Bittner VA, Chaitman BR, et al. Impact of chronic kidney disease on outcomes of myocardial revascularization in patients with diabetes. *J Am Coll Cardiol*. 2019;73:400–411. doi: 10.1016/j.jacc.2018.11.044
78. Bangalore S, Maron DJ, O'Brien SM, Fleg JL, Kretov EI, Briguori C, Kaul U, Reynolds HR, Mazurek T, Sidhu MS, et al; ISCHEMIA-CKD Research Group. Management of coronary disease in patients with advanced kidney disease. *N Engl J Med*. 2020;382:1608–1618. doi: 10.1056/NEJMoa1915925
79. Schrauben SJ, Hsu JY, Amaral S, Anderson AH, Feldman HI, Dember LM. Effect of kidney function on relationships between lifestyle behaviors and mortality or cardiovascular outcomes: a pooled cohort analysis. *J Am Soc Nephrol*. 2021;32:663–675. doi: 10.1681/ASN.2020040394

80. Beetham KS, Krishnasamy R, Stanton T, Sacre JW, Douglas B, Isbel NM, Coombes JS, Howden EJ. Effect of a 3-year lifestyle intervention in patients with chronic kidney disease: a randomized clinical trial. *J Am Soc Nephrol*. 2022;33:431–441. doi: 10.1681/ASN.2021050668
81. Pun PH, Dupre ME, Starks MA, Tyson C, Vellano K, Svetkey LP, Hansen S, Frizzelle BG, McNally B, Jollis JG, et al. Outcomes for hemodialysis patients given cardiopulmonary resuscitation for cardiac arrest at outpatient dialysis clinics. *J Am Soc Nephrol*. 2019;30:461–470. doi: 10.1681/asn.2018090911
82. Bansal N, Zelnick L, Bhat Z, Dobre M, He J, Lash J, Jaar B, Mehta R, Raj D, Rincon-Choles H, et al; CRIC Study Investigators. Burden and outcomes of heart failure hospitalizations in adults with chronic kidney disease. *J Am Coll Cardiol*. 2019;73:2691–2700. doi: 10.1016/j.jacc.2019.02.071
83. Ho JE, Lyass A, Courchesne P, Chen G, Liu C, Yin X, Hwang SJ, Massaro JM, Larson MG, Levy D. Protein biomarkers of cardiovascular disease and mortality in the community. *J Am Heart Assoc*. 2018;7:e008108. doi: 10.1161/JAHA.117.008108
84. Schei J, Stefansson VT, Mathisen UD, Eriksen BO, Solbu MD, Jenssen TG, Melsom T. Residual associations of inflammatory markers with eGFR after accounting for measured GFR in a community-based cohort without CKD. *Clin J Am Soc Nephrol*. 2016;11:280–286. doi: 10.2215/CJN.07360715
85. Centers for Disease Control and Prevention and National Center for Health Statistics. National Health and Nutrition Examination Survey (NHANES) public use data files. Accessed April 1, 2023. https://cdc.gov/nchs/nhanes/

# 13. SLEEP

*See Charts 13-1 through 13-4*

Click here to return to the Table of Contents

Click here to return to the Abbreviations

In 2022, the AHA has added sleep duration as an eighth metric of cardiometabolic health to Life's Simple 7, which became elevated to Life's Essential 8.[1] Sleep can be characterized in many different ways, including quantity (sleep duration), quality, or the presence of a sleep disorder (eg, insomnia or OSA). Sleep health is a construct that includes various parameters related to regularity, satisfaction, alertness, timing, efficiency, and duration of sleep that has been associated with lower risk of adverse emotional, cognitive, social, and physical outcomes.[2] Sleep quality is frequently assessed with the Pittsburgh Sleep Quality Index, for which a score >5 is considered poor sleep quality.[3] The composite score of sleep health is assessed with a 7-day sleep diary and questionnaire and defined by 6 components: (1) regularity (midpoint of sleep deviating by ≤1 hour), (2) satisfaction (rating fair or very good to question related to satisfaction with sleep), (3) alertness (score ≤7.5 on a sleepiness scale), (4) timing (average midpoint of sleep between 2 and 4 AM), (5) efficiency (average ≥85%), and (6) duration (average total sleep duration within recommendations for age group).[2]

The American Academy of Sleep Medicine and the Sleep Research Society recommend that adults obtain ≥7 hours of sleep per night to promote optimal health.[4] Sleeping >9 hours may be appropriate for some individuals (eg, younger individuals or ill adults), but for others, it is unclear whether this much sleep is associated with health benefits or health risks. The American Academy of Sleep Medicine also published guidelines for pediatric populations: Infants 4 to 12 months of age should sleep 12 to 16 h/d; children 1 to 2 years of age should sleep 11 to 14 h/d; children 3 to 5 years of age should sleep 10 to 13 h/d; children 6 to 12 years of age should sleep 9 to 12 h/d; and adolescents 13 to 18 years of age should sleep 8 to 10 h/d.[5] Unless otherwise noted, throughout this chapter, short sleep refers to <7 hours of sleep per night for adults and less than the minimum recommended for age for children; long sleep refers to >9 h/night for adults and more than the upper range of recommended duration for children.

SDB represents upper airway dysfunction and is characterized by snoring or increased resistance to airflow with or without partial or total occlusion of the airways. SDB encompasses loud snoring, OSA, and central apneas. OSA is the most common type of SDB and is categorized by the frequency of complete and incomplete occlusion of airways during sleep (apneas and hypopneas, respectively) that results in reduced oxygen saturation and arousals or awakenings at night. The AHI is calculated as the number of breathing interruptions per hour of sleep. OSA is characterized as mild (AHI 5–<15 events per hour), moderate (AHI 15–30 events per hour), and severe (AHI >30 events per hour) and diagnosed with overnight polysomnography or home sleep test. Insomnia is characterized by 3 symptoms assessed by questionnaire: difficulty initiating sleep, difficulty maintaining sleep, and early morning awakening. Adults with insomnia report dissatisfaction with their sleep, feeling unrefreshed on awakening, and experiencing sleep difficulties despite having adequate opportunity for sleep. Acute insomnia may occur over a short period of time and resolve on its own. In chronic insomnia, symptoms occur at least 3 times/wk and persist for ≥3 months. It is important to note that insomnia may or may not be accompanied by short sleep duration.

## Prevalence

## (See Charts 13-1 through 13-3)

- Data from NHANES 2017 to 2020, completed before the COVID-19 pandemic, showed that adults ≥20 years of age had shorter sleep duration on workdays (7.6 hours [95% CI, 7.5–7.6]) compared with free days (8.2 hours [95% CI, 8.2–8.3]).[6] Overall, 23.1% (95% CI, 21.3%–24.9%) of adults had short sleep on workdays compared with 12.9% (95% CI, 11.6%–14.1%) on free days, and 19.7% (95% CI, 18.5%–21.0%) of adults had long sleep on workdays compared with 38.5% (95% CI, 36.7%–40.3%) on free days. Females reported 7.7 hours of sleep (95% CI, 7.7–7.8) on workdays and 8.4 hours (95% CI, 8.3–8.5) on free days compared with 7.4 hours (95% CI, 7.4–7.5) and 8.1 hours (95% CI, 8.0–8.2) of sleep for males on workdays and free days, respectively. Sleep debt, the difference between sleep duration on workdays and free days, was 0.73 hours (95% CI, 0.68–0.77). On average, 30.5% of adults had ≥1-hour sleep debt (95% CI, 26.8%–33.3%) and 9.75% had ≥2 hours sleep debt (high sleep debt; 95% CI, 8.65%–10.8%). Prevalence of high sleep debt was greater in

The 2024 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2024. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

younger adults, NH Black adults, full-time workers, and regular shift workers.

- Analysis of BRFSS 2020 data indicates that the proportion of adults reporting insufficient sleep (<7 hours) was 32.8% (females, 32.2%; males, 33.4%). The prevalence of reporting insufficient sleep was lowest among older adults (>65 years of age) with 27.3% of females and 24.7% of males in this older age group reporting <7 hours of sleep per night (Chart 13-1).[7]
- The prevalence of insufficient sleep differs by disability status. According to BRFSS 2016 data, 43.8% of adults with at least 1 disability reported insufficient sleep compared with 31.6% of adults with no disability. Having an increasing number of disabilities was associated with a higher likelihood of reporting insufficient sleep compared with having no disability in the fully adjusted model: adjusted PR, 1.20 (95% CI, 1.17–1.23) for 1 type, 1.34 (95% CI, 1.30–1.38) for 2 types, 1.41 (95% CI, 1.35–1.47) for 3 types, and 1.55 (95% CI, 1.49–1.62) for ≥4 types. The functional disability types included serious difficulty in hearing, vision, cognition, or mobility or any difficulty in self-care and independent living.[8]
- The NHIS 2020 asked respondents, "During the past 30 days, how often did you wake up feeling well rested?" Results indicated that 43.7% responded never or some of the days, with females reporting this more frequently than males (46.9% versus 40.4%; unpublished tabulation using NHIS[7]; Chart 13-2).
- In adulthood, insomnia symptoms were least frequent in adults 26 to 40 years of age and most frequent in adults >65 years of age. The prevalence of insomnia symptoms was 1.5 to 2.9 times more frequent in the United States across all adults >25 years of age compared with those in the Netherlands. Females had higher odds of reporting difficulty initiating sleep (OR, 2.26 [95% CI, 2.16–2.36]), difficulty maintaining sleep (OR, 2.05 [95% CI, 1.91–2.19]), and early morning awakening (OR, 1.49 [95% CI, 1.37–1.62]) than males after adjustment for demographics.[9]
- The NHIS 2020 asked respondents, "During the past 30 days, how often did you have trouble falling asleep?" and "During the past 30 days, how often did you have trouble staying asleep?" Results showed that 32.1% responded never, 43.6% responded some of the days, and 24.3% responded most or all days to either one of those questions. Females more often reported having any sleep problem on most or all days than males (27.8% versus 20.6%; unpublished tabulation using NHIS[7]; Chart 13-3).
- Data from NHANES 2017 to 2020 showed that trouble sleeping was more prevalent in older adults, females, NH White adults, and unemployed individuals.[6] Daytime sleepiness was more prevalent among younger adults, females, NH White adults, people who were unemployed, and people with lower income.

## Children/Adolescents

- According to parental report in the 2020 to 2021 National Survey of Children's Health, 34.4% of children 4 months to 17 years of age slept less than recommended for their age. Prevalence of short sleep duration was 36.8% (95% CI, 35.5%–38.1%) in infants and children 4 months to 5 years of age, 35.2% (95% CI, 33.9%–36.5%) for children 6 to 11 years of age, and 31.6% (95% CI, 30.4%–32.8%) for adolescents 12 to 17 years of age.[10]
- In a meta-analysis of population studies in the Netherlands, insomnia symptoms were higher from childhood into adolescence: 4% of children 3 to 5 years of age reported difficulty initiating sleep and 6% reported difficulty maintaining sleep compared with 13% and 9%, respectively, for children 6 to 13 years of age. Sex differences in insomnia symptoms become evident at puberty and remain throughout adulthood.[9]

### *Adults: Young, Middle-Aged, and Old*

- Older adults, but not middle-aged adults, are less likely to report short sleep than younger adults. The RR of reporting short sleep in adults ≥65 years of age, relative to those 20 to 44 years of age, in NHANES 2005 to 2016 was 0.81 (95% CI, 0.75–0.87).[11] In middle-aged adults 45 to 64 years of age, the RR was 1.02 (95% CI, 0.97–1.08). Middle-aged adults had lower risk of reporting long sleep (RR, 0.80 [95% CI, 0.71–0.90]), whereas older adults had greater risk of reporting long sleep (RR, 1.41 [95% CI, 1.25–1.59]).

## Risk Factors

- Data from the Canadian Health Measures Survey 2009 to 2011 and 2012 to 2013 revealed higher odds of short sleep for non-White versus White preschoolers (OR, 1.94 [95% CI, 1.03–3.65]) and preschoolers who lived in lower-income-adequacy households (OR, 2.59 [95% CI, 1.12–5.65]).[12] Non-White children (OR, 2.08 [95% CI, 1.42–3.04]), children living in a single-parent household (OR, 1.76 [95% CI, 1.07–2.91]), and children exposed to secondhand smoke at home (OR, 2.54 [95% CI, 1.25–5.16]) had higher odds of short sleep. Male children with learning disability/attention-deficit hyperactivity disorder and who engaged in more screen time–based sedentary behavior had higher odds of short sleep. Chronic stress in adults 18 to 64 years of age (OR, 1.63 [95% CI, 1.14–2.33]) and

>65 years of age (OR, 1.95 [95% CI, 1.01–3.87]) was associated with higher odds of short sleep. In adults 18 to 64 years of age, other predictors of short sleep included the presence of arthritis (OR, 1.53 [95% CI, 1.08–2.16]), non-White ethnicity (OR, 1.41 [95% CI, 1.11–1.79]), and having poor or fair self-perceived mental health (OR, 1.82 [95% CI, 1.22–2.75]). Among adults >65 years of age, arthritis (OR, 1.42 [95% CI, 1.01–1.98]) and having less than secondary school education (OR, 1.83 [95% CI, 1.22–2.75]) were associated with higher odds of short sleep. Among adults 18 to 64 years of age, being female (OR, 0.76 [95% CI, 0.59–0.98]), and among adults ≥65 years of age, being unemployed (OR, 0.46 [95% CI, 0.22–0.96]) or employed part-time (OR, 0.40 [95% CI, 0.18–0.87]) were associated with lower odds of short sleep.

- According to NHANES data from 2017 to 2020, the odds of reporting trouble sleeping were higher in adults 40 to 59 years of age (OR, 1.62 [95% CI, 1.37–1.92]) and 60 to 74 years of age (OR, 1.44 [95% CI, 1.21–1.71]) compared with adults 20 to 39 years of age.[6] Males had lower odds than females (OR, 0.80 [95% CI, 0.68–0.93]). Hispanic and NH Black adults had lower odds than NH White adults (Hispanic adults: OR, 0.64 [95% CI, 0.50–0.81]; NH Black adults: OR, 0.64 [95% CI, 0.53–0.76]).
- Data from the MESA showed that greater AHI score was associated with obesity (+19 events/h per 11 kg/m$^2$), male sex (+13 events/h versus female), older age (+7 events/h per 20 years of age), and Chinese ancestry (+5 events/h versus White, adjusted for obesity).[13]
- Data from the Canadian Community Health Survey 2002 and 2012 cycles were used to assess predictors of trouble sleeping.[14] Being female was associated with higher odds of an increase in trouble sleeping between cycles (OR, 1.14 [95% CI, 1.08–1.22]). Having a secondary school degree (OR, 1.13 [95% CI, 1.01–1.27]), some postsecondary school education (OR, 1.22 [95% CI, 1.01–1.47]), and a postsecondary degree (OR, 1.08 [95% CI, 1.01–1.16]) were associated with higher odds of increased trouble sleeping. Those reporting very good physical health (OR, 1.17 [95% CI, 1.06–1.28]) and good (OR, 1.09 [95% CI, 1.01–1.19]) or fair/poor (OR, 1.23 [95% CI, 1.09–1.38]) mental health also had higher odds of increased trouble sleeping.
- NHANES data from 2005 to 2014 in 22 471 adults showed that the prevalence of sleep disorders increased from 7.5% in 2005 to 2006 to 10.4% in 2013 to 2014. Having a higher HEI score, indicative of a higher diet quality, was associated with reduced risk of reporting a sleep disorder (optimal HEI score versus inadequate: aOR, 0.913 [95% CI, 0.912–0.915]). Higher intakes of greens and beans, total vegetables, and total protein foods and lower intakes of added sugars and saturated fats were the top 5 most important components, accounting for 85% of the weights for sleep disorders.[15]
- In MESA, participants with a high alternative Mediterranean diet score were less likely to report insomnia symptoms (OR, 0.81 [95% CI, 0.62–0.98]) after adjustment for sociodemographic variables.[16] In a community cohort of females, higher Mediterranean diet score was associated with better sleep quality (β, −0.31 [SE, 0.08]), better sleep efficiency (β, −0.31 [SE, 0.08]), and fewer sleep disturbances (β, −0.31 [SE, 0.08]) on the Pittsburgh Sleep Quality Index after 1 year.[17]

## Social Determinants/Health Equity

### *Race and Ethnicity and Sleep*

***(See Chart 13-4)***

- According to parental report in the 2020 to 2021 National Survey of Children's Health, among children 4 months to 17 years of age, 38.1% (95% CI, 36.2%–40.1%) of Hispanic children and 51.2% (95% CI, 49.1%–53.4%) of NH Black children slept less than recommended for their age compared with 28.4% (95% CI, 27.6%–29.1%) of NH White children.[10]
- In 2014, the prevalence of healthy sleep duration was lower among Native Hawaiian/Pacific Islander people (52.5%), NH Black people (50.4%), and NH multiracial people (49.6%) compared with White people (62.6%). There was no difference between White people and Hispanic people (61.1%) and Asian people (64.2%). All racial and ethnic groups other than Asian people were more likely to report short sleep than White people (RR for Native Hawaiian/Pacific Islander people, 1.61 [95% CI, 1.40–1.85]; Black people, 1.64 [95% CI, 1.48–1.82]; Hispanic people, 1.11 [95% CI, 1.00–1.23]; and NH multiracial people, 1.73 [95% CI, 1.18–2.55]). Long sleep was more likely in Black people than White people (RR reduction, 1.21 [95% CI, 1.02–1.43]) and less likely in Asian people than White people (RR reduction, 0.72 [95% CI, 0.55–0.94]).[18]
- In BRFSS 2020, NH Black adults had the highest percentage of respondents reporting sleeping <7 h/night (43.5%), whereas NH Asian (30.5%) and NH White (30.7%) adults had the lowest percentage of respondents reporting sleeping <7 hours (Chart 13-4).
- In the NHIS 2020, Asian adults reported the lowest prevalence of never being well rested or being well rested some of the time (36.1% versus 43.9%–47.0% for other racial and ethnic groups). White and

NH American Indian/Alaska Native adults reported the lowest prevalence of never having difficulty falling asleep or maintaining sleep (27.8% and 30.2%, respectively, versus 37.4%–32.3% for other racial and ethnic groups).

- In a sample of Black adults from the JHS, average sleep duration was 6.7±1.1 hours, 61.5% had short sleep duration, and the prevalence of moderate to severe OSA (AHI ≥15 events per hour) was 23.6%.[19] In this sample, participants who expressed increasing everyday discrimination between examinations 1 and 3 (spanning 2000–2004 and 2008–2013) had worsening sleep quality (β, –0.13 [SE, 0.06]) compared with those with stable low discrimination.[20] There was no association with self-reported sleep duration.

### *Other Social Determinants of Sleep*

- In the combined BRFSS 2014 and 2016 surveys, bisexual males had higher rates of very short (≤4 h/night; 6.5% versus 4.0%) and long (≥9 h/night; 10.4% versus 6.5%) sleep durations compared with heterosexual males. Lesbian and bisexual females had higher rates of very short (6.8% and 7.6%, respectively) and short (5–6 h/night; 36.5% and 37.1%, respectively) sleep durations compared with heterosexual females (very short sleep, 3.7%; short sleep, 30.5%). Among males, gay Black people (OR, 6.07 [95% CI, 2.34–15.73]) and gay Latino people (OR, 4.61 [95% CI, 1.54–13.76]) had higher adjusted odds of very short sleep compared with gay White people. Asian and Pacific Islander gay people had lower odds of very short (OR, 0.14 [95% CI, 0.02–0.93]) and long (OR, 0.16 [95% CI, 0.03–0.74]) sleep but higher odds of short sleep (OR, 3.04 [95% CI, 1.25–7.41]) compared with gay White people.[21]
- Among Native Hawaiian and Pacific Islander adults from the NHIS, low neighborhood social cohesion was associated with increased odds of short sleep duration (OR, 1.53 [95% CI, 1.10–2.13]). Neighborhood social cohesion was not associated with trouble falling or staying asleep or with feeling well rested.[22]
- In a cross-sectional survey of 3284 adults, sleep health was better with successively higher age groups. In all age groups, higher frequency of fast food consumption (young $r$=–0.135; middle-aged $r$=–0.126; older $r$=–0.135), daily minutes of television watching (young $r$=–0.132; middle-aged $r$=–0.171; older $r$=–0.129), social media use (young $r$=–0.131; middle-aged $r$=–0.196; older $r$=–0.163), internet use (young $r$=–0.152; middle-aged $r$=–0.233; older $r$=–0.093]), and lower regularity of lifestyle behaviors (young $r$=–0.320; middle-aged $r$=–0.340; older $r$=–0.283) were correlated with lower sleep health. In young adults 18 to 34 years of age, number of pets ($r$=–0.063) and daily reading minutes ($r$=–0.066) were also inversely related to sleep health, whereas in middle-aged adults 35 to 54 years of age, higher daily minutes of reading ($r$=–0.111) and lower moderate to vigorous PA ($r$=0.075) were associated with poorer sleep health. In older adults ≥55 years of age, less time in moderate to vigorous PA ($r$=0.090) and higher percent of sedentary time ($r$=–0.102) were associated with poorer sleep health.[23]

## Family History and Genetics

- Heritability estimates for sleep disorders, including OSA, are ≈40%.[24]
- A UK Biobank study (N=85 670) using accelerometer-derived measures of sleep and rest-activity patterns identified 47 loci across 8 sleep traits encompassing sleep duration, quality, and timing.[25] Ten novel variants for sleep duration and 26 novel variants for sleep quality that were not detected in much larger studies of self-reported sleep traits were identified, including a missense variant (p.Tyr727Cys) in *PDE11A*. The cumulative variance explained by these loci ranged from 0.04% for sleep midpoint timing to 0.8% for number of nocturnal sleep episodes. These cumulative variance–explained estimates are considerably smaller than the expected proportion of phenotypic variance explained by commonly occurring SNPs, which ranged from 2.8% (variation in sleep duration) to 22.3% (number of nocturnal sleep episodes).
- Several variants have been found to be associated with self-reported chronotype, insomnia, and sleep duration in >446 000 participants in the UK Biobank, including *PAX8*, *VRK2*, and *FBXL12/UBL5/PIN1*, with evidence for shared genetics between insomnia and cardiometabolic traits.[26]
- A GWAS of self-reported daytime napping in the UK Biobank (N=452 633) and the 23andMe research cohort (N=541 333) identified 61 replicated loci, including missense variants in established drug targets for sleep disorders (*HCRTR1*, *HCRTR2*). Many of the loci colocalized with loci for other sleep phenotypes and cardiometabolic outcomes. For example, mendelian randomization suggested a causal link between more frequent daytime napping and higher BP and WC.[27]
- A GWAS of rapid-eye movement sleep behavioral disorder, a more severe sleep subtype, identified 5 loci at or near *SNCA*, *GBA*, *TMEM175*, *INPP5F*, and *SCARB2* in 2 case-control GWASs (n cases=2843, n controls=139 636).[28] Colocalization analyses to examine whether lead variants at these 5 loci also are associated with brain or whole-blood gene

expression found strong evidence of colocalization in the *SNCA* locus with *SNCA* antisense-1 expression in the brain.

- Genetic factors may influence sleep either directly by controlling sleep disorders or indirectly through modulation of risk factors such as obesity. In a study of >120 000 individuals, gene-sleep interactions were identified for some lipid loci, including *LPL* and *PCSK9*, and 4.25% of the variance in triglycerides could be explained from gene–short sleep interactions.[29]
- Data from 404 044 participants in the UK Biobank were used to derive a GRS for sleep duration. Mendelian randomization analyses showed increased odds of CVD with genetically predicted short sleep duration ≤6 hours: PE (OR, 1.30 [95% CI, 1.11–1.53]), arterial hypertension (OR, 1.15 [95% CI, 1.09–1.20]), AF (OR, 1.13 [95% CI, 1.03–1.24]), chronic IHD (OR, 1.15 [95% CI, 1.06–1.25]), CAD (OR, 1.24 [95% CI, 1.12–1.37]), and MI (OR, 1.21 [95% CI, 1.09–1.34]). There was no association with genetically predicted long sleep duration ≥9 hours.[30]
- Data from the FinnGen study (217 955 individuals) estimated the heritability of OSA at 0.08 (95% CI, 0.06–0.11) and identified 5 loci associated with OSA located near *GAPVD1*, *RMST/NEDD1*, *CXCR4*, *CAMK1D*, and *FTO*. Genetic correlations were found between OSA and BMI ($r_g$=0.72 [95% CI, 0.62–0.83]), hypertension ($r_g$=0.35 [95% CI, 0.23–0.48]), type 2 diabetes ($r_g$=0.52 [95% CI, 0.37–0.66]), CHD ($r_g$=0.38 [95% CI, 0.17–0.58]), and stroke ($r_g$=0.33 [95% CI, 0.03–0.63]).[31]
- The genetic architecture of sleep shares commonalities with several psychiatric disorders and plasma proteins. In the UK Biobank, significant genetic correlations were noted between a sleep health score composed of measures of sleep duration, snoring, insomnia, chronotype, and daytime dozing with 4 psychiatric disorders (major depressive disorder, attention deficit/hyperactivity disorder, schizophrenia, and autism spectrum disorder) and 9 plasma proteins, including cytochrome c oxidase.[32] Elevated cytochrome c oxidase levels were associated with long-term sleep deprivation in rats.[33]

## Awareness, Treatment, and Control

- A retrospective chart review of 75 pediatric patients (7–17 years of age) referred to a sleep clinic for snoring compared 6-month change in BP between 3 groups (25 patients in each): snorers without OSA (AHI <1 event per hour), with OSA but no treatment (AHI >1 event per hour), and with OSA with CPAP treatment. SBP was higher at baseline in the 2 OSA groups ($P$<0.05) but decreased in the CPAP-treated group over 6 months (median change, −5 mm Hg [25th–75th percentile, −19 to 0 mm Hg]), whereas SBP increased in the untreated OSA group (median change, 4 mm Hg [25th–75th percentile, 0–10 mm Hg]). DBP did not differ between groups at baseline, nor did the 6-month change in DBP differ between groups.[34]
- A meta-analysis of 7 RCTs examining patients with moderate to severe OSA randomized to either CPAP therapy or control for a mean follow-up of 37 months did not reveal any reduction in the risk of major cardiovascular events (RR, 0.74 [95% CI, 0.47–1.17]). All-cause mortality (RR, 0.95 [95% CI, 0.53–1.73]), MI (RR, 0.99 [95% CI, 0.57–1.72]), stroke (RR, 0.95 [95% CI, 0.72–1.24]), cardiovascular mortality (RR, 0.70 [95% CI, 0.27–1.80]), and noncardiovascular mortality (RR, 1.53 [95% CI, 0.61–3.82]) were not influenced by CPAP treatment. However, in sensitivity analyses using prespecified CPAP adherence of ≥4 h/night for the SAVE trial, CPAP treatment reduced the risk of major cardiovascular events (RR, 0.70 [95% CI, 0.50–0.98]) and stroke (RR, 0.56 [95% CI, 0.37–0.84]).[35]

## Mortality

- A community-based prospective cohort study examined associations between sleep duration trajectories between 2006 and 2010 and mortality through 2017 in adults free of CVD and cancer.[36] Compared with those with normal stable sleep (defined as sleep duration 7–8 h/night for 4 years), risk of all-cause mortality was increased in those with normal-decreasing (HR, 1.34 [95% CI, 1.15–1.57]) and those with low-stable (HR, 1.50 [95% CI, 1.07–2.10]) sleep patterns.
- Data from the Southern Community Cohort Study revealed racial differences in associations between sleep duration and mortality in a predominantly low-income US population.[37] Sleeping <5 h/night versus 8 h/night was associated with increased all-cause mortality in NH White individuals (weekday: HR, 1.23 [95% CI, 1.04–1.46]; weekend: HR, 1.26 [95% CI, 1.06–1.51]) but not Black individuals (weekday: HR, 1.08 [95% CI, 0.97–1.20]; weekend: HR, 1.11 [95% CI, 1.00–1.24]). Similar findings were observed for long sleep. For NH White individuals but not Black individuals, sleeping ≥10 h/night versus 8 h/night was associated with higher risk of all-cause mortality (White individuals, weekday: HR, 1.23 [95% CI, 1.02–1.48]; weekend: HR, 1.25 [95% CI, 1.08–1.46]; Black individuals, weekday: HR, 1.14 [95% CI, 1.04–1.25]; weekend: HR, 1.08 [95% CI, 1.00–1.16]).
- A meta-analysis of 137 prospective cohort studies with a total of 5 134 036 participants found that

long sleep duration (cutoff varied by study, ranging between >6.5 and ≥10 h/night) was associated with increased mortality risk (RR, 1.39 [95% CI, 1.31–1.47]).[38]

- The Japan Multi-Institutional Collaborative Cohort assessed sleep regularity using a single question, "Are your bedtimes and wake times regular?"[39] In adults 35 to 69 years of age, having irregular sleep increased the risk of all-cause mortality compared to regular sleep (HR, 1.30 [95% CI, 1.18–1.44]). Data were significant in adults <60 years of age (HR, 1.36 [95% CI, 1.14–1.55]) and ≥60 years of age (HR, 1.15 [95% CI, 1.00–1.31]) and in males (HR, 1.31 [95% CI, 1.16–1.48]) but not females (HR, 1.06 [95% CI, 0.89–1.27]).
- In the Sleep Heart Health Study, middle-aged to older adults were followed up for 11.8 years (IQR, 10.4–15.9 years).[40] Insomnia was not associated with all-cause mortality (crude model: HR, 1.06 [95% CI, 0.75–1.50]); fully adjusted model: HR, 1.11 [95% CI, 0.77–1.62]). Presence of OSA, defined as AHI ≥15 events per hour, was associated with increased risk of all-cause mortality in crude (HR, 1.47 [95% CI, 1.30–1.65]) but not fully adjusted (HR, 1.01 [95% CI, 0.89–1.15]) models. Presence of co-occurring insomnia and OSA was associated with risk of all-cause mortality in crude (HR, 1.77 [95% CI, 1.29–2.42]) and fully adjusted (HR, 1.47 [95% CI, 1.06–2.04]) models. Similar findings for co-occurring insomnia and OSA were observed in the Wisconsin Sleep Cohort.[41]
- A meta-analysis of 19 cohort studies reported an increased risk of all-cause mortality in those reporting difficulty initiating sleep (HR, 1.13 [95% CI, 1.03–1.23]) that was more pronounced in adults <65 years of age (HR, 1.33 [95% CI, 1.16–1.53]). Difficulty initiating sleep also was associated with an increased risk of cardiovascular mortality (HR, 1.20 [95% CI, 1.01–1.43]). From 13 studies, there was no added risk of all-cause mortality (HR, 1.05 [95% CI, 0.96–1.14]) or cardiovascular mortality (HR, 1.03 [95% CI, 0.82–1.31]) in those reporting difficulty maintaining sleep. From 6 studies, there was no added risk of all-cause mortality (HR, 0.97 [95% CI, 0.91–1.04]) or cardiovascular mortality (HR, 0.93 [95% CI, 0.76–1.13]) in those reporting difficulty maintaining sleep.[42]
- In the PURE study, which included participants 35 to 70 years of age from 21 countries, risk of mortality was increased in those sleeping ≤6 h/d (HR, 1.09 [95% CI, 0.99–1.20]), 8 to 9 h/d (HR, 1.05 [95% CI, 0.99–1.12]), 9 to 10 h/d (HR, 1.17 [95% CI, 1.09–1.25]), and ≥10 h/d (HR, 1.41 [95% CI, 1.30–1.53]) compared with those sleeping 6 to 8 h/d in fully adjusted models.[43]
- Data from the 2020 Canadian Community Health Survey revealed that adults who met recommended sleep duration had 1.24 years (95% CI, 0.87–1.61) longer life expectancy at 20 years of age than those with short sleep and 2.56 years (95% CI, 1.97–3.12) longer life expectancy than those with long sleep.[44]

## Complications

### *Sleep Duration*

- A meta-analysis examined sleep duration and total CVD (26 articles), CHD (22 articles), and stroke (16 articles). Relative to sleep of 7 to 8 h/night, every 1-hour reduction in sleep was associated with increased risk of total CVD (RR, 1.06 [95% CI, 1.03–1.08]), CHD (RR, 1.07 [95% CI, 1.03–1.12]), and stroke (RR, 1.05 [95% CI, 1.01–1.09]). Every 1-hour increase in sleep was associated with increased risk of total CVD (RR, 1.12 [95% CI, 1.08–1.16]), CHD (RR, 1.05 [95% CI, 1.00–1.10]), and stroke (RR, 1.18 [95% CI, 1.14–1.21]).[45]
- A study in Spain estimated sleep duration with wrist actigraphy and measured atherosclerotic plaque burden with 3-dimensional vascular ultrasound in 3804 adults between 40 and 54 years of age without a history of CVD or OSA.[46] In fully adjusted models, sleeping <6 h/night was significantly associated with a higher noncoronary plaque burden compared with sleeping 7 to 8 h/night (OR, 1.27 [95% CI, 1.06–1.52]), whereas sleeping 6 to 7 h/night (OR, 1.10 [95% CI, 0.94–1.30]) or >8 h/night (OR, 1.31 [95% CI, 0.92–1.85]) did not differ from sleeping 7 to 8 h/night.
- A cross-sectional study in Greece (N=1752) reported associations between self-reported sleep duration and carotid IMT from a carotid duplex ultrasonography examination. Compared with adequate sleep duration (7–8 hours), sleeping <6 hours (b=0.067 mm [95% CI, 0.003–0.132]) and sleeping >8 hours (b=0.054 mm [95% CI, 0.002–0.106]) were associated with larger mean carotid IMT. There was no difference between those reporting sleeping 7 to 8 hours and those reporting sleeping 6 to <7 hours (b=0.012 mm [95% CI, −0.043 to 0.068]). Maximum carotid IMT differed only for those reporting sleeping <6 hours (b=0.16 mm [95% CI, 0.033–0.287]) compared with those with adequate sleep duration, whereas those who reported sleeping 6 to <7 hours (b=0.057 mm [95% CI, −0.052 to 0.166]) or >8 hours (b=0.082 mm [95% CI, −0.019 to 0.184]) did not differ.[47]
- Analysis of the UK Biobank study (N=468 941) found that participants who reported short sleep or long sleep had an increased risk of incident HF compared with adequate sleepers. In males, the

aHR was 1.24 (95% CI, 1.08–1.42) for short sleep and 2.48 (95% CI, 1.91–3.23) for long sleep. In females, the aHR was 1.39 (95% CI, 1.17–1.65) for short sleep and 1.99 (95% CI, 1.34–2.95) for long sleep.[48]

- A prospective, population-based cohort study in China enrolled 52 599 Chinese adults 18 to 98 years of age and examined self-reported sleep duration trajectories over 4 years. They identified 4 sleep patterns: adequate stable (mean range, 7.4–7.5 hours), adequate decreasing (mean decrease, 7.0 to 5.5 hours), short increasing (mean increase, 4.9 to 6.9 hours), and short stable (mean range, 4.2–4.9 hours). Compared with the adequate stable group, increased risk of incident cardiovascular events was observed for the short-increasing group (HR, 1.22 [95% CI, 1.04–1.43]) and the short-stable group (HR, 1.47 [95% CI, 1.05–2.05]) but not the adequate-decreasing group (HR, 1.13 [95% CI, 0.97–1.32]). Risk of all-cause mortality was higher for the adequate-decreasing group (HR, 1.34 [95% CI, 1.15–1.57]) and the short-stable group (HR, 1.50 [95% CI, 1.07–2.10]) but not the short-increasing group (HR, 0.95 [95% CI, 0.80–1.13]).[36]
- The association between daytime napping and stroke was evaluated in a meta-analysis of 7 prospective studies. After adjustment for total sleep duration, the pooled RR of stroke was 1.38 (95% CI, 1.19–1.60).[49]
- In the Rush Memory and Aging Project, daytime napping in older adults (81.4±7.5 years of age) was associated with higher risk of HF (per 1-SD increase in square root–transformed nap duration: HR, 1.38 [95% CI, 1.12–1.69]; frequency >1.7 times per day: HR, 2.20 [95% CI, 1.41–3.46]).[50]
- In MESA, adding short sleep duration to Life's Simple 7 score improved prediction of incident CVD. Those in the highest versus lowest tertile of Life's Simple 7 had 38% lower risk of developing CVD (HR, 0.62 [95% CI, 0.37–1.04]).[51] When adequate sleep duration was added to the score, those in the highest tertile had 43% lower risk of incident CVD (HR, 0.57 [95% CI, 0.33–0.97]).
- Data from NHANES 2005 to 2014 showed that having high CVH, assessed with Life's Essential 8, which includes sleep duration, was associated with lower all-cause (HR, 0.60 [95% CI, 0.48–0.90]) and cardiovascular (HR, 0.46 [95% CI, 0.31–0.68]) mortality.[52] Meeting ideal sleep health metrics was associated with reduced all-cause (HR, 0.97 [95% CI, 0.95–0.99]) but not cardiovascular (HR, 0.97 [95% CI, 0.93–1.00]) mortality.

### Restful Sleep and Sleepiness

- Medical records from patients in Japan (N=1 980 476) were examined to determine whether restful sleep was associated with incident CVD over an average of 1122 days (≈3 years). Restful sleep was assessed with the question, "Do you have a good rest with sleep?" Restful sleep, defined by answering "yes," was associated with lower risk of MI (HR, 0.89 [95% CI, 0.82–0.96]), AP (HR, 0.85 [95% CI, 0.83–0.87]), stroke (HR, 0.86 [95% CI, 0.83–0.90]), HF (HR, 0.86 [95% CI, 0.83–0.88]), and AF (HR, 0.93 [95% CI, 0.88–0.98]) compared with nonrestful sleep (answering "no").[53]
- In the UK Biobank, a 1-point increase in healthy sleep score, including chronotype (morning), sleep duration (7–8 h/d), insomnia (never/rarely or sometimes), snoring (no), and excessive daytime sleepiness (never/rarely or sometimes), was associated with reduced incidence of HF (HR, 0.85 [95% CI, 0.83–0.87]).[54]
- A meta-analysis combined data from 17 prospective cohort studies with a total of 153 909 participants to examine the association between excessive daytime sleepiness and risk of CVD events. Mean follow-up time was 5.4 years (range, 2–13.8 years). Excessive daytime sleepiness was associated with a higher risk of any cardiovascular event (RR, 1.28 [95% CI, 1.09–1.50]), CHD (RR, 1.28 [95% CI, 1.12–1.46]), stroke (RR, 1.52 [95% CI, 1.10–2.12]), and cardiovascular mortality (RR, 1.47 [95% CI, 1.09–1.98]) compared with no excessive daytime sleepiness.[55]
- Data from the MIDUS study examined the association of a composite sleep health measure (Regularity, Satisfaction, Alertness, Timing, Efficiency, Duration) with risk of HD (yes/no to question on diagnosis of HD). Sleep was assessed by questionnaire and actigraphy. Each 1-unit increase in the self-reported sleep health composite was associated with 54% higher risk of HD (b=0.43 [95% CI, 0.26–0.60]); the actigraphy sleep health composite was associated with 141% higher risk (b=0.88 [95% CI, 0.44–1.32]).[56]

### Obstructive Sleep Apnea

- In the JHS Sleep Study, the associations between OSA and BP control or resistant hypertension were examined among 664 Black adults with hypertension (average, 65 years of age). In fully adjusted models, uncontrolled hypertension was not associated with either moderate to severe OSA or nocturnal hypoxemia. However, resistant hypertension was associated with moderate or severe OSA (OR, 2.04 [95% CI, 1.14–3.67]) and nocturnal hypoxemia (OR, 1.25 [95% CI, 1.01–1.55] per SD of percent sleep time <90% oxyhemoglobin saturation).[57]
- A prospective study examined 744 adults without hypertension or severe OSA at baseline and found that mild to moderate OSA was significantly associated with incident hypertension over an average of 9.2 years of follow-up (aHR, 2.94 [95% CI,

1.96–4.41]). This association also varied by age: Mild to moderate OSA was significantly associated with incident hypertension in those ≤60 years of age (HR, 3.62 [95% CI, 2.34–5.60]) but not in adults >60 years of age (HR, 1.36 [95% CI, 0.50–3.72]).[58]

- A prospective observational study enrolled patients with suspected metabolic disorders and possible OSA and examined incident major adverse cardiovascular and cerebrovascular events. A significant elevated risk of major adverse cardiovascular and cerebrovascular events was observed for patients with moderate OSA (HR, 3.85 [95% CI, 1.07–13.88] versus no OSA) and severe OSA (HR, 3.54 [95% CI, 1.03–12.22] versus no OSA). Using CPAP for ≥4 h/night for ≥5 d/wk was not significantly associated with major adverse cardiovascular and cerebrovascular events (HR, 1.44 [95% CI, 0.80–2.59] versus less frequent or no CPAP use).[59]
- A meta-analysis of 15 prospective studies indicated a significant association between the presence of OSA and the risk of cerebrovascular disease (HR, 1.94 [95% CI, 1.31–2.89]).[60]
- In a meta-analysis of 3350 patients with ACS (7 studies) or AMI (3 studies) and OSA, OSA was associated with an increased risk of major cardiovascular and cerebrovascular events (RR, 2.18 [95% CI, 1.45–3.26]). OSA was associated with an increased risk of revascularization in 8 studies (3036 patients; RR, 1.93 [95% CI, 1.23–3.02]) and increased the risk of hospitalization for HF (RR, 2.06 [95% CI, 1.20–3.54]). Recurrent MI (RR, 1.44 [95% CI, 0.83–2.51]), all-cause death (RR, 1.22 [95% CI, 0.58–2.54]), and stroke (RR, 1.37 [95% CI, 0.53–3.52]) were not different between patients with and those without OSA.[61]
- In a cohort of 297 243 veterans with a diagnosed sleep disorder between 2006 and 2012, 6002 were diagnosed with central sleep apnea. Prevalences of hypertension (72.4 % versus 60.8%), HF (23.6% versus 8.3%), IHD (33.4% versus 18.9%), cerebrovascular disease (9.2% versus 3.9%), COPD (22.0% versus 15.2%), diabetes (37.7% versus 29.0%), PH (4.4% versus 1.3%), arrhythmia (19.2% versus 7.3%), and AF (14.6% versus 4.6%) were higher in patients with central sleep apnea compared with those with other sleep disorders. Patients with central sleep apnea were more likely to have PH (RR, 2.06 [95% CI, 1.20–3.54]), AF (RR, 2.06 [95% CI, 1.20–3.54]), and HF (RR, 2.06 [95% CI, 1.20–3.54]) than those with other sleep disorders. Central sleep apnea was associated with higher risk of cardiac disease–related hospitalization (IRR, 1.50 [95% CI, 1.16–1.95]).[62]

### *Insomnia*

- In 14 cohort studies with a mean follow-up of 10.8 years, risk of hypertension was increased in adults with insomnia (RR, 1.21 [95% CI, 1.10–1.33]) with high heterogeneity.[63]
- A meta-analysis of 7 prospective studies with sample sizes of 2960 to 487 200 and a mean follow-up of 10.6 years examined the association of insomnia symptoms and CVD. Patients with nonrestful sleep, difficulty initiating sleep, and difficulty maintaining sleep had 16% (HR, 1.16 [95% CI, 1.07–1.24]), 22% (HR, 1.22 [95% CI, 1.06–1.40]), and 14% (HR, 1.14 [95% CI, 1.02–1.27]) higher risk of CVD, respectively, compared with those without. Having any insomnia complaint was associated with 13% higher risk (HR, 1.13 [95% CI, 1.08–1.19]).[64]

## Costs

- Analysis of direct and indirect costs related to inadequate sleep (defined as reporting difficulty initiating or maintaining sleep or having impaired daytime alertness at least several days per week) in Australia suggested that the approximate cost for a population the size of the US population would be more than $585 billion for the 2016 to 2017 financial year.[65]

## Global Burden

- An analysis of the global prevalence and burden of OSA estimated that 936 million (95% CI, 903–970 million) males and females 30 to 69 years of age have mild to severe OSA and 425 million (95% CI, 399–450 million) have moderate to severe OSA globally.[66]

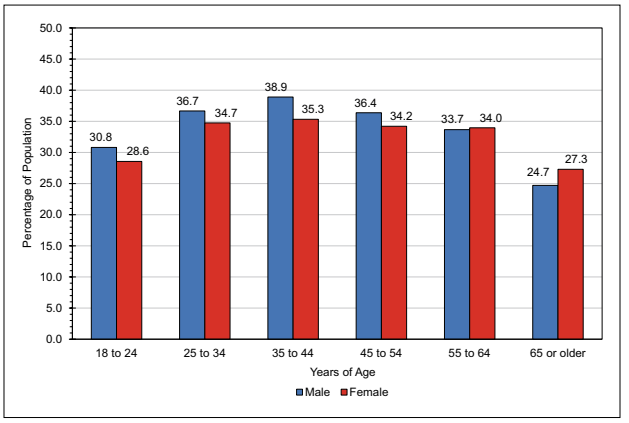



**Chart 13-1. Prevalence of reporting sleep duration <7 h/night in US adults, by sex and age, 2020.**
Percentages are adjusted for complex sampling design, including primary sampling units, strata, and sampling weights. The survey question was, "On average, how many hours of sleep do you get in a 24-hour period?"
Source: Unpublished tabulation using Behavioral Risk Factor Surveillance Survey.[7]

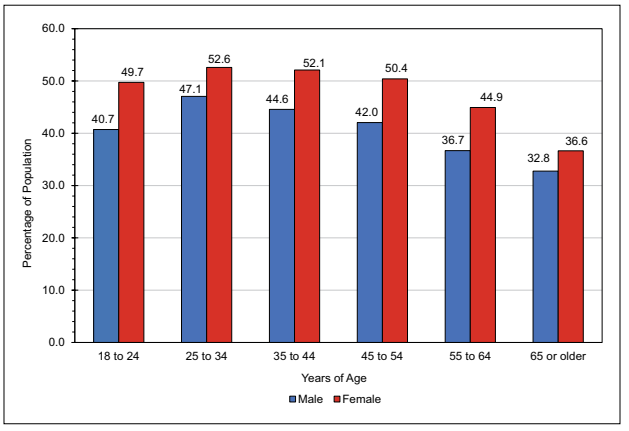



**Chart 13-2. Prevalence of reporting being well rested never or some days, by sex and age, 2020.**
Percentages are adjusted for complex sampling design, including primary sampling units, strata, and sampling weights. The survey question was, "During the past 30 days, how often did you wake up feeling well rested?"
Source: Unpublished tabulation using National Health Interview Survey.[67]

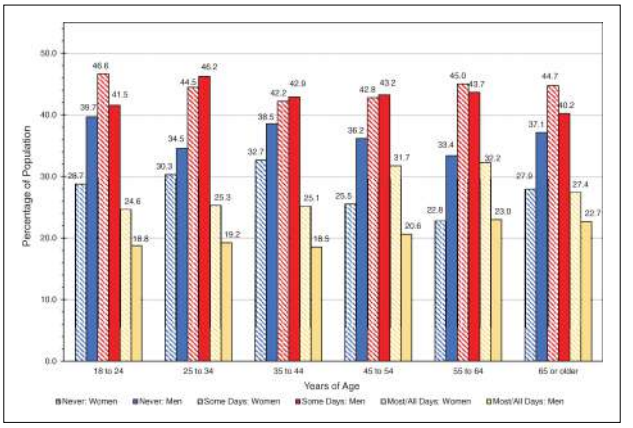



**Chart 13-3. Prevalence of reporting difficulty falling asleep or maintaining sleep never, some, or most/all days in US adults, by sex and age, 2020.**
Percentages are age adjusted for complex sampling design, including primary sampling units, strata, and sampling weights. The survey questions were, "During the past 30 days, how often did you have difficulty falling asleep?" and "During the past 30 days, how often did you have difficulty maintaining sleep?"
Source: Unpublished tabulation using National Health Interview Survey.[67]

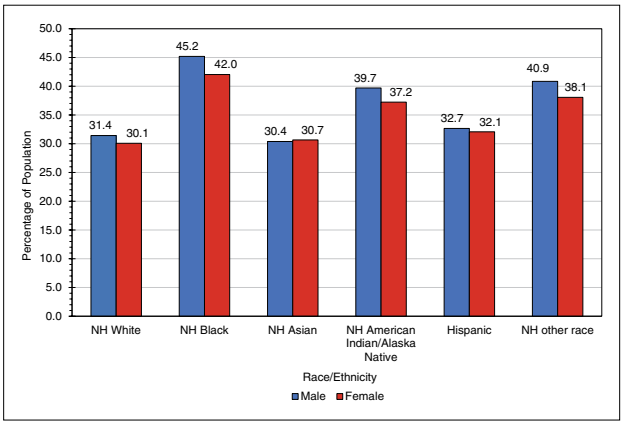



**Chart 13-4. Prevalence of reporting sleep duration <7 h/night in US adults, by sex and race, 2020.**
Percentages are adjusted for complex sampling design, including primary sampling units, strata, and sampling weights. The survey question was, "On average, how many hours of sleep do you get in a 24-hour period?"
NH indicates non-Hispanic.
Source: Unpublished tabulation using Behavioral Risk Factor Surveillance Survey.[7]




*Circulation*. 2024;149:e347–e913. DOI: 10.1161/CIR.0000000000001209

## REFERENCES


1. Lloyd-Jones DM, Allen NB, Anderson CAM, Black T, Brewer LC, Foraker RE, Grandner MA, Lavretsky H, Perak AM, Sharma G, et al; on behalf of the American Heart Association. Life's Essential 8: updating and enhancing the American Heart Association's construct of cardiovascular health: a presidential advisory from the American Heart Association. *Circulation*. 2022;146:e18–e43. doi: 10.1161/CIR.0000000000001078
2. Dong L, Martinez AJ, Buysse DJ, Harvey AG. A composite measure of sleep health predicts concurrent mental and physical health outcomes in adolescents prone to eveningness. *Sleep Health*. 2019;5:166–174. doi: 10.1016/j.sleh.2018.11.009
3. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*. 1989;28:193–213. doi: 10.1016/0165-1781(89)90047-4
4. Watson NF, Badr MS, Belenky G, Bliwise DL, Buxton OM, Buysse D, Dinges DF, Gangwisch J, Grandner MA, Kushida C, et al. Recommended amount of sleep for a healthy adult: a joint consensus statement of the American Academy of Sleep Medicine and Sleep Research Society. *Sleep*. 2015;38:843–844. doi: 10.5665/sleep.4716
5. Paruthi S, Brooks LJ, D'Ambrosio C, Hall WA, Kotagal S, Lloyd RM, Malow BA, Maski K, Nichols C, Quan SF, et al. Consensus statement of the American Academy of Sleep Medicine on the recommended amount of sleep for healthy children: methodology and discussion. *J Clin Sleep Med*. 2016;12:1549–1561. doi: 10.5664/jcsm.6288
6. Di H, Guo Y, Daghlas I, Wang L, Liu G, Pan A, Liu L, Shan Z. Evaluation of sleep habits and disturbances among US adults, 2017-2020. *JAMA Netw Open*. 2022;5:e2240788. doi: 10.1001/jamanetworkopen.2022.40788
7. Centers for Disease Control and Prevention and National Center for Chronic Disease Prevention and Health Promotion. Behavioral Risk Factor Surveillance System (BRFSS): BRFSS prevalence & trends Data. Accessed March 27, 2023. https://cdc.gov/brfss/brfssprevalence/
8. Okoro CA, Courtney-Long E, Cyrus AC, Zhao G, Wheaton AG. Self-reported short sleep duration among US adults by disability status and functional disability type: results from the 2016 Behavioral Risk Factor Surveillance System. *Disabil Health J*. 2020;13:100887. doi: 10.1016/j.dhjo.2020.100887
9. Kocevska D, Lysen TS, Dotinga A, Koopman-Verhoeff ME, Luijk M, Antypa N, Biermasz NR, Blokstra A, Brug J, Burk WJ, et al. Sleep characteristics across the lifespan in 11 million people from the Netherlands, United Kingdom and United States: a systematic review and meta-analysis. *Nat Hum Behav*. 2021;5:113–122. doi: 10.1038/s41562-020-00965-x
10. Data Resource Center for Child and Adolescent Health and The Child and Adolescent Health Measurement Initiative. 2020-2021 National Survey of Children's Health Interactive Query. Accessed March 9, 2023. https://www.childhealthdata.org/browse/survey/results?q=9563&r=1&g=1003
11. Jean-Louis G, Shochat T, Youngstedt SD, Briggs AQ, Williams ET, Jin P, Bubu OM, Seixas AA. Age-associated differences in sleep duration in the US population: potential effects of disease burden. *Sleep Med*. 2021;87:168–173. doi: 10.1016/j.sleep.2021.09.004
12. Chang VC, Chaput JP, Roberts KC, Jayaraman G, Do MT. Factors associated with sleep duration across life stages: results from the Canadian Health Measures Survey. *Health Promot Chronic Dis Prev Can*. 2018;38:404–418. doi: 10.24095/hpcdp.38.11.02
13. Sands SA, Alex RM, Mann D, Vena D, Terrill PI, Gell LK, Zinchuk A, Sofer T, Patel SR, Taranto-Montemurro L, et al. Pathophysiology underlying demographic and obesity determinants of sleep apnea severity. *Ann Am Thorac Soc*. 2023;20:440–449. doi: 10.1513/AnnalsATS.202203-271OC
14. Garland SN, Rowe H, Repa LM, Fowler K, Zhou ES, Grandner MA. A decade's difference: 10-year change in insomnia symptom prevalence in Canada depends on sociodemographics and health status. *Sleep Health*. 2018;4:160–165. doi: 10.1016/j.sleh.2018.01.003
15. Deng MG, Nie JQ, Li YY, Yu X, Zhang Z-J. Higher HEI-2015 scores are associated with lower risk of sleep disorder: results from a nationally representative survey of United States adults. *Nutrients*. 2022;14:873. doi: 10.3390/nu14040873
16. Castro-Diehl C, Wood AC, Redline S, Reid M, Johnson DA, Maras JE, Jacobs DR Jr, Shea S, Crawford A, St-Onge MP. Mediterranean diet pattern and sleep duration and insomnia symptoms in the Multi-Ethnic Study of Atherosclerosis. *Sleep*. 2018;41:zsy158. doi: 10.1093/sleep/zsy158
17. Zuraikat FM, Makarem N, St-Onge MP, Xi H, Akkapeddi A, Aggarwal B. A Mediterranean dietary pattern predicts better sleep quality in US women from the American Heart Association Go Red for Women Strategically Focused Research Network. *Nutrients*. 2020;12:2830. doi: 10.3390/nu12092830
18. McElfish PA, Narcisse MR, Selig JP, Felix HC, Scott AJ, Long CR. Effects of race and poverty on sleep duration: analysis of patterns in the 2014 Native Hawaiian and Pacific Islander National Health Interview Survey and General National Health Interview Survey Data. *J Racial Ethn Health Disparities*. 2021;8:837–843. doi: 10.1007/s40615-020-00841-4
19. Johnson DA, Guo N, Rueschman M, Wang R, Wilson JG, Redline S. Prevalence and correlates of obstructive sleep apnea among African Americans: the Jackson Heart Sleep Study. *Sleep*. 2018;41:zsy154. doi: 10.1093/sleep/zsy154
20. Johnson DA, Lewis TT, Guo N, Jackson CL, Sims M, Wilson JG, Diez Roux AV, Williams DR, Redline S. Associations between everyday discrimination and sleep quality and duration among African-Americans over time in the Jackson Heart Study. *Sleep*. 2021;44:zsab162. doi: 10.1093/sleep/zsab162
21. Caceres BA, Hickey KT, Heitkemper EM, Hughes TL. An intersectional approach to examine sleep duration in sexual minority adults in the United States: findings from the Behavioral Risk Factor Surveillance System. *Sleep Health*. 2019;5:621–629. doi: 10.1016/j.sleh.2019.06.006
22. Young MC, Gerber MW, Ash T, Horan CM, Taveras EM. Neighborhood social cohesion and sleep outcomes in the Native Hawaiian and Pacific Islander National Health Interview Survey. *Sleep*. 2018;41:zsy097. doi: 10.1093/sleep/zsy097
23. Dzierzewski JM, Sabet SM, Ghose SM, Perez E, Soto P, Ravyts SG, Dautovich ND. Lifestyle factors and sleep health across the lifespan. *Int J Environ Res Public Health*. 2021;18:6626. doi: 10.3390/ijerph18126626
24. Mukherjee S, Saxena R, Palmer LJ. The genetics of obstructive sleep apnoea. *Respirology*. 2018;23:18–27. doi: 10.1111/resp.13212
25. Jones SE, van Hees VT, Mazzotti DR, Marques-Vidal P, Sabia S, van der Spek A, Dashti HS, Engmann J, Kocevska D, Tyrrell J, et al. Genetic studies of accelerometer-based sleep measures yield new insights into human sleep behaviour. *Nat Commun*. 2019;10:1585. doi: 10.1038/s41467-019-09576-1
26. Dashti HS, Jones SE, Wood AR, Lane JM, van Hees VT, Wang H, Rhodes JA, Song Y, Patel K, Anderson SG, et al. Genome-wide association study identifies genetic loci for self-reported habitual sleep duration supported by accelerometer-derived estimates. *Nat Commun*. 2019;10:1100. doi: 10.1038/s41467-019-08917-4
27. Dashti HS, Daghlas I, Lane JM, Huang Y, Udler MS, Wang H, Ollila HM, Jones SE, Kim J, Wood AR, et al. Genetic determinants of daytime napping and effects on cardiometabolic health. *Nat Commun*. 2021;12:900. doi: 10.1038/s41467-020-20585-3
28. Krohn L, Heilbron K, Blauwendraat C, Reynolds RH, Yu E, Senkevich K, Rudakou U, Estiar MA, Gustavsson EK, Brolin K, et al. Genome-wide association study of REM sleep behavior disorder identifies polygenic risk and brain expression effects. *Nat Commun*. 2022;13:7496. doi: 10.1038/s41467-022-34732-5
29. Noordam R, Bos MM, Wang H, Winkler TW, Bentley AR, Kilpelainen TO, de Vries PS, Sung YJ, Schwander K, Cade BE, et al. Multi-ancestry sleep-by-SNP interaction analysis in 126,926 individuals reveals lipid loci stratified by sleep duration. *Nat Commun*. 2019;10:5121. doi: 10.1038/s41467-019-12958-0
30. Ai S, Zhang J, Zhao G, Wang N, Li G, So HC, Liu Y, Chau S-H, Chen J, Tan X, et al. Causal associations of short and long sleep durations with 12 cardiovascular diseases: linear and nonlinear Mendelian randomization analyses in UK Biobank. *Eur Heart J*. 2021;42:3349–3357. doi: 10.1093/eurheartj/ehab170
31. Strausz S, Ruotsalainen S, Ollila HM, Karjalainen J, Kiiskinen T, Reeve M, Kurki M, Mars N, Havulinna AS, Luonsi E, et al. Genetic analysis of obstructive sleep apnoea discovers a strong association with cardiometabolic health. *Eur Respir J*. 2021;57:2003091. doi: 10.1183/13993003.03091-2020
32. Yao Y, Jia Y, Wen Y, Cheng B, Cheng S, Liu L, Yang X, Meng P, Chen Y, Li C, et al. Genome-wide association study and genetic correlation scan provide insights into its genetic architecture of sleep health score in the UK Biobank cohort. *Nat Sci Sleep*. 2022;14:1–12. doi: 10.2147/nss.s326818
33. Cirelli C, Pfister-Genskow M, McCarthy D, Woodbury R, Tononi G. Proteomic profiling of the rat cerebral cortex in sleep and waking. *Arch Ital Biol*. 2009;147:59–68.
34. DelRosso LM, King J, Ferri R. Systolic blood pressure elevation in children with obstructive sleep apnea is improved with positive airway pressure use. *J Pediatr*. 2018;195:102–107.e1. doi: 10.1016/j.jpeds.2017.11.043
35. Khan SU, Duran CA, Rahman H, Lekkala M, Saleem MA, Kaluski E. A meta-analysis of continuous positive airway pressure therapy in prevention of

cardiovascular events in patients with obstructive sleep apnoea. *Eur Heart J*. 2018;39:2291–2297. doi: 10.1093/eurheartj/ehx597
36. Wang YH, Wang J, Chen SH, Li JQ, Lu QD, Vitiello MV, Wang F, Tang XD, Shi J, Lu L, et al. Association of longitudinal patterns of habitual sleep duration with risk of cardiovascular events and all-cause mortality. *JAMA Netw Open*. 2020;3:e205246. doi: 10.1001/jamanetworkopen.2020.5246
37. Xiao Q, Blot WJ, Matthews CE. Weekday and weekend sleep duration and mortality among middle-to-older aged White and Black adults in a low-income southern US cohort. *Sleep Health*. 2019;5:521–527. doi: 10.1016/j.sleh.2019.04.008
38. Jike M, Itani O, Watanabe N, Buysse DJ, Kaneita Y. Long sleep duration and health outcomes: a systematic review, meta-analysis and meta-regression. *Sleep Med Rev*. 2018;39:25–36. doi: 10.1016/j.smrv.2017.06.011
39. Omichi C, Koyama T, Kadotani H, Ozaki E, Tomida S, Yoshida T, Otonari J, Ikezaki H, Hara M, Tanaka K, et al. Irregular sleep and all-cause mortality: a large prospective cohort study. *Sleep Health*. 2022;8:678–683. doi: 10.1016/j.sleh.2022.08.010
40. Lechat B, Appleton S, Melaku YA, Hansen K, McEvoy RD, Adams R, Catcheside P, Lack L, Eckert DJ, Sweetman A. Comorbid insomnia and sleep apnoea is associated with all-cause mortality. *Eur Respir J*. 2022;60:2101958. doi: 10.1183/13993003.01958-2021
41. Lechat B, Loffler KA, Wallace DM, Reynolds A, Appleton SL, Scott H, Vakulin A, Lovato N, Adams R, Eckert DJ, et al. All-cause mortality in people with co-occurring insomnia symptoms and sleep apnea: analysis of the Wisconsin Sleep Cohort. *Nat Sci Sleep*. 2022;14:1817–1828. doi: 10.2147/NSS.S379252
42. Ge L, Guyatt G, Tian J, Pan B, Chang Y, Chen Y, Li H, Zhang J, Li Y, Ling J, et al. Insomnia and risk of mortality from all-cause, cardiovascular disease, and cancer: systematic review and meta-analysis of prospective cohort studies. *Sleep Med Rev*. 2019;48:101215. doi: 10.1016/j.smrv.2019.101215
43. Wang C, Bangdiwala SI, Rangarajan S, Lear SA, AlHabib KF, Mohan V, Teo K, Poirier P, Tse LA, Liu Z, et al. Association of estimated sleep duration and naps with mortality and cardiovascular events: a study of 116 632 people from 21 countries. *Eur Heart J*. 2019;40:1620–1629. doi: 10.1093/eurheartj/ehy695
44. Chaput JP, Carrier J, Bastien C, Gariepy G, Janssen I. Years of life gained when meeting sleep duration recommendations in Canada. *Sleep Med*. 2022;100:85–88. doi: 10.1016/j.sleep.2022.08.006
45. Yin J, Jin X, Shan Z, Li S, Huang H, Li P, Peng X, Peng Z, Yu K, Bao W, et al. Relationship of sleep duration with all-cause mortality and cardiovascular events: a systematic review and dose-response meta-analysis of prospective cohort studies. *J Am Heart Assoc*. 2017;6:e005947. doi: 10.1161/JAHA.117.005947
46. Dominguez F, Fuster V, Fernandez-Alvira JM, Fernandez-Friera L, Lopez-Melgar B, Blanco-Rojo R, Fernandez-Ortiz A, Garcia-Pavia P, Sanz J, Mendiguren JM, et al. Association of sleep duration and quality with subclinical atherosclerosis. *J Am Coll Cardiol*. 2019;73:134–144. doi: 10.1016/j.jacc.2018.10.060
47. Oikonomou E, Theofilis P, Vogiatzi G, Lazaros G, Tsalamandris S, Mystakidi VC, Goliopoulou A, Anastasiou M, Fountoulakis P, Chasikidis C, et al. The impact of sleeping duration on atherosclerosis in the community: insights from the Corinthia study. *Sleep Breath*. 2021;25:1813–1819. doi: 10.1007/s11325-020-02267-y
48. Sillars A, Ho FK, Pell GP, Gill JMR, Sattar N, Gray S, Celis-Morales C. Sex differences in the association of risk factors for heart failure incidence and mortality. *Heart*. 2020;106:203–212. doi: 10.1136/heartjnl-2019-314878
49. Jin X, Chen H, Li Y, Xu W, Chen X, Tian L, Teng W. Association between daytime napping and stroke: a dose-response meta-analysis. *J Sleep Res*. 2021;30:e13366. doi: 10.1111/jsr.13366
50. Li P, Gaba A, Wong PM, Cui L, Yu L, Bennett DA, Buchman AS, Gao L, Hu K. Objective assessment of daytime napping and incident heart failure in 1140 community-dwelling older adults: a prospective, observational cohort study. *J Am Heart Assoc*. 2021;10:e019037. doi: 10.1161/JAHA.120.019037
51. Makarem N, Castro-Diehl C, St-Onge MP, Redline S, Shea S, Lloyd-Jones D, Ning H, Aggarwal B. Redefining cardiovascular health to include sleep: prospective associations with cardiovascular disease in the MESA Sleep Study. *J Am Heart Assoc*. 2022;11:e025252. doi: 10.1161/JAHA.122.025252
52. Yi J, Wang L, Guo X, Ren X. Association of Life's Essential 8 with all-cause and cardiovascular mortality among US adults: a prospective cohort study from the NHANES 2005-2014. *Nutr Metab Cardiovasc Dis*. 2023;33:1134–1143. doi: 10.1016/j.numecd.2023.01.021
53. Kaneko H, Itoh H, Kiriyama H, Kamon T, Fujiu K, Morita K, Michihata N, Jo T, Takeda N, Morita H, et al. Restfulness from sleep and subsequent cardiovascular disease in the general population. *Sci Rep*. 2020;10:19674. doi: 10.1038/s41598-020-76669-z
54. Li X, Xue Q, Wang M, Zhou T, Ma H, Heianza Y, Qi L. Adherence to a healthy sleep pattern and incident heart failure: a prospective study of 408 802 UK Biobank participants. *Circulation*. 2021;143:97–99. doi: 10.1161/CIRCULATIONAHA.120.050792
55. Wang L, Liu Q, Heizhati M, Yao X, Luo Q, Li N. Association between excessive daytime sleepiness and risk of cardiovascular disease and all-cause mortality: a systematic review and meta-analysis of longitudinal cohort studies. *J Am Med Dir Assoc*. 2020;21:1979–1985. doi: 10.1016/j.jamda.2020.05.023
56. Lee S, Mu CX, Wallace ML, Andel R, Almeida DM, Buxton OM, Patel SR. Sleep health composites are associated with the risk of heart disease across sex and race. *Sci Rep*. 2022;12:2023. doi: 10.1038/s41598-022-05203-0
57. Johnson DA, Thomas SJ, Abdalla M, Guo N, Yano Y, Rueschman M, Tanner RM, Mittleman MA, Calhoun DA, Wilson JG, et al. Association between sleep apnea and blood pressure control among Blacks. *Circulation*. 2019;139:1275–1284. doi: 10.1161/CIRCULATIONAHA.118.036675
58. Vgontzas AN, Li Y, He F, Fernandez-Mendoza J, Gaines J, Liao D, Basta M, Bixler EO. Mild-to-moderate sleep apnea is associated with incident hypertension: age effect. *Sleep*. 2019;42:zsy265. doi: 10.1093/sleep/zsy265
59. Baratta F, Pastori D, Fabiani M, Fabiani V, Ceci F, Lillo R, Lolli V, Brunori M, Pannitteri G, Cravotto E, et al. Severity of OSAS, CPAP and cardiovascular events: a follow-up study. *Eur J Clin Invest*. 2018;48:e12908. doi: 10.1111/eci.12908
60. Wu Z, Chen F, Yu F, Wang Y, Guo Z. A meta-analysis of obstructive sleep apnea in patients with cerebrovascular disease. *Sleep Breath*. 2018;22:729–742. doi: 10.1007/s11325-017-1604-4
61. Yang SH, Xing YS, Wang ZX, Liu YB, Chen HW, Ren YF, Chen JL, Li SB, Wang ZF. Association of obstructive sleep apnea with the risk of repeat adverse cardiovascular events in patients with newly diagnosed acute coronary syndrome: a systematic review and meta-analysis. *Ear Nose Throat J*. 2021;100:260–270. doi: 10.1177/0145561321989450
62. Ratz D, Wiitala W, Badr MS, Burns J, Chowdhuri S. Correlates and consequences of central sleep apnea in a national sample of US veterans. *Sleep*. 2018;41:zsy058. doi: 10.1093/sleep/zsy058
63. Li L, Gan Y, Zhou X, Jiang H, Zhao Y, Tian Q, He Y, Liu Q, Mei Q, Wu C, et al. Insomnia and the risk of hypertension: a meta-analysis of prospective cohort studies. *Sleep Med Rev*. 2021;56:101403. doi: 10.1016/j.smrv.2020.101403
64. Hu S, Lan T, Wang Y, Ren L. Individual insomnia symptom and increased hazard risk of cardiocerebral vascular diseases: a meta-analysis. *Front Psychiatry*. 2021;12:654719. doi: 10.3389/fpsyt.2021.654719
65. Hillman D, Mitchell S, Streatfeild J, Burns C, Bruck D, Pezzullo L. The economic cost of inadequate sleep. *Sleep*. 2018;41:zsy083. doi: 10.1093/sleep/zsy083
66. Benjafield AV, Ayas NT, Eastwood PR, Heinzer R, Ip MSM, Morrell MJ, Nunez CM, Patel SR, Penzel T, Pepin JL, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *Lancet Respir Med*. 2019;7:687–698. doi: 10.1016/S2213-2600(19)30198-5
67. Centers for Disease Control and Prevention and National Center for Health Statistics. National Health Interview Survey: public-use data files and documentation. Accessed March 15, 2023. https://cdc.gov/nchs/nhis/index.htm

# 14. TOTAL CARDIOVASCULAR DISEASES

***ICD-9 390 to 459; ICD-10 I00 to I99. See Tables 14-1 through 14-3 and Charts 14-1 through 14-16***

Click here to return to the Table of Contents

Click here to return to the Abbreviations

## Prevalence

## (See Table 14-1 and Chart 14-1)

- On the basis of NHANES 2017 to March 2020 data,[1] the prevalence of CVD (comprising CHD, HF, stroke, and hypertension) in adults ≥20 years of age is 48.6% overall (127.9 million in 2020) and increases with age in both males and females. CVD prevalence excluding hypertension (CHD, HF, and stroke only) is 9.9% overall (28.6 million in 2020; Table 14-1). Chart 14-1 presents the prevalence breakdown of CVD by age and sex, with and without hypertension in the CVD definition.
- According to the NHIS[2] 2018:
  - The age-adjusted prevalence of all HD (CHD, angina, or heart attack, excluding hypertension) was 11.2%; the corresponding age-adjusted prevalences of HD among self-described racial and ethnic groups in which only 1 race was reported were 11.5% among NH White, 10.0% among NH Black, 8.2% among Hispanic, 7.7% among Asian, and 14.6% among American Indian or Alaska Native individuals.
  - The age-adjusted prevalences of HD, CHD, hypertension, and stroke in males were 12.6%, 7.4%, 26.1%, and 3.1%, respectively, and in females were 10.1%, 4.1%, 23.5%, and 2.6%, respectively.
  - The age-adjusted prevalences of HD, CHD, hypertension, and stroke among unemployed individuals who had previously worked were as follows: HD, 13.9%; CHD, 7.7%; hypertension, 30.5%; and stroke, 4.7%. The age-adjusted prevalences of HD, CHD, hypertension, and stroke among currently employed individuals were 9.5%, 4.0%, 21.8%, and 1.6%, respectively. The age-adjusted prevalences of HD, CHD, hypertension, and stroke among individuals who had never worked were 10.2%, 6.7%, 24.6%, and 3.2%, respectively.
- In a cross-sectional study of 56 716 adults ≥40 years of age from northern China, 22.7% had high 10-year risk of CVD according to WHO/International Society of Hypertension risk prediction charts.[3] The age-adjusted prevalences of hypertension, dyslipidemia, obesity, and diabetes among all respondents were 54.3%, 36.5%, 24.8%, and 18.2%, respectively.

## Incidence

- In a meta-analysis of 32 studies assessing CVD burden among Asian adults 18 to 92 years of age who were free of CVD at baseline and with >10 years of follow-up, the incidence of fatal CVD was 3.68 (95% CI, 2.84–4.53) events per 1000 person-years.[4] Risk factors for long-term fatal CVD were male sex (1.49, [95% CI, 1.36–1.64]), older age (7.55 [95% CI, 5.59–10.19]), and current smoking (1.68 [95% CI, 1.26–2.24]).

## Lifetime Risk and Cumulative Incidence

- Pooled data from 7 US cohort studies (1960–2015) of Black and White males and females (ARIC, CHS, CARDIA, FHS, FHS Offspring Cohort Study, JHS, and MESA; N=19 630) demonstrated that risk for CVD (MI or stroke) between 55 and 85 years of age ranged from 15.3% to 38.6% in females with fasting glucose <5.0 mmol/L (90 mg/dL) at baseline to 38.6% in females with fasting glucose ≥7.0 mmol/L (126 mg/dL; or taking diabetes medication at baseline).[5] In males, the risk varied between 21.5% in those with fasting glucose of 5.0 to 5.5 mmol/L (90–99 mg/dL) at baseline and 47.7% in those with fasting glucose ≥7.0 mmol/L (or taking diabetes medication at baseline).
- The Cardiovascular Lifetime Risk Pooling Project estimated the long-term risks of CVD among 30 447 participants with a mean age of 55.0 years (SD, 13.9 years) from 7 US cohort studies.[6] After 538 477 person-years of follow-up, the 40-year risk of CVD for an adult <40 years of age with high CVH was 0.7% (95% CI, 0.0%–1.7%) for White males, 2.1% (95% CI, 0.0%–5.0%) for Black males, 1.7% (95% CI, 0.4%–3.0%) for White females, and 2.0% (95% CI, 0.0%–4.7%) for Black females. For an adult <40 years of age with low CVH, the 40-year risk of CVD was 14.4% (95% CI, 9.1%–19.6%)

The 2024 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2024. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

for White males, 17.6% (95% CI, 9.9%–25.3%) for Black males, 8.6% (95% CI, 2.1%–15.2%) for White females, and 8.4% (95% CI, 5.3%–11.5%) for Black females. White females ≥60 years of age with high CVH had a 35-year risk of CVD of 38.6% (95% CI, 22.6%–54.7%), but this risk was incalculable for older, high-CVH individuals in other race-sex groups because of insufficient follow-up. Among individuals ≥60 years of age with low CVH, the 35-year risk of CVD was highest in White males (65.5% [95% CI, 62.1%–68.9%]), followed by White females (57.1% [95% CI, 54.4%–59.7%]), Black females (51.9% [95% CI, 43.1%–60.8%]), and Black males (48.4% [95% CI, 41.9%–54.9%]). These estimated risks accounted for competing risks of death resulting from non-CVD causes.

- The remaining lifetime risk for ASCVD among predominantly White participants from the FHS in 3 epochs (epoch 1, 1960–1979; epoch 2, 1980–1999; epoch 3, 2000–2018) was examined.[7] Life expectancy increased by 10.1 years among males and 11.9 years among females across the 3 epochs. Furthermore, the remaining lifetime risk of ASCVD from 45 years reduced from 43.7% in epoch 1 to 28.1% in epoch 3 ($P<0.0001$) in both sexes and across BMI, BP, diabetes, cholesterol, smoking, and FRS strata ($P<0.001$ for all).

## Secular Trends

- According to data from the COAST study (2000–2012), of 9012 people living with HIV in British Columbia, Canada, and free of CVD at baseline, the adjusted incidence rate of CVD per 1000 person-years remained relatively stable at 9.11 (95% CI, 5.87–14.13) in 2000 compared with 10.01 (95% CI, 7.55–13.27) in 2012.[8] However, incidence rates of hypertension per 1000 person-years increased significantly.

## Risk Factors

- Eating disorders are another risk factor for CVD. In a registry-based study of 416 709 females hospitalized in Quebec, Canada, from 2006 and 2018, 818 females who were hospitalized for bulimia nervosa were compared with 415 891 females without bulimia nervosa who were hospitalized for pregnancy-related events for a total follow-up period of 2 957 677 person-years.[9] Females hospitalized for bulimia nervosa had a higher incidence of CVD (10.34 [95% CI, 7.77–13.76] per 1000 person-years) than females hospitalized for pregnancy-related events (1.02 [95% CI, 0.99–1.06] per 1000 person-years). Furthermore, the risk of any CVD (4.25 [95% CI, 2.98–6.07]) or death (4.72 [95% CI, 2.05–10.84]) was higher among females hospitalized for bulimia nervosa compared with females hospitalized for pregnancy-related events (comparison group).
- Among participants of the WHS (N=27 858; 629 353 person-years of follow-up), those with a self-reported history of migraine with aura had a higher incidence rate of major CVD (3.36 [95% CI, 2.72–3.99 per 1000 person-years]) than females with migraine without aura or no migraine (2.11 [95% CI, 1.98–2.24]).[10]
- Air pollution, as defined by increased ambient exposure to particulate matter (particles with median aerodynamic diameter <2.5 μm), is associated with elevated blood glucose, poor endothelial function, incident CVD events, and all-cause mortality and accounts in part for the racial differences in all-cause mortality and incident CVD. According to data from HeartScore, a community-based cohort of adults residing in western Pennsylvania with exposure to ambient fine particular (PM2.5) and black carbon, mean PM2.5 exposure among Black individuals was 16.1±0.75 μg/m$^3$ versus 15.7±0.73 μg/m$^3$ in White individuals ($P=0.0001$). Black carbon exposure among Black individuals was 1.19±0.11 μg/m$^3$, and mean black carbon exposure among White individuals was 1.16±0.13 μg/m$^3$ ($P=0.0001$). Mediation analysis demonstrated that 24% of the association between race and the composite outcome of CVD deaths and nonfatal CVD events was mediated by exposure to PM2.5 and that the association between race and composite clinical outcome was no longer significant after adjustment for income and education.[11]
- Among 31 162 adults 35 to 74 years of age in the Henan Rural Cohort Study, each 1–μg/m$^3$ increase in particulate matter (PM1 [particles with aerodynamic diameter <1 μm], PM2.5, PM10 [particles with aerodynamic diameter <10 μm], and $NO_2$) was associated with a 4.4% (OR, 1.04 [95% CI, 1.03–1.06]) higher 10-year ASCVD risk for PM1, 9.1% (OR, 1.09 [95% CI, 1.08–1.10]) higher 10-year ASCVD risk for PM2.5, 4.6% (OR, 1.05 [95% CI, 1.04–1.05]) higher 10-year ASCVD risk for PM10, and 6.4% (OR, 1.06 [95% CI, 1.06–1.07]) higher 10-year ASCVD risk for $NO_2$ (all $P<0.001$). However, PA attenuated the association between air pollution and 10-year ASCVD risk.[12]
- In a meta-analysis of sex differences in the association between diabetes and CVD mortality (49 studies representing 5 162 654 participants), the pooled RR ratio demonstrated a 30% greater risk of all-cause mortality among females and males with diabetes (95% CI, 1.13–1.49). Females with diabetes also had a 58% greater risk of CHD.[13]

- In a meta-analysis of dietary sodium intake and CVD risk (36 studies representing 616 905 participants), those with high sodium intake had a higher adjusted risk of CVD (rate ratio, 1.19 [95% CI, 1.08–1.30]) than individuals with low sodium intake. CVD risk was up to 6% higher for every 1-g increase in dietary sodium intake.[14] However, an increase in potassium intake may be beneficial in lowering BP levels, but excessive potassium supplementation should be avoided.[15]
- A prospective analysis of dietary patterns among adults in the NHS (1984–2016), NHS II (1991–2017), and HPFS (1986–2012) with 5 257 190 person-years of follow-up found that greater adherence to healthy eating patterns was inversely and consistently associated with CVD risk (HEI-2015: HR, 0.83 [95% CI, 0.79–0.86]; AHEI: HR, 0.79 [95% CI, 0.75–0.82]; Alternate Mediterranean Diet Score: HR, 0.83 [95% CI, 0.79–0.86]; and Healthful Plant-Based Diet Index: HR, 0.86 [95% CI, 0.82–0.89]).[16]
- In a systematic review of 19 observational studies aimed at assessing the association between dietary patterns and cardiometabolic risk in adolescents, findings revealed that the highest intake of unhealthy foods was associated with a higher BMI (0.57 kg/m$^2$ [95% CI, 0.51–0.63]) and higher WC (0.57 cm [95% CI, 0.47–0.67]) compared with a low intake of unhealthy foods.[17] Children and adolescents with a Western dietary pattern (high intake of beef/lamb/other red meat, wheat, starch fibers, and light-colored vegetables) had a significantly higher odds of obesity (OR, 2.04 [95% CI, 1.38–-3.02]) compared with youth who followed a healthier eating pattern (milk, yogurt, fruit, and vegetables, with less sugar, beef/lamb/other red meat).
- In a prospective cohort study of 414 588 adults without CVD in the UK Biobank (2006–2010) with follow-up through 2018, perinatal exposure to maternal smoking was associated with higher risk of CVD (aHR, 1.10 [95% CI, 1.05–1.14]), MI (aHR, 1.10 [95% CI, 1.05–1.16]), and stroke (aHR, 1.10 [95% CI, 1.03–1.18]).[18] Furthermore, there were significant interactions between perinatal exposure to maternal smoking and adulthood smoking behaviors on MI and CVD (all $P<0.05$).
- Among 116 806 individuals in the UK Biobank who had a mean follow-up of 4.9 years, there were 4245 cases of total CVD, 838 cases of fatal CVD, and 3629 deaths resulting from all causes.[19] Dietary patterns, assessed with a 24-hour online dietary assessment on at least 2 occasions, revealed a positive linear association between diets that were high in chocolate and confectionery, butter, and low-fiber bread and low in fresh fruit and vegetables and total CVD (aHR, 1.40 [95% CI, 1.31–1.50]) and all-cause mortality (aHR, 1.37 [95% CI, 1.27–1.47] in the highest quintile).
- In a prospective analysis of data of 3612 individuals 17 to 77 years of age from the Framingham Offspring Study who were examined between 1979 and 2014, 533 (15%) were diagnosed with asthma and 897 (25%) developed CVD.[20] Asthma was associated with higher risk of incident CVD (aHR, 1.28 [95% CI, 1.07–1.54]).
- Among 29 260 adults with type 2 diabetes in the LEAD cohort study (2013 and 2018) with mean follow-up of 4.2 years, there were 3746 incident CVD events. HbA1c variability, measured by SD, was associated with higher risk of CVD.[21] The aHR for incident CVD was higher across the second (aHR, 1.30 [95% CI, 1.18–1.42]), third (aHR, 1.40 [95% CI, 1.26–1.55]), and fourth (aHR, 1.59 [95% CI, 1.41–1.77]) quartiles of HbA1c SD than the first quartile ($P_{trend}<0.001$).
- Among 2 prospective cohorts of US males (HPFS, 1990–2018) and females (Nurses' Health Study, 1990–2018) free of CVD or cancer at baseline,[22] participants who had higher intake of olive oil (>7 g/d or >0.5 tablespoon) had 19% lower risk of CVD mortality (aHR, 0.81 [95% CI, 0.75–0.87]) than those who had lower consumption of olive oil (never or less than once per month).
- In a meta-analysis of 10 studies including 9 cohorts (N=698 707) with 137 969 CVD events, higher adherence to a plant-based diet was associated with lower risk of CVD (aRR, 0.84 [95% CI, 0.79–0.89]) and CHD (aRR, 0.88 [95% CI, 0.81–0.94)] compared with low adherence.[23]
- Among 15 103 individuals with type 2 diabetes without CVD and with serum 25-hydroxyvitamin D measurements in the UK Biobank, there were 3534 incident CVD events over a median of 11.2 years of follow-up.[24] Participants with higher serum 25-hydroxyvitamin D concentrations had lower CVD risk. The multivariable-adjusted HRs across categories of serum 25-hydroxyvitamin D of <25.0, 25.0 to 49.9, 50.0 to 74.9, and ≥75.0 nmol/L were 1.00 (reference), 0.87 (95% CI, 0.80–0.96), 0.80 (95% CI, 0.72–0.88), and 0.75 (95% CI, 0.64–0.88) for total CVD events ($P_{trend}<0.001$).
- In a retrospective cohort study of medical records of females who had ≥1 singleton live births (N=2 359 386) from the National Health Service hospitals in England between 1997 and 2015, females who had prior gestational hypertension or prior preeclampsia had 1.45 (95% CI, 1.33–1.59) and 1.62 (95% CI, 1.48–1.78) higher adjusted hazards of total CVD, respectively, than those who were normotensive.[25]
- Among 103 388 adults in the web-based NutriNet-Santé cohort (mean age, 42.2±14.4 years; 79.8%

female; 904 206 person-years), consuming artificial sweeteners from all dietary sources, including beverages, tabletop sweeteners, and dairy products, among others, was associated with 1.09 (95% CI, 1.01–1.18) higher CVD risk.[26] Similarly, among 109 043 females in the WHS, during an average of 17.4 years of follow-up, 11 597 CVD events occurred.[27] Higher intake of added sugar (≥15.0% energy intake daily) was positively associated with total CVD (HR, 1.08 [95% CI, 1.01–1.15]). Consuming ≥1 servings of SSBs or ASBs daily was associated with 1.29 ([95% CI, 1.17–1.42]) and (1.14 [95% CI, 1.03–1.26]) higher risk of total CVD, respectively.

- A prospective analysis of participants in the International Cardiovascular Cohort evaluated whether 5 childhood cardiovascular risk factors (BMI, SBP, TC level, triglyceride level, and youth smoking) were associated with fatal or nonfatal CVD events in adulthood after an average follow-up of 35 years.[27a] Each 1-unit increase in combined-risk *z* score (unweighted mean of the 5 risk scores) was associated with a 2.71 (95% CI, 2.23–3.29) and 2.75 (95% CI, 2.48–3.06) higher risk of a fatal or nonfatal CVD event, respectively. The HR for fatal CVD in adulthood ranged from 1.30 (95% CI, 1.14–1.47) per unit increase in the *z* score for TC level to 1.61 (95% CI, 1.21–2.13) for youth smoking (yes versus no).

## Social Determinants of Health/Health Equity

- Among older adults in the NIH-AARP Diet and Health Study, the highest tertile of neighborhood socioeconomic deprivation in 1990 and 2000 compared with the lowest tertile was associated with a higher risk of CVD mortality (aHR for males, 1.47 [95% CI, 1.40–1.54]; aHR for females, 1.78 [95% CI, 1.63–1.95]) after accounting for individual socioeconomic factors and CVD risk factors.[28] A 30-percentile-point reduction in neighborhood deprivation was associated with 11% and 19% reductions in total mortality among males and females, respectively, whereas a 30% increase in neighborhood deprivation was associated with an 11% increase in CVD and cancer-related death.
- In a retrospective cohort study of patients (N=2876) receiving care at a large health system in Miami, FL, patients in the highest quartile of weighted social determinants of health score (including foreign-born status, underrepresented race or ethnicity status, social isolation, financial strain, health literacy, education, stress, delayed care, census-based income) had higher CVD risk, measured with the FRS (OR, 1.84 [95% CI, 1.21–2.45]), than those in the lowest quartile.[29]
- Being divorced/separated or widowed or living alone was associated with a higher CVD risk (HR, 1.21 [95% CI, 1.08–1.35]) compared with being married or cohabitating in the Swedish Twin Registry (N=10 058; median follow-up, 9.8 years).[30]
- Among Black and White adults in the ARIC study, residence in the lowest quartile of neighborhood socioeconomic status during young, middle, and older adulthood was associated with 18% (HR, 1.18 [95% CI,1.02–1.36]), 21% (HR, 1.21 [95% CI, 1.04–1.39]), and 12% (HR, 1.12 [95% CI, 0.99–1.26]) higher risk of total CVD, respectively, compared with residence in the highest quartile.[31]
- In a cross-sectional analysis of data on 387 044 adults in the 2016 to 2019 BRFSS, 9% had self-reported ASCVD (CHD or stroke).[32] Female sex, household income below $75 000, unemployment, and challenges with health care access were significantly associated with a higher burden of comorbidities (hypertension, hyperlipidemia, diabetes, current cigarette smoking, and CKD) among those with ASCVD. An analysis using the CDC WONDER database to examine sex- and race-based differences in cardiovascular mortality from 1999 to 2019 determined that the age-adjusted mortality in Black and White females declined over observation years (from 602.1 and 447.0 per 100 000 population in 2009, respectively, to 351.8 and 267.5 per 100 000 population in 2019, respectively).[33] Cardiovascular mortality rates decreased for Black males from 824.1 in 1999 to 526.3 per 100 000 population in 2019 and in White males from 637.5 in 1999 to 396.0 per 100 000 population in 2019. The rate ratio for cardiovascular mortality in 2019 was 1.32 (95% CI, 1.30–1.33) for Black females and 1.33 (95% CI, 1.32–1.34) for Black males relative to their White counterparts.

## Psychological Health

- A prospective analysis of females 65 to 99 years of age from the WHI Extension Study II who were free of MI, stroke, or CHD at baseline found that after adjustment for sociodemographic factors, health behaviors, and health status, social isolation and loneliness were associated with 1.08 (95% CI, 1.03–1.12) and 1.05 (95% CI, 1.01–1.09) higher risk of CVD, respectively.[34] Having high social isolation and high loneliness scores was associated with 1.13 (95% CI, 1.06–1.20) higher risk of CVD.
- In a cross-sectional analysis of data from the 2005 to 2018 NHANES among adults 20 to 39 years of age (n=10 588) and adults 40 to 79 years of age (n=16 848), depression, measured by the Patient Health Questionnaire-9, was significantly associated with 10-year ASCVD risk, measured

by the PCE.[35] The 10-year ASCVD risk was higher among those with mild depression (6.9%) and major depression (7.6%) compared with those with no depression (6.0%) among females 40 to 79 years of age ($P<0.001$). Similarly, among males 40 to 79 years of age, the 10-year ASCVD risk was higher among those with mild depression (11.1%) and major depression (11.3%) compared with those with no depression (9.9%; $P<0.001$). Lifetime CVD risk was higher among males and females 20 to 39 years of age with mild depression or major depression compared with those with no depression ($P<0.001$).

- In a cross-sectional analysis of electronic health record data of 591 257 adults who received primary care in Minnesota and Wisconsin between 2016 and 2018, those with a history of serious mental illness (bipolar disorder, schizophrenia, or schizoaffective disorder) had a higher 10-year FRS (mean, 9.44% [95% CI, 9.29%–9.60%]) than those without serious mental illness (mean, 7.99% [95% CI, 7.97%–8.02%]).[36] Likewise, 30-year CVD rate was significantly higher in those with serious mental illness (25% in the highest-risk group) compared with those without (11% in the highest-risk group; $P<0.001$). In a follow-up study using the same data set, patients with current depression had higher 10-year CVD risk (b=0.59 [95% CI, 0.44–0.74]) and 30-year CVD risk (OR, 1.32 [95% CI, 1.26–1.39]) than those with controlled depression.[37] Those with current depression also had higher 10-year CVD risk (b=0.55 [95% CI, 0.37–0.73]) and 30-year CVD risk (OR, 1.56 [95% CI,1.48–1.65]) than those without depression.

## Risk Prediction

- In a meta-analysis of studies assessing the performance of the FRS, ATP III score, and PCE score for predicting 10-year risk of CVD, the pooled ratio of observed number of CVD events within 10 years versus the expected number of events varied in score/sex strata from 0.58 (95% CI, 0.43–0.73) for the FRS in males to 0.79 (95% CI, 0.60–0.97) for the ATP III score in females. In other words, these equations overestimated the number of events over 10 years by as little as 3% and as much as 57%, depending on sex and equation.[38]
- The addition of walking pace (change in C index: PCE score, +0.0031; SCORE, +0.0130), grip strength (PCE score, +0.0017; SCORE, +0.0047), or both (PCE score, +0.0041; SCORE, +0.0148) improved 10-year CVD risk prediction in the UK Biobank (N=406 834).[39]
- In an analysis of electronic health record data from 56 130 Asian (Asian Indian, Chinese, Filipino, Vietnamese, Japanese, and other Asian) and 19 760 Hispanic (Mexican, Puerto Rican, and other Hispanic) individuals who received care in Northern California between 2006 and 2015, the PCE overestimated ASCVD risk by 20% to 60%.[40]
- SCORE2, a risk prediction algorithm derived from 45 cohorts in 13 European countries (677 684 adults, 30 121 CVD events), was used to estimate the 10-year risk of fatal and nonfatal CVD among adults 40 to 69 years of age who were free of diabetes or CVD, and C indices ranged from 0.67 (95% CI, 0.65–0.68) to 0.81 (95% CI, 0.76–0.86) across the countries.[41] Furthermore, the SCORE2–Older Persons risk prediction algorithm was developed to estimate 5- and 10- year risk of CVD among adults >65 years of age without preexisting ASCVD from the Cohort of Norway (28 503 individuals, 10 089 CVD events) with C indices ranging between 0.63 (95% CI, 0.61–0.65) and 0.67 (95% CI, 0.64–0.69) in 4 geographic risk regions in Europe.[42]
- Among 6701 participants in MESA who were free of ASCVD during a median follow-up of 13.2 years for ASCVD and 12.5 years for ASCVD-CAC, 2 novel LDL-C calculations, $LDL_{Martin}$ and $LDL_{Sampson}$, did not underestimate or overestimate ASCVD risk compared with the traditional $LDL_{Friedewald}$ equation in primary prevention using AHA/ACC guidelines.[43] However, the $LDL_{Friedewald}$ equation underestimated ASCVD risk in adults who were at low risk.
- Higher LTPA promotes cardiovascular wellness. Higher LTPA was associated with lower ASCVD risk (aHR per 1-SD higher LTPA, 0.91 [95% CI, 0.86–0.96]). The addition of LTPA did not improve the performance of the PCE among 18 824 adults in 3 prospective cohort studies (MESA, ARIC, and CHS).[44] There was no difference in PCE risk discrimination (C statistic, 0.76–0.78) and risk calibration (all $\chi^2$ $P>0.10$) across 4 LTPA groups (inactive, less than guideline recommended, guideline recommended, and greater than guideline recommended).
- A pooled analysis of data from 4 cohort studies, 147 645 individuals from 21 countries in the PURE study and 40 countries in 3 prospective studies, demonstrated that the association between fish intake and risk of major CVD events varied by CVD status, with a lower risk found among those with established vascular disease but not in general populations (for major CVD, $I^2$=82.6, $P$=0.02; for death, $I^2$=90.8, $P$=0.001).[45] Furthermore, among 3 cohorts of patients with vascular disease, risk of major CVD (aHR, 0.84 [95% CI, 0.73–0.96]) was lower among those with intakes of ≥175 g/wk (or ≈2 servings/wk) compared with ≤50 g/mo.
- Including a history of APO (placenta previa, preterm delivery, placenta abruption, stillbirth, abortion, pregnancy-induced hypertension/preeclampsia, gestational

diabetes, and ectopic pregnancy) in the FRS enhanced the prediction of CVD among 4013 females in the Tehran Lipid and Glucose Study compared with the original FRS that included traditional CVD risk factors (C statistic difference, 0.0053).[46] Females who had a history of multiple APOs had a higher CVD risk compared with those with 1 or no adverse pregnancy outcomes (1 APO: aHR, 1.22 [95% CI, 1.01–1.47]; 2 APOs: aHR,1.94 [95% CI, 1.54–2.51], ≥3 APOs: aHR, 2.48 [95% CI, 1.51–4.07]). Among 95 465 ever-gravid females who participated in the NHS, a history of pregnancy loss was associated with a higher risk for CVD (aHR, 1.21 [95% CI, 1.10–1.33]) over a mean follow-up of 23.10 years.[47]

## Borderline Risk Factors/Subclinical/Unrecognized Disease

- Among 2119 participants in the Framingham Offspring Cohort study, the aHR for CVD events among those with concurrent high central pulse pressure and high carotid-femoral PWV versus those with concurrent low central pulse pressure and low carotid-femoral PWV was 1.52 (95% CI, 1.10–2.11).[48]
- Among 1005 patients with known CAD who had 2 CCTA scans in the PARADIGM study, those with a high ASCVD risk score (>20%) had a larger average annual increase in total plaque (1%) compared with those with an intermediate ASCVD risk score (7.5%–20% risk; 0.6% increase of total plaque; $P<0.001$) or low ASCVD risk score (<7.5% risk; 0.5% increase in total plaque; $P<0.001$).[49]
- Among 1849 females participating in the Mexican Teachers' Cohort living in Chiapas, Yucatán, or Nuevo León who were sampled to be included in an ancillary study on CVD, having a family member incarcerated was associated with an OR of 1.41 (95% CI, 1.04–2.00) for carotid atherosclerosis (mean left or right IMT ≥0.8 mm or plaque). This OR was adjusted for age, site, and demographic variables such as indigenous background, education, and marital status, as well as exposure to violence.[50]
- Among individuals ≥45 years of age participating in the CORE-Thailand registry, having a low ABI <0.9 was associated with a 49% increased (OR, 1.49 [95% CI, 1.08–2.08]) risk of a decline in glomerular filtration rate >40%, eGFR <15 $mL{\cdot}min^{-1}{\cdot}1.73\ m^{-2}$, doubling of serum creatinine, or initiation of dialysis.[51]

## Genetics and Family History

- Genetic contributors to the end points that compose total CVD are described elsewhere (see Chapters 8 [High Blood Pressure], 15 [Stroke (Cerebrovascular Diseases)], 21 [Coronary Heart Disease, Acute Coronary Syndrome, and Angina Pectoris], 22 [Cardiomyopathy and Heart Failure], and 25 [Peripheral Artery Disease and Aortic Diseases]).
- Genome-wide data on 47 309 cases and 930 014 controls identified 12 independent variant associations for HF at 11 genomic loci. These loci are associated with modifiable risk factors such as AF (*PITX2*), BMI (*FTO*), and CAD (*9p21, LPA*). At this time, however, there is no conclusive evidence that HF is genetically determined in the majority of cases or that it develops independently of known risk factors such as obesity, hypertension, or AF in the majority of cases.[52]
- Investigation of data from >450 000 individuals from the UK Biobank found that reduced telomeric length was associated with an increased risk of CVD (HR, 1.08 [95% CI, 1.07–1.09]).[53]
- The performance of an ASCVD GRS for prediction of ASCVD incidence has been evaluated.[54] In populations with diverse ethnicity and ancestry from the ARIC, MESA, and UK Biobank studies, improved prediction of ASCVD for White, African, and South Asian populations was demonstrated over the PCE when an ASCVD GRS was incorporated. Net reclassification improvement was 2.7% (95% CI, 1.1%–4.2%) for self-identified White individuals, 2.5% (95% CI, 0.6%–4.3%) for Black/African American/Black Caribbean/Black African individuals, and 8.7% (95% CI, 3.1–14.4) for individuals of South Asian descent.
- Among 3259 participants of the CHS, FHS, and WHI with leukocyte telomere collection dates between 1992 and 1998, a participant with a 1-kb shorter leukocyte telomere length than average for an individual 50 years of age had an HR of 1.28 (95% CI, 1.08–1.52) for cardiovascular mortality compared with a participant with an average leukocyte telomere length for an individual 50 years of age.[55]

## Prevention

## (See Chapter 2 [Cardiovascular Health] for more detailed statistics on healthy lifestyle and low risk factor levels.)

- During >5 million person-years of follow-up combined in the NHS and HPFS, regular consumption of peanuts and tree nuts (≥2 times weekly) or walnuts (≥1 time weekly) compared with no or almost no consumption of nuts was associated with a total CVD HR of 0.86 (95% CI, 0.81–0.91).[56]
- Among young adults 18 to 30 years of age in the CARDIA study without clinical risk factors, a

Healthy Heart Score combined with self-reported information on modifiable lifestyle factors, including smoking status, alcohol intake, and healthful dietary pattern, predicted risk for early ASCVD (before 55 years of age).[57]

- According to data from NHANES, REGARDS, and RCTs on BP-lowering treatments, it is estimated that achieving the 2017 ACC/AHA BP goals could prevent 3.0 (UI, 1.1–5.1) million CVD events (CHD, stroke, and HF) compared with achieving prior BP goals from the 2003 Seventh Joint National Committee Report and the 2014 Eighth Joint National Committee. However, achieving the 2017 ACC/AHA BP goals could also increase serious adverse events by 3.3 (UI, 2.2–4.4) million.[58]
- The US IMPACT Food Policy Model, a computer simulation model, projected that a national policy combining a 30% fruit and vegetable subsidy targeted to low-income Supplemental Nutrition Assistance Program recipients and a population-wide 10% price reduction in fruits and vegetables in the remaining population could prevent ≈230 000 deaths by 2030 and reduce the socioeconomic disparity in CVD mortality by 6%.[59]
- Comparison of 3 healthy eating patterns over a total 52-week period in youth 9 to 18 years of age with BMI >95th percentile, including the AHA, Mediterranean, and plant-based diets, identified significant differences in compliance and CVD risk factors.[60] The plant-based diet was associated with best compliance (96% versus 72% for plant-based diet and 70% for AHA diet; *P*=0.026). At 52 weeks of follow-up, all 3 healthy eating patterns were associated with improvement in TC, LDL-C, fasting glucose, myeloperoxidase, and WC. Median changes in BMI were not significant at 52 weeks.

## Awareness, Treatment, and Control

- Among 5246 individuals from rural China participating in the MIND-China study, the prevalence of CVD was 35%. CVD was defined as the presence of ischemic HD, HF, AF, or stroke from a combination of self-reported medical history, ECG, and a neurological examination. Among those with prevalent CVD, the most commonly used therapies were calcium channel blockers (17.7%), traditional Chinese medicine products (16.7%), antithrombotic agents (14.0%), and lipid-lowering agents (9.4%). Approximately 50% of participants with prevalent CVD reported taking no medication for secondary prevention of CVD.[61]
- Among 202 072 participants 35 to 70 years of age in the PURE study followed up from 2005 to 2019, which included participants from 27 countries, the ORs for treatment with pharmacotherapy for secondary prevention of CVD in females compared with males varied by agent. The OR for treatment in females compared with males was 0.65 (95% CI, 0.69–0.72) for antiplatelet drugs, 0.93 (95% CI, 0.83–1.04) for β-blockers, 0.86 (95% CI, 0.77–0.96) for ACE inhibitors or ARBs, and 1.56 (95% CI, 1.37–1.77) for diuretics. These ORs were adjusted for age, education, urban versus rural location, and INTERHEART risk score.[62]
- Among 284 954 privately insured and Medicare Advantage enrollees from the OptumLab Data Warehouse database at least 21 years of age with an incident ASCVD event between 2007 and 2016, the use of statins increased modestly from 50.3% in 2007 to 59.9% in 2016; the use of high-intensity statins increased from 25% to 49.2% with an associated slight increase in statin intolerance from 4% in 2007 to 5% in 2016 among patients after stroke or TIA in receipt of high-intensity statin; the out-of-pocket costs for a 30-day supply of statins fell from $20 to $2; and the 1-year cumulative risk for a major cardiac adverse event decreased from 8.9% to 6.5%. However, among females and Black, Hispanic, and Asian individuals, statins were less likely to be prescribed or adhered to.[63]

## Mortality

### (See Tables 14-2 and 14-3 and Charts 14-2 through 14-13)

### *ICD-10 I00* to I99 for CVD; C00 to C97 for cancer; C33 to C34 for lung cancer; C50 for breast cancer; J40 to J47 for chronic lower respiratory disease; G30 for AD; E10 to E14 for diabetes; and V01 to X59 and Y85 to Y86 for accidents.

- Deaths attributable to diseases of the heart (Chart 14-2) and CVD (Chart 14-3) in the United States increased steadily during the 1900s to the 1980s, declined into the 2010s, but increased again in the later 2010s to 2020.
- CHD (40.3%) was the leading cause of CVD death in the United States in 2021, followed by stroke (17.5%), other minor CVD causes combined (17.1%), HBP (13.4%), HF (9.1%), and diseases of the arteries (2.6%; Chart 14-4).
- The age-adjusted death rate attributable to CVD increased from 228.6 per 100 000 people in 2011 to 233.3 per 100 000 in 2021, which amounts to a 2.1% increase (unpublished NHLBI tabulation using CDC WONDER[64]).
- There was a decrease in life expectancy disparity between White and Black males. In 1980, the disparity in life expectancy between the 2 groups was

7 years; however, in 2016, when the life expectancies were 76.4 and 72 years, respectively, the disparity was 4 years.[65]

- On the basis of these national CVD mortality data, the Million Hearts 2022 Initiative focuses on preventing a combined 1 million heart attacks, strokes, and other cardiovascular events[66]:
  - In 2016, >1000 deaths caused by heart attack, stroke, or other cardiovascular events occurred daily.
  - 2.2 million hospitalizations and 415 480 deaths occurred in 2016 related to CVD.
  - In addition, 35% of the life-changing cardiovascular events occurred in adults 35 to 64 years of age. This age group accounted for 775 000 hospitalizations and 73 000 deaths attributable to cardiovascular events.
  - There is remarkable geographic variation in life-changing cardiovascular events, with the highest rates being evident in the Southeast and Midwest regions of the United States.
  - The lowest CVD event rates (comprising deaths, hospitalizations, and ED visits) were in Utah (805.7), Wyoming (828.9), and Vermont (840.6), whereas the highest were noted in Washington, DC (2048.2), Tennessee (1551.6), and Kentucky (1510.3).
- On the basis of 2021 mortality data (unpublished NHLBI tabulation using the NVSS[67]):
  - HD and stroke currently claim more lives each year than cancer and chronic lower respiratory disease combined. In 2021, 214.9 of 100 000 people died of HD and stroke.
  - In 2021, 3 464 231 resident deaths were registered in the United States, which exceeds the 2020 figure by 80 502 deaths. Of all registered deaths, the 10 leading causes accounted for 74.5%. The 10 leading causes of death in 2021 were similar to those in 2020, with the addition of chronic liver disease and cirrhosis as the No. 9 cause replacing influenza and pneumonia, which dropped from the top 10. From 2020 to 2021, 8 of the 10 leading causes of death had an increase in age-adjusted death rates. The age-adjusted rate increased 3.3% for HD, 1.7% for cancer, 22.5% for COVID-19, 12.3% for unintentional injuries, 5.9% for stroke, 2.4% for diabetes, 9.0% for chronic liver disease and cirrhosis, and 7.1% for kidney disease. The age-adjusted death rates decreased 4.7% for chronic lower respiratory disease and 4.3% for AD.[68]
- CHD accounted for 375 476 of the total 931 578 CVD deaths in 2021 (unpublished NHLBI tabulation using NVSS[67]).
- The number of CVD deaths for both sexes and by age category is shown in Table 14-2.
- The percentages of total deaths caused by CVD and other leading causes by race and ethnicity are presented in Charts 14-5 through 14-8.
- The number of CVD deaths per year for all males and females in the United States declined from 1980 to 2010 but increased in recent years from 783 475 in 2011 to 931 578 in 2021 (Chart 14-9). Although the number of CVD deaths per year was greatest among females between 1984 and 2013, beginning in 2013, CVD deaths in males exceeded the number of CVD-related deaths in females. The difference in age-adjusted death rates for HD also narrowed among US racial and ethnic groups between 1999 and 2021. Nonetheless, there was a decrease in the rate of decline in the overall age-adjusted HD death rate in recent years, and differences in death rates persisted among major US racial and ethnic groups. In 1999, there were 337.4 deaths per 100 000 individuals among NH Black people compared with 156.5 among NH Asian people and NH Native Hawaiian and other Pacific Islander people. In 2021, the death rates per 100 000 people for these 2 groups were 226.2 and 88.1, respectively, thus preserving the >2-fold difference in death rates observed in 1999 (unpublished NHLBI tabulation using CDC WONDER[64]).
- The age-adjusted death rates per 100 000 people for CVD, CHD, and stroke differ by US state (Table 14-3) and globally (Charts 14-10 through 14-13).
- Among individuals with additional risk factors associated with increased CVD risk (eg, patients with diabetes and target organ damage, CKD stages 3 to 4, index CVD-related event within 2 years after prior MI or ischemic stroke, and polyvascular disease), risk for MACEs (ie, composite of MI, ischemic stroke, and cardiovascular-related death) persists after initial MI or ischemic stroke despite the use of moderate- or high-intensity statins.[69] Compared with the overall population, risks for incident MI were 2 to 3 times higher among individuals with stated additional risk factors than among individuals without additional stated risk factors. MACE rates are highest in the first 1 to 2 years after the event (MI, ischemic stroke, or cardiovascular-related death).

## Complications

- Among 392 participants in the National Health and Aging Trends Study who were at least 65 years of age and functionally independent at baseline, 23.8% of those with CVD at baseline experienced rapid functional decline compared with 16.2% of those without CVD at baseline. The Short Physical Performance Battery was used to assess physical function.[70]

- In a meta-analysis of 18 studies (N=4858 patients) in patients with COVID-19 conducted from November 2019 through April 2020, the OR for severe COVID-19 in those with preexisting CVD compared with those without CVD was 3.14 (95% CI, 2.32–4.24). The meta-analysis included both cohort and case-control studies from China (16 studies) and the United States (2 studies).[71]
- In a meta-analysis of 25 studies of individuals diagnosed with COVID-19 (65 484 individuals), the authors investigated associations between preexisting conditions and death attributable to COVID-19. In the 14 studies that investigated CVD, preexisting CVD had an RR of 2.25 (95% CI, 1.60–3.17).[72]

## Health Care Use: Hospital Discharges/ Ambulatory Care Visits

## (See Table 14-1 and Chart 14-14)

- Between 2005 and 2016, delays (or nonreceipt) of medical care over the preceding 12 months decreased among individuals <18, 18 to 44, and ≥65 years of age but increased among those 45 to 64 years of age.[65] Among adults 18 to 64 years of age, the percentage who reported delays or failed receipt of medical care because of cost decreased from 11.7% in 2006 to 9.8% in 2016. Those most affected by cost-related delays in care included adults 18 to 64 years of age with family income <100% or at 100% to 199% of the poverty level; these individuals were 3 times as likely as those at ≥400% above the poverty level to experience delays in receiving or failure to receive necessary medical care.
- In 2019, 8.3% (95% CI, 7.9%–8.8%) of US adults ≥18 years of age did not obtain needed medical care because of cost within the previous 12 months.[73]
- From 2010 to 2020, the number of inpatient discharges from short-stay hospitals with CVD as the principal diagnosis decreased from ≈5.1 million to 4.4 million (Table 14-1). Readers comparing data across years should note that beginning October 1, 2015, a transition was made from *ICD-9* to *ICD-10*. This should be kept in consideration because coding changes could affect some statistics, especially when comparisons are made across these years (unpublished NHLBI tabulation using HCUP[74]).
- From 1993 to 2020, the number of hospital discharges for CVD in the United States increased in the first decade and then began to generally decline in the second decade (Chart 14-14).
- In 2019, there were 106 381 000 physician office visits with a primary diagnosis of CVD (unpublished NHLBI tabulation using NAMCS[75]). In 2020, there were 6 874 280 ED visits with a primary diagnosis of CVD (unpublished NHLBI tabulation using HCUP[74]).
- Between 2008 and 2018, there has been a declining trend in hospitalization rates from 5.6 million to 5 million per year.[76] The recent decline in CVD hospitalization rates has been driven by a decline in CVD hospitalization rates among NH Black and Hispanic US residents.

## Cost

## (See Chapter 28 [Economic Cost of Cardiovascular Disease] for detailed information.)

- The estimated direct and indirect cost of CVD for 2019 to 2020 was $422.3 billion (MEPS,[77] unpublished NHLBI tabulation).
- Type 2 diabetes accounts for >95% of all cases of diabetes in the United States among individuals >45 years of age.[78] Health care resource use was assessed with data from IBM Watson Health Analytics' MarketScan Commercial and Medicare supplemental databases. Data were collected between January 1, 2014, and September 30, 2018. Cost of CVD-related care among adults with type 2 diabetes was assessed. Costs associated with CVD in the type 2 diabetes population are high. Average all-cause health care cost per patient at baseline is $38 985 with follow-up (12 months) costs of $35 260 per patient for patients with type 2 diabetes experiencing a CVD-related event (MI, TIA, stroke).

## Global Burden

## Charts 14-10 through 14-13, 14-15, and 14-16 and Supplemental Material

- Death rates for CVD, CHD, stroke, and all CVD in selected countries in 2020 are presented in Charts 14-10 through 14-13.
- CVD mortality and prevalence vary widely among world regions. In 204 countries and territories[79]:
  - In 2021, 19.91 (95% UI, 18.38–21.20) million deaths were estimated for CVD globally, which amounted to an increase of 21.56% (95% UI, 16.41%–27.49%) from 2010. The age-standardized death rate per 100 000 population was 237.91 (95% UI, 219.24–253.71), which represents a decrease of 14.46% (95% UI, −18.09% to −10.38%) from 2010. There were 614.51 (95% UI, 581.23–646.65) million prevalent cases of CVD in 2021, an increase of 33.64% (95% UI, 31.38%–36.37%) compared with 2010. The age-standardized prevalence rate was 7239.08

(95% UI, 6858.23–7609.10) per 100 000, an increase of 1.54% (95% UI, −0.11% to 3.71%) from 2010.
  - In 2021, the highest mortality rates estimated for CVD were in central Asia, with high levels also seen in eastern Europe, Oceania, central sub-Saharan Africa, and North Africa and the Middle East. Rates were lowest for high-income Asia Pacific and Australasia (Chart 14-15).
  - In 2021, CVD prevalence was estimated as highest in North Africa and the Middle East followed by southern sub-Saharan Africa. Prevalence was lowest in high-income Asia Pacific and Southeast Asia. (Chart 14-16).
- CVD represents 37% of deaths in individuals <70 years of age that are attributable to noncommunicable diseases.[80]
- In 2019, 27% of the world's deaths were caused by CVD, making it the predominant cause of death globally.[80]
- See the Supplemental Material for additional global and regional CVD statistics.

**Table 14-1. CVDs in the United States**

| Population group | Total CVD prevalence,* 2017–2020: ≥20 y of age | Prevalence, 2017–2020: ≥20 y of age† | Mortality, 2021: all ages‡ | Hospital discharges, 2020: all ages | Cost, 2019–2020 |
|---|---|---|---|---|---|
| Both sexes | 127 900 000 (48.6%) | 28 600 000 (9.9%) | 931 578 | 4 449 679 | $422.3 Billion |
| Males | 65 400 000 (52.4%) | 14 800 000 (10.9%) | 491 849 (52.8%)§ | … | $260.7 Billion |
| Females | 62 500 000 (44.8%) | 13 800 000 (9.2%) | 439 729 (47.2%)§ | … | $161.6 Billion |
| NH White males | 51.2% | 11.3% | 368 383 | … | … |
| NH White females | 44.6% | 9.2% | 332 174 | … | … |
| NH Black males | 58.9% | 11.3% | 66 044 | … | … |
| NH Black females | 59.0% | 11.1% | 59 464 | … | … |
| Hispanic males | 51.9% | 8.7% | 36 680 | … | … |
| Hispanic females | 37.3% | 8.4% | 30 216 | … | … |
| NH Asian males | 51.5% | 6.9% | 13 468‖ | … | … |
| NH Asian females | 38.5% | 4.9% | 12 536‖ | … | … |
| NH American Indian/Alaska Native | … | … | 4967 | … | … |
| NH Native Hawaiian or Pacific Islander | | | 1355 | | |

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.[81]

COVID-19 indicates coronavirus disease 2019; CVD, cardiovascular disease; ellipses (…), data not available; NHANES, National Health and Nutrition Examination Survey; and NH, non-Hispanic.

*Total CVD prevalence includes coronary heart disease, heart failure, stroke, and hypertension. CVD prevalence rates do not include peripheral artery disease (PAD) because the ankle-brachial index measurement used to ascertain PAD was discontinued after the NHANES 2003 to 2004 cycle.

†Prevalence excluding hypertension.

‡Mortality for Hispanic, American Indian or Alaska Native, and Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting Hispanic origin or race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native, Asian and Pacific Islander, and Hispanic decedents, as well as undercounts of these groups in censuses.

§These percentages represent the portion of total CVD mortality that is attributable to males versus females.

‖Includes Chinese, Filipino, Japanese, and other Asian people.

Sources: Prevalence: Unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using NHANES.[1] Percentages for racial and ethnic groups are age adjusted for Americans ≥20 years of age. Age-specific percentages are extrapolated to the 2020 US population estimates. Mortality (for underlying cause of CVD): Unpublished NHLBI tabulation using National Vital Statistics System.[67] These data represent underlying cause of death only for *International Classification of Diseases, 10th Revision* codes I00 to I99 (diseases of the circulatory system). Hospital discharges (with a principal diagnosis of CVD): Unpublished NHLBI tabulation using Healthcare Cost and Utilization Project.[74] Cost: Unpublished NHLBI tabulation using Medical Expenditure Panel Survey,[77] average annual 2019 to 2020 (direct costs) and mortality data from National Center for Health Statistics, and present value of lifetime earnings from the Institute for Health and Aging, University of California, San Francisco (indirect costs).

**Table 14-2. CVD and Other Major Causes of Death: All Ages, <85 Years of Age, and ≥85 Years of Age, by Sex, 2021**

| Cause | *ICD-10* code | Total deaths | Deaths, <85 y of age | Deaths, ≥85 y of age |
|---|---|---|---|---|
| CVD | I00–I99 | 931 552 | 596 786 | 334 766 |
| Males | | 491 828 | 360 678 | 131 150 |
| Females | | 439 724 | 236 108 | 203 616 |
| HD | I00–I09, I11, I13, I20–I51 | 695 523 | 451 790 | 243 733 |
| Males | | 384 867 | 283 896 | 100 971 |
| Females | | 310 656 | 167 894 | 142 762 |
| Cancer | C00–C97 | 605 206 | 502 847 | 102 359 |
| Males | | 318 666 | 268 717 | 49 949 |
| Females | | 286 540 | 234 130 | 52 410 |
| COVID-19 | U07.1 | 416 890 | 335 956 | 80 934 |
| Males | | 236 607 | 198 922 | 37 685 |
| Females | | 180 283 | 137 034 | 43 249 |
| Accidents | V01–X59, Y85–Y86 | 224 916 | 198 267 | 26 649 |
| Males | | 149 589 | 138 366 | 11 223 |
| Females | | 75 327 | 59 901 | 15 426 |
| Stroke | I60–I69 | 162 889 | 96 492 | 66 397 |
| Males | | 70 851 | 49 310 | 21 541 |
| Females | | 92 038 | 47 182 | 44 856 |
| CLRD | J40–J47 | 142 340 | 106 448 | 35 892 |
| Males | | 67 526 | 52 954 | 14 572 |
| Females | | 74 814 | 53 494 | 21 320 |
| AD | G30 | 119 398 | 45 086 | 74 312 |
| Males | | 36 974 | 16 645 | 20 329 |
| Females | | 82 424 | 28 441 | 53 983 |
| All other CVD | Residual, I10, I12, I15, I70–I99 | 73 140 | 48 504 | 24 636 |
| Males | | 36 110 | 27 472 | 8638 |
| Females | | 37 030 | 21 032 | 15 998 |

Deaths with age not stated are not included in the totals.

AD indicates Alzheimer disease; CLRD, chronic lower respiratory disease; COVID-19, coronavirus disease 2019; CVD, cardiovascular disease; HD, heart disease; and *ICD-10*, *International Classification of Diseases, 10th Revision*.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System data.[67]

**Table 14-3. Age-Adjusted Death Rates per 100 000 People for CVD, CHD, and Stroke, by US State, 2019 to 2021**

| | CVD | | | CHD | | | Stroke | | |
|---|---|---|---|---|---|---|---|---|---|
| State | Rank | Death rate | % Change, 2009–2011 to 2019–2021 | Rank | Death rate | % Change, 2009–2011 to 2019–2021 | Rank | Death rate | % Change, 2009–2011 to 2019–2021 |
| Alabama | 50 | 308.6 | 0.6 | 19 | 82.9 | −22.8 | 50 | 53.6 | 4.1 |
| Alaska | 8 | 194.2 | −6.9 | 7 | 69.6 | −18.9 | 25 | 37.1 | −8.7 |
| Arizona | 10 | 197.2 | −1.2 | 25 | 86.1 | −20.6 | 13 | 33.0 | 5.1 |
| Arkansas | 48 | 290.3 | 0.2 | 51 | 132.0 | −8.1 | 45 | 44.6 | −14.9 |
| California | 14 | 201.9 | −7.7 | 22 | 83.5 | −24.4 | 27 | 39.4 | 4.7 |
| Colorado | 4 | 179.8 | −2.4 | 2 | 62.5 | −20.0 | 20 | 35.1 | −0.6 |
| Connecticut | 5 | 181.0 | −9.9 | 8 | 70.5 | −21.2 | 4 | 28.2 | −6.3 |
| Delaware | 30 | 225.4 | −3.0 | 24 | 85.7 | −26.8 | 49 | 51.5 | 24.9 |
| District of Columbia | 38 | 246.8 | −6.9 | 38 | 103.4 | −29.9 | 31 | 40.1 | 18.4 |
| Florida | 17 | 204.1 | −1.7 | 27 | 89.2 | −18.4 | 39 | 43.4 | 33.6 |
| Georgia | 39 | 247.8 | −3.7 | 10 | 72.3 | −18.8 | 44 | 44.2 | −2.3 |

(*Continued*)

**Table 14-3. Continued**

| State | CVD | | | CHD | | | Stroke | | |
|---|---|---|---|---|---|---|---|---|---|
| | Rank | Death rate | % Change, 2009–2011 to 2019–2021 | Rank | Death rate | % Change, 2009–2011 to 2019–2021 | Rank | Death rate | % Change, 2009–2011 to 2019–2021 |
| Hawaii | 3 | 176.5 | −6.7 | 4 | 63.0 | −13.4 | 29 | 39.7 | 6.2 |
| Idaho | 21 | 207.4 | −2.9 | 14 | 79.0 | −15.6 | 22 | 36.1 | −11.5 |
| Illinois | 32 | 226.1 | −4.3 | 15 | 79.7 | −28.1 | 36 | 41.7 | 7.1 |
| Indiana | 37 | 245.4 | −3.6 | 31 | 94.8 | −18.7 | 37 | 41.9 | −5.3 |
| Iowa | 34 | 228.3 | −0.2 | 41 | 104.1 | −17.2 | 12 | 32.6 | −14.3 |
| Kansas | 29 | 224.8 | −0.3 | 34 | 99.2 | 4.4 | 24 | 36.6 | −11.4 |
| Kentucky | 44 | 265.7 | −3.2 | 39 | 103.8 | −17.8 | 40 | 43.5 | −3.4 |
| Louisiana | 47 | 283.0 | −1.7 | 36 | 100.6 | −17.4 | 48 | 47.6 | 3.4 |
| Maine | 12 | 200.0 | −1.1 | 17 | 81.9 | −11.3 | 11 | 32.3 | −10.5 |
| Maryland | 31 | 225.7 | −4.2 | 28 | 89.5 | −25.5 | 41 | 43.8 | 13.3 |
| Massachusetts | 1 | 169.2 | −13.6 | 3 | 62.9 | −31.6 | 2 | 25.6 | −18.4 |
| Michigan | 43 | 264.2 | 1.1 | 46 | 113.7 | −16.2 | 38 | 43.3 | 10.1 |
| Minnesota | 2 | 170.7 | 0.0 | 1 | 59.7 | −11.6 | 14 | 33.1 | −5.7 |
| Mississippi | 51 | 322.0 | −0.4 | 48 | 118.3 | −4.8 | 51 | 54.7 | 9.0 |
| Missouri | 40 | 249.2 | −4.9 | 40 | 103.8 | −22.0 | 28 | 39.7 | −10.0 |
| Montana | 23 | 210.0 | 0.7 | 32 | 94.8 | 8.1 | 7 | 30.3 | −23.6 |
| Nebraska | 19 | 205.0 | −1.8 | 9 | 71.3 | −13.9 | 17 | 34.7 | −11.4 |
| Nevada | 41 | 258.7 | 3.6 | 43 | 104.7 | 4.0 | 30 | 40.0 | 12.9 |
| New Hampshire | 6 | 191.8 | −4.1 | 11 | 76.1 | −20.0 | 5 | 29.5 | −11.4 |
| New Jersey | 20 | 207.0 | −8.8 | 23 | 84.6 | −27.7 | 10 | 31.5 | −4.5 |
| New Mexico | 18 | 204.3 | 1.5 | 42 | 104.4 | 2.1 | 19 | 35.0 | −1.9 |
| New York | 26 | 213.7 | −13.4 | 47 | 114.9 | −23.1 | 1 | 24.8 | −9.9 |
| North Carolina | 28 | 221.4 | −6.4 | 18 | 82.7 | −23.0 | 43 | 44.1 | −2.0 |
| North Dakota | 9 | 196.5 | −6.8 | 16 | 81.2 | −24.0 | 8 | 31.0 | −21.4 |
| Ohio | 42 | 260.4 | 3.2 | 37 | 102.8 | −16.5 | 47 | 45.4 | 8.5 |
| Oklahoma | 49 | 303.2 | 1.4 | 45 | 113.1 | −25.0 | 33 | 40.6 | −16.4 |
| Oregon | 11 | 199.8 | 0.7 | 5 | 63.7 | −19.6 | 35 | 41.6 | −0.2 |
| Pennsylvania | 33 | 227.7 | −6.8 | 29 | 92.8 | −20.6 | 23 | 36.5 | −8.4 |
| Rhode Island | 13 | 201.2 | −5.5 | 33 | 96.8 | −22.8 | 3 | 27.5 | −10.5 |
| South Carolina | 36 | 237.5 | −6.4 | 20 | 83.1 | −21.6 | 46 | 44.6 | −7.8 |
| South Dakota | 22 | 209.1 | −4.4 | 35 | 99.5 | −16.7 | 16 | 34.4 | −15.6 |
| Tennessee | 46 | 276.5 | −1.2 | 49 | 124.3 | −17.2 | 42 | 43.8 | −9.3 |
| Texas | 35 | 229.9 | −3.7 | 30 | 94.4 | −15.1 | 34 | 41.2 | −5.8 |
| Utah | 15 | 202.2 | 3.8 | 6 | 65.5 | −8.3 | 15 | 33.8 | −10.0 |
| Vermont | 25 | 213.7 | 6.8 | 44 | 108.9 | 5.7 | 6 | 29.9 | −4.9 |
| Virginia | 24 | 211.7 | −6.0 | 12 | 78.6 | −17.9 | 32 | 40.1 | −4.8 |
| Washington | 7 | 192.5 | −5.5 | 13 | 78.8 | −21.1 | 21 | 35.8 | −3.5 |
| West Virginia | 45 | 267.7 | −5.2 | 50 | 127.2 | −7.0 | 26 | 39.4 | −15.2 |
| Wisconsin | 27 | 215.3 | −1.1 | 26 | 88.7 | −11.5 | 18 | 34.8 | −8.0 |
| Wyoming | 16 | 203.9 | −6.4 | 21 | 83.3 | −12.8 | 9 | 31.3 | −19.8 |
| Total United States | | 224.0 | −4.5 | | 90.8 | −19.9 | | 38.9 | 0.2 |

Rates are most current data available as of March 2020. Rates are per 100 000 people. *International Classification of Diseases, 10th Revision* codes used were I00 to I99 for CVD, I20 to I25 for CHD, and I60 to I69 for stroke.

CHD indicates coronary heart disease; and CVD, cardiovascular disease.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System data.[67]

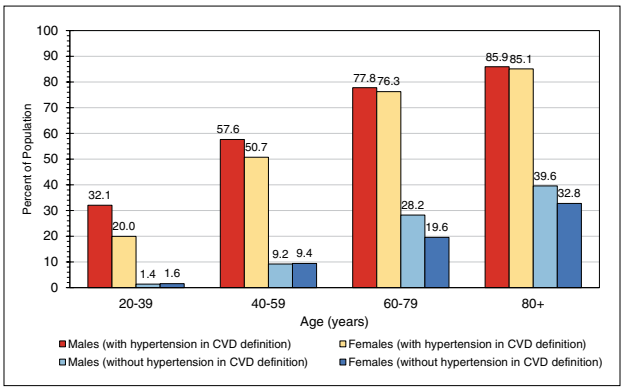



**Chart 14-1. Prevalence of CVD in US adults ≥20 years of age, by age and sex (NHANES, 2017–2020).**
These data include CHD, HF, stroke, and with and without hypertension.
CHD indicates coronary heart disease; CVD, cardiovascular disease; HF, heart failure; and NHANES, National Health and Nutrition Examination Survey.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.[1]

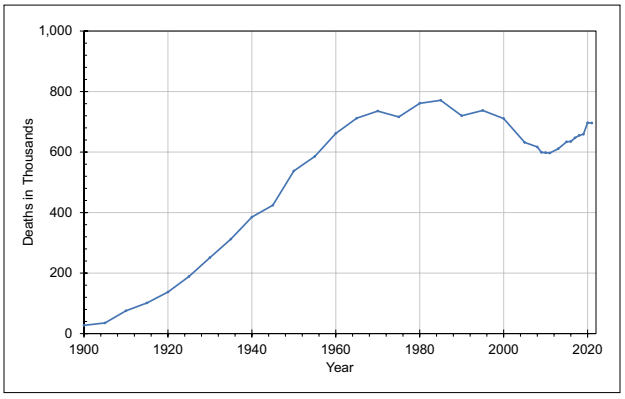



**Chart 14-2. Deaths attributable to diseases of the heart, United States, 1900 to 2021.**
See Glossary (Chapter 30) for an explanation of diseases of the heart. In the years 1900 to 1920, the *ICD* codes were 77 to 80; for 1925, 87 to 90; for 1930 to 1945, 90 to 95; for 1950 to 1960, 402 to 404 and 410 to 443; for 1965, 402 to 404 and 410 to 443; for 1970 to 1975, 390 to 398 and 404 to 429; for 1980 to 1995, 390 to 398, 402, and 404 to 429; and for 2000 to 2019, I00 to I09, I11, I13, and I20 to I51. Before 1933, data are for a death registration area, not the entire United States. In 1900, only 10 states were included in the death registration area, and this increased over the years, so part of the increase in numbers of deaths is attributable to an increase in the number of states.
*ICD* indicates *International Classification of Diseases*.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System.[67]

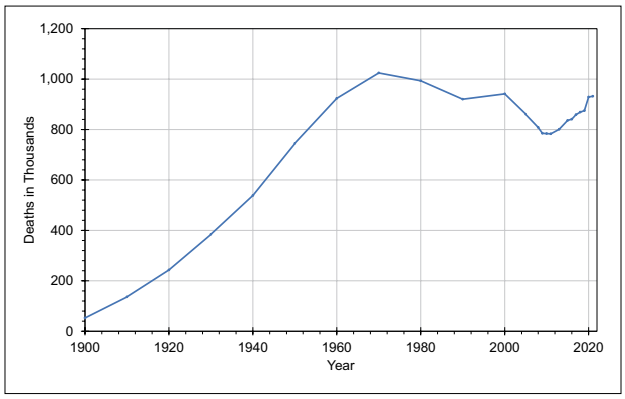



**Chart 14-3. Deaths attributable to CVD, United States, 1900 to 2021.**
CVD (*ICD-10* codes I00–I99) does not include congenital heart disease. Before 1933, data are for a death registration area, not the entire United States.
CVD indicates cardiovascular disease; and *ICD-10*, *International Classification of Diseases, 10th Revision*.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System.[67]

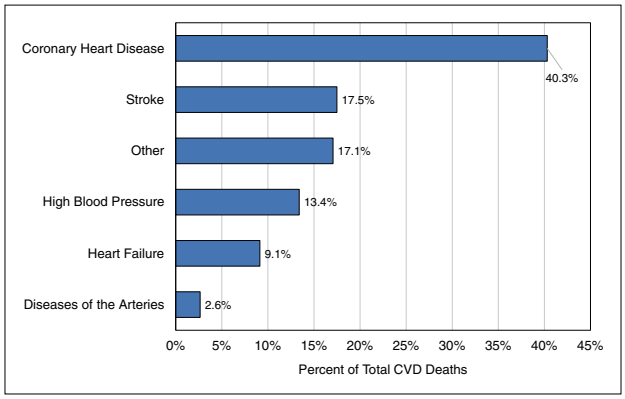



**Chart 14-4. Percentage breakdown of deaths attributable to CVD, United States, 2021.**
Total may not add to 100 because of rounding. CHD includes *ICD-10* codes I20 to I25; stroke, I60 to I69; HF, I50; HBP, I10 to I15; diseases of the arteries, I70 to I78; and other, all remaining *ICD-10* I categories.
CHD indicates coronary heart disease; CVD, cardiovascular disease; HBP, high blood pressure; HF, heart failure; and *ICD-10*, *International Classification of Diseases, 10th Revision*.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System.[67]

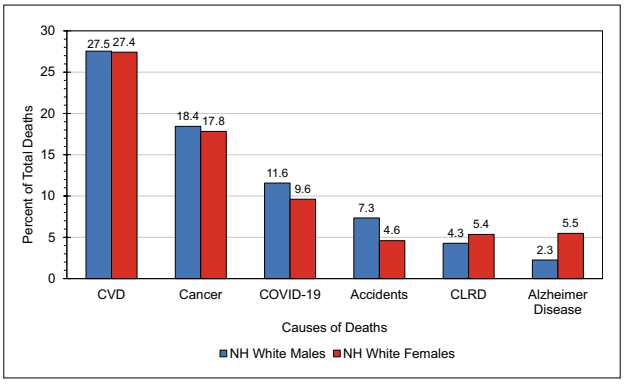



**Chart 14-5. CVD and other major causes of death for NH White males and females, United States, 2021.**
Diseases included CVD (*ICD-10* codes I00–I99), cancer (C00–C97), CLRD (J40–J47), COVID-19 (U07.1), accidents (V01–X59 and Y85–Y86), and AD (G30).
AD indicates Alzheimer disease; CLRD, chronic lower respiratory disease; COVID-19, coronavirus disease 2019; CVD, cardiovascular disease; *ICD-10*, *International Classification of Diseases, 10th Revision*; and NH, non-Hispanic.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System.[67]

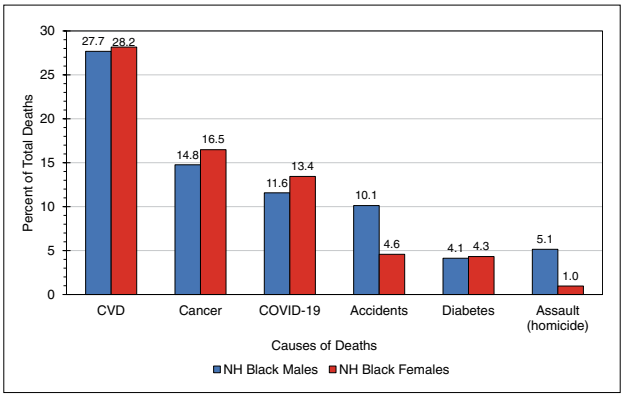



**Chart 14-6. CVD and other major causes of death for NH Black males and females, United States, 2021.**
Diseases included CVD (*ICD-10* codes I00–I99), cancer (C00–C97), COVID-19 (U07.1), accidents (V01–X59, Y85, and Y86), assault (homicide; U01, U02, X85–Y09, and Y87.1), and diabetes (E10–E14).
CLRD indicates chronic lower respiratory disease; COVID-19, coronavirus disease 2019; CVD, cardiovascular disease; *ICD-10*, *International Classification of Diseases, 10th Revision*; and NH, non-Hispanic.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System.[67]

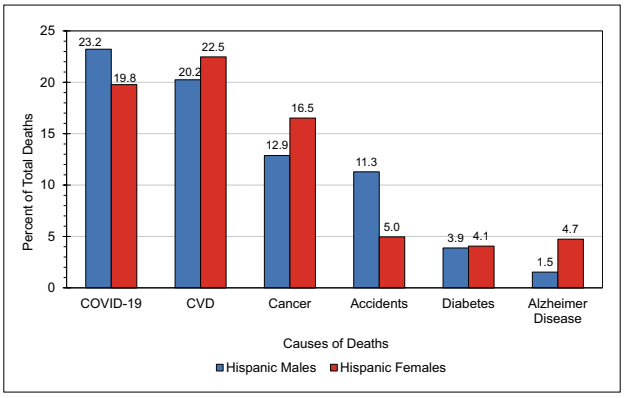



**Chart 14-7. CVD and other major causes of death for Hispanic or Latino males and females, United States, 2021.**
Number of deaths shown may be lower than actual because of underreporting in this population. Diseases included CVD (*ICD-10* codes I00–I99), COVID-19 (U07.1), cancer (C00–C97), accidents (V01–X59 and Y85–Y86), diabetes (E10–E14), and AD (G30).
AD indicates Alzheimer disease; COVID-19, coronavirus disease 2019; CVD, cardiovascular disease; and *ICD-10*, *International Classification of Diseases, 10th Revision*.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System.[67]

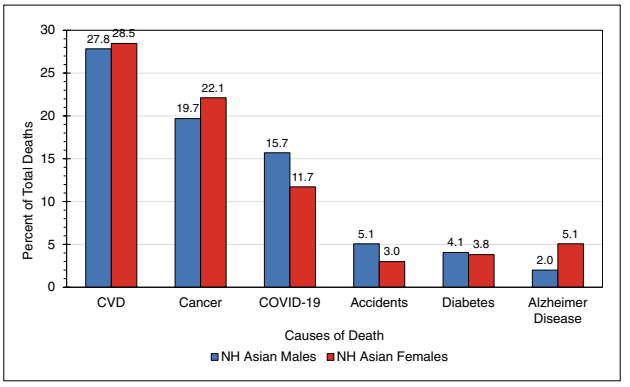



**Chart 14-8. CVD and other major causes of death for NH Asian or Pacific Islander males and females, United States, 2021.**
Asian or Pacific Islander is a heterogeneous category that includes people at high CVD risk (eg, South Asian people) and people at low CVD risk (eg, Japanese people). More specific data on these groups are not available. Number of deaths shown may be lower than actual because of underreporting in this population. Diseases included CVD (*ICD-10* codes I00–I99), cancer (C00–C97), COVID-19 (U07.1), accidents (V01–X59, Y85, and Y86), diabetes (E10–E14), and AD (G30).
AD indicates Alzheimer disease; COVID-19, coronavirus disease 2019; CVD, cardiovascular disease; *ICD-10*, *International Classification of Diseases, 10th Revision*; and NH, non-Hispanic.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System.[67]

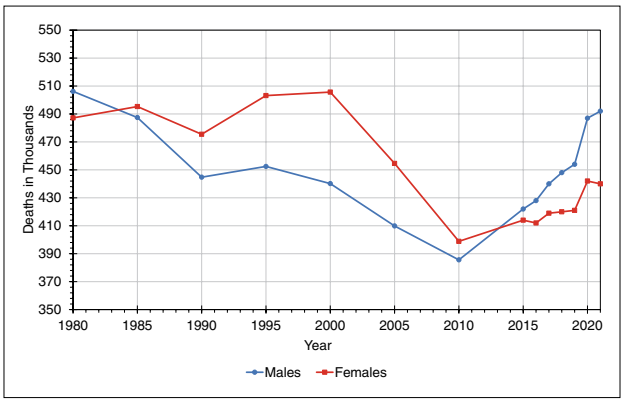



**Chart 14-9. CVD mortality trends for US males and females, 1980 to 2021.**
CVD excludes congenital cardiovascular defects (*ICD-10* codes I00–I99). The overall comparability for CVD between *ICD-9* (1979–1998) and *ICD-10* (1999–2015) is 0.9962. No comparability ratios were applied.
CVD indicates cardiovascular disease; *ICD-9*, *International Classification of Diseases, 9th Revision*; and *ICD-10*, *International Classification of Diseases, 10th Revision*.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System.[67]

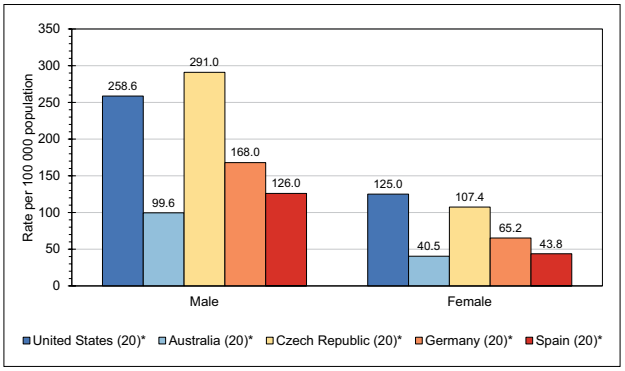



**Chart 14-10. Death rates per 100 000 population for CVD in selected countries for adults 35 to 74 years of age, 2020.**
Rates are adjusted to the European Standard Population. *ICD-10* codes are I00 to I99 for CVD.
CVD indicates cardiovascular disease; and *ICD-10*, *International Classification of Diseases, 10th Revision*.
*Number in parentheses indicates year of most recent data available (20 is 2020).
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using World Health Organization Mortality Database.[82]

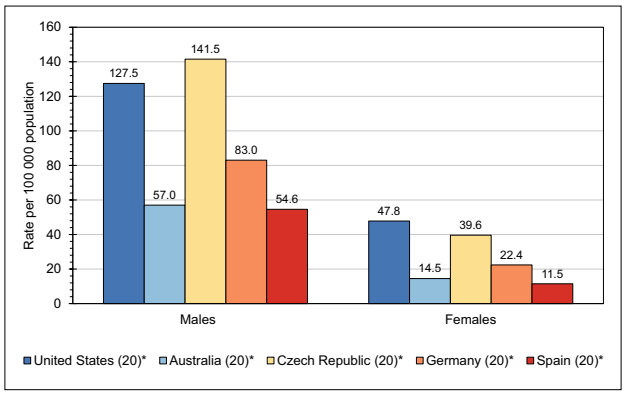



**Chart 14-11. Death rates per 100 000 population for CHD in selected countries for adults 35 to 74 years of age, 2020.**
Rates are adjusted to the European Standard Population. *ICD-10* codes are I20 to I25 for CHD.
CHD indicates coronary heart disease; and *ICD-10*, *International Classification of Diseases, 10th Revision*.
*Number in parentheses indicates year of most recent data available (20 is 2020).
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using World Health Organization Mortality Database.[82]

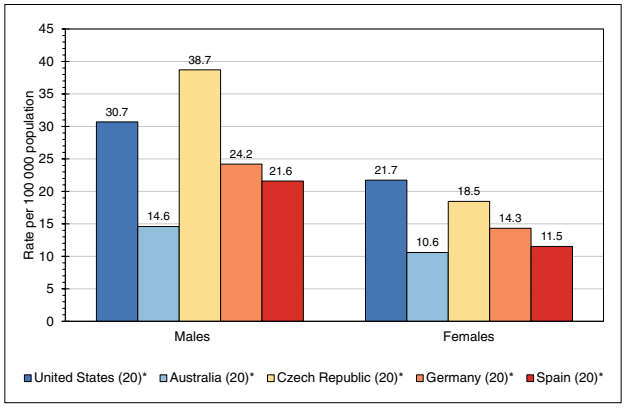



**Chart 14-12. Death rates per 100 000 population for stroke in selected countries for adults 35 to 74 years of age, 2020.**
Rates are adjusted to the European Standard Population. *ICD-10* codes are I60 to I69 for stroke.
*ICD-10* indicates *International Classification of Diseases, 10th Revision*.
*Number in parentheses indicates year of most recent data available (20 is 2020).
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using World Health Organization Mortality Database.[82]

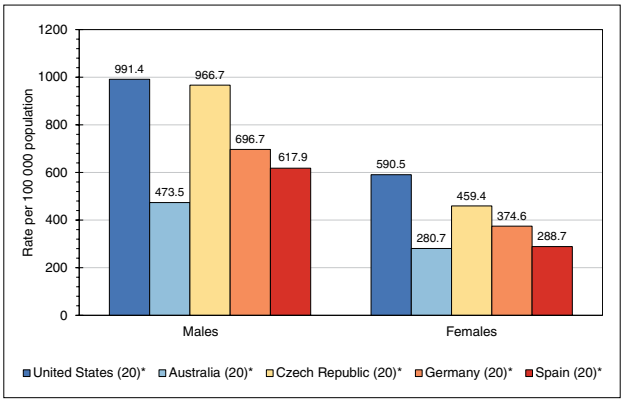



**Chart 14-13. Death rates per 100 000 population for all causes in selected countries for adults 35 to 74 years of age, 2020.**
Rates are adjusted to the European Standard Population.
*ICD-10* codes are A00 to Y89 for all causes.
*ICD-10* indicates *International Classification of Diseases, 10th Revision*.
*Number in parentheses indicates year of most recent data available (20 is 2020).
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using World Health Organization Mortality Database.[82]

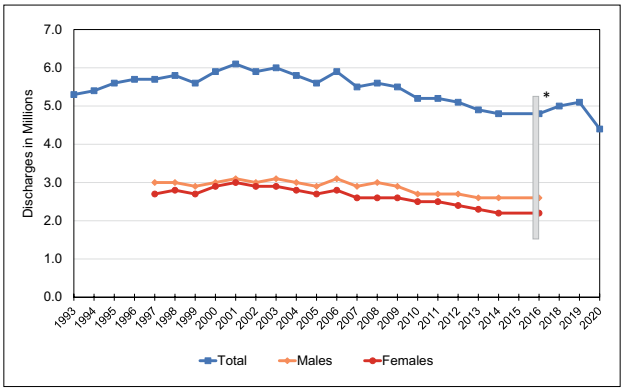



**Chart 14-14. Hospital discharges for CVD, US adults, 1993 to 2020.**
Hospital discharges include people discharged alive, dead, and status unknown. Data not available for males and females separately from 1993 to 1996 and after 2016.
CVD indicates cardiovascular disease.
*Data not available for 2015. Readers comparing data across years should note that beginning October 1, 2015, a transition was made from *International Classification of Diseases, 9th Revision* to *International Classification of Diseases, 10th Revision*. This should be kept in consideration because coding changes could affect some statistics, especially when comparisons are made across these years.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Healthcare Cost and Utilization Project.[74]

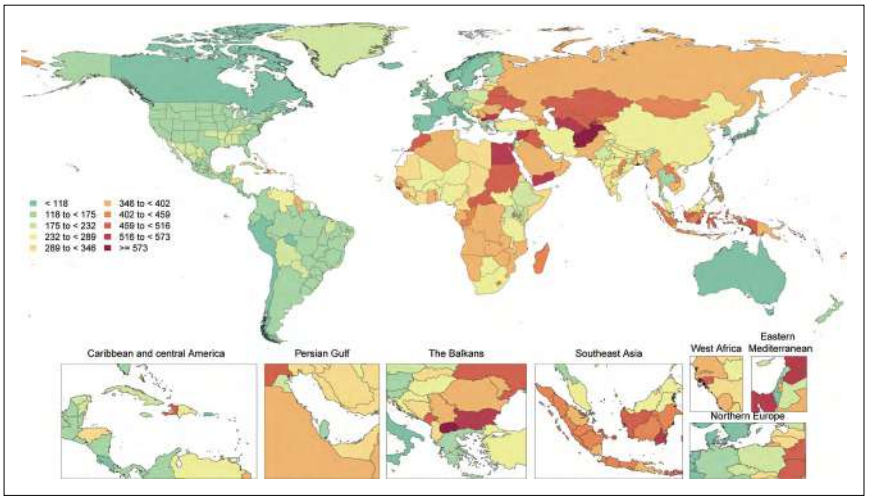



**Chart 14-15. Age-standardized global mortality rates of CVDs per 100 000, both sexes, 2021.**
During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.
CVD indicates cardiovascular disease; and GBD, Global Burden of Disease.
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[79]

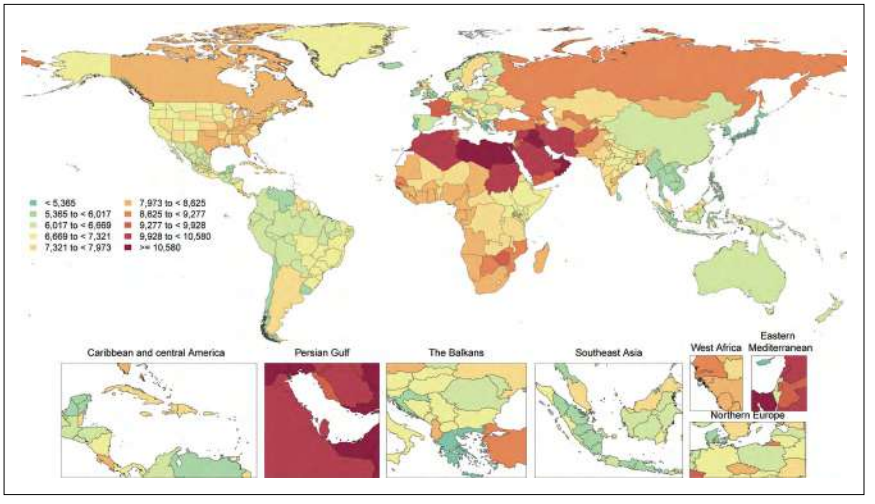



**Chart 14-16. Age-standardized global prevalence rates of CVDs per 100 000, both sexes, 2021.**
During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.
CVD indicates cardiovascular disease; and GBD, Global Burden of Disease.
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[79]

## REFERENCES


1. Centers for Disease Control and Prevention and National Center for Health Statistics. National Health and Nutrition Examination Survey (NHANES) public use data files. Accessed April 1, 2023. https://cdc.gov/nchs/nhanes/
2. Centers for Disease Control and Prevention and National Center for Health Statistics. Summary Health Statistics: National Health Interview Survey, 2018: table A-1. Accessed March 22, 2023. https://ftp.cdc.gov/pub/Health_Statistics/NCHS/NHIS/SHS/2018_SHS_Table_A-1.pdf
3. Zhu H, Xi Y, Bao H, Xu X, Niu L, Tao Y, Cao N, Wang W, Zhang X. Assessment of cardiovascular disease risk in northern China: a cross-sectional study. *Ann Hum Biol*. 2020;47:498–503. doi: 10.1080/03014460.2020.1779814
4. Irawati S, Wasir R, Floriaan Schmidt A, Islam A, Feenstra T, Buskens E, Wilffert B, Hak E. Long-term incidence and risk factors of cardiovascular events in Asian populations: systematic review and meta-analysis of population-based cohort studies. *Curr Med Res Opin*. 2019;35:291–299. doi: 10.1080/03007995.2018.1491149
5. Bancks MP, Ning H, Allen NB, Bertoni AG, Carnethon MR, Correa A, Echouffo-Tcheugui JB, Lange LA, Lloyd-Jones DM, Wilkins JT. Long-term absolute risk for cardiovascular disease stratified by fasting glucose level. *Diabetes Care*. 2019;42:457–465. doi: 10.2337/dc18-1773
6. Bundy JD, Ning H, Zhong VW, Paluch AE, Lloyd-Jones DM, Wilkins JT, Allen NB. Cardiovascular health score and lifetime risk of cardiovascular disease: the Cardiovascular Lifetime Risk Pooling Project [published online ahead of print June 30, 2020]. *Circ Cardiovasc Qual Outcomes*. doi: 10.1161/CIRCOUTCOMES.119.006450. https://www.ahajournals.org/doi/10.1161/CIRCOUTCOMES.119.006450?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed
7. Vasan RS, Enserro DM, Xanthakis V, Beiser AS, Seshadri S. Temporal trends in the remaining lifetime risk of cardiovascular disease among middle-aged adults across 6 decades: the Framingham study. *Circulation*. 2022;145:1324–1338. doi: 10.1161/CIRCULATIONAHA.121.057889
8. Gali B, Eyawo O, Hull MW, Samji H, Zhang W, Sereda P, Lima VD, McGrail K, Montaner JSG, Hogg RS, et al; COAST Study Team. Incidence of select chronic comorbidities among a population-based cohort of HIV-positive individuals receiving highly active antiretroviral therapy. *Curr Med Res Opin*. 2019;35:1955–1963. doi: 10.1080/03007995.2019.1645999
9. Tith RM, Paradis G, Potter BJ, Low N, Healy-Profitós J, He S, Auger N. Association of bulimia nervosa with long-term risk of cardiovascular disease and mortality among women. *JAMA Psychiatry*. 2020;77:44–51. doi: 10.1001/jamapsychiatry.2019.2914
10. Kurth T, Rist PM, Ridker PM, Kotler G, Bubes V, Buring JE. Association of migraine with aura and other risk factors with incident cardiovascular disease in women. *JAMA*. 2020;323:2281–2289. doi: 10.1001/jama.2020.7172
11. Erqou S, Clougherty JE, Olafiranye O, Magnani JW, Aiyer A, Tripathy S, Kinnee E, Kip KE, Reis SE. Particulate matter air pollution and racial differences in cardiovascular disease risk. *Arterioscler Thromb Vasc Biol*. 2018;38:935–942. doi: 10.1161/ATVBAHA.117.310305
12. Tu R, Hou J, Liu X, Li R, Dong X, Pan M, Mao Z, Huo W, Chen G, Guo Y, et al. Physical activity attenuated association of air pollution with estimated 10-year atherosclerotic cardiovascular disease risk in a large rural Chinese adult population: a cross-sectional study. *Environ Int*. 2020;140:105819. doi: 10.1016/j.envint.2020.105819
13. Wang Y, O'Neil A, Jiao Y, Wang L, Huang J, Lan Y, Zhu Y, Yu C. Sex differences in the association between diabetes and risk of cardiovascular disease, cancer, and all-cause and cause-specific mortality: a systematic review and meta-analysis of 5,162,654 participants. *BMC Med*. 2019;17:136. doi: 10.1186/s12916-019-1355-0
14. Wang YJ, Yeh TL, Shih MC, Tu YK, Chien KL. Dietary sodium intake and risk of cardiovascular disease: a systematic review and dose-response meta-analysis. *Nutrients*. 2020;12:2934. doi: 10.3390/nu12102934
15. Filippini T, Naska A, Kasdagli MI, Torres D, Lopes C, Carvalho C, Moreira P, Malavolti M, Orsini N, Whelton PK, et al. Potassium intake and blood pressure: a dose-response meta-analysis of randomized controlled trials. *J Am Heart Assoc*. 2020;9:e015719. doi: 10.1161/JAHA.119.015719
16. Shan Z, Li Y, Baden MY, Bhupathiraju SN, Wang DD, Sun Q, Rexrode KM, Rimm EB, Qi L, Willett WC, et al. Association between healthy eating patterns and risk of cardiovascular disease. *JAMA Intern Med*. 2020;180:1090–1100. doi: 10.1001/jamainternmed.2020.2176
17. Cunha CM, Costa PRF, de Oliveira LPM, Queiroz VAO, Pitangueira JCD, Oliveira AM. Dietary patterns and cardiometabolic risk factors among adolescents: systematic review and meta-analysis. *Br J Nutr*. 2018;119:859–879. doi: 10.1017/S0007114518000533
18. Song Q, Sun D, Zhou T, Li X, Ma H, Liang Z, Wang H, Cardoso MA, Heianza Y, Qi L. Perinatal exposure to maternal smoking and adulthood smoking behaviors in predicting cardiovascular diseases: a prospective cohort study. *Atherosclerosis*. 2021;328:52–59. doi: 10.1016/j.atherosclerosis.2021.05.009
19. Gao M, Jebb SA, Aveyard P, Ambrosini GL, Perez-Cornago A, Carter J, Sun X, Piernas C. Associations between dietary patterns and the incidence of total and fatal cardiovascular disease and all-cause mortality in 116,806 individuals from the UK Biobank: a prospective cohort study. *BMC Med*. 2021;19:83. doi: 10.1186/s12916-021-01958-x
20. Pollevick ME, Xu KY, Mhango G, Federmann EG, Vedanthan R, Busse P, Holguin F, Federman AD, Wisnivesky JP. The relationship between asthma and cardiovascular disease: an examination of the Framingham Offspring Study. *Chest*. 2021;159:1338–1345. doi: 10.1016/j.chest.2020.11.053
21. Shen Y, Zhou J, Shi L, Nauman E, Katzmarzyk PT, Price-Haywood EG, Horswell R, Bazzano AN, Nigam S, Hu G. Association between visit-to-visit HbA1c variability and the risk of cardiovascular disease in patients with type 2 diabetes. *Diabetes Obes Metab*. 2021;23:125–135. doi: 10.1111/dom.14201
22. Guasch-Ferré M, Li Y, Willett WC, Sun Q, Sampson L, Salas-Salvadó J, Martínez-González MA, Stampfer MJ, Hu FB. Consumption of olive oil and risk of total and cause-specific mortality among U.S. adults. *J Am Coll Cardiol*. 2022;79:101–112. doi: 10.1016/j.jacc.2021.10.041
23. Gan ZH, Cheong HC, Tu YK, Kuo PH. Association between plant-based dietary patterns and risk of cardiovascular disease: a systematic review and meta-analysis of prospective cohort studies. *Nutrients*. 2021;13:3952. doi: 10.3390/nu13113952
24. Wan Z, Geng T, Li R, Chen X, Lu Q, Lin X, Chen L, Guo Y, Liu L, Shan Z, et al. Vitamin D status, genetic factors, and risks of cardiovascular disease among individuals with type 2 diabetes: a prospective study. *Am J Clin Nutr*. 2022;116:1389–1399. doi: 10.1093/ajcn/nqac183
25. Oliver-Williams C, Stevens D, Payne RA, Wilkinson IB, Smith GCS, Wood A. Association between hypertensive disorders of pregnancy and later risk of cardiovascular outcomes. *BMC Med*. 2022;20:19. doi: 10.1186/s12916-021-02218-8
26. Debras C, Chazelas E, Sellem L, Porcher R, Druesne-Pecollo N, Esseddik Y, de Edelenyi FS, Agaësse C, De Sa A, Lutchia R, et al. Artificial sweeteners and risk of cardiovascular diseases: results from the prospective NutriNet-Santé cohort. *BMJ*. 2022;378:e071204. doi: 10.1136/bmj-2022-071204
27. Yang B, Glenn AJ, Liu Q, Madsen T, Allison MA, Shikany JM, Manson JE, Chan KHK, Wu WC, Li J, et al. Added sugar, sugar-sweetened beverages, and artificially sweetened beverages and risk of cardiovascular disease: findings from the Women's Health Initiative and a network meta-analysis of prospective studies. *Nutrients*. 2022;14:4226. doi: 10.3390/nu14204226

27a. Jacobs DR Jr, Woo JG, Sinaiko AR, Daniels SR, Ikonen J, Juonala M, Kartiosuo N, Lehtimäki T, Magnussen CG, Viikari JSA, et al. Childhood cardiovascular risk factors and adult cardiovascular events. *N Engl J Med*. 2022;386:1877–1888. doi: 10.1056/NEJMoa2109191

28. Xiao Q, Berrigan D, Powell-Wiley TM, Matthews CE. Ten-year change in neighborhood socioeconomic deprivation and rates of total, cardiovascular disease, and cancer mortality in older US adults. *Am J Epidemiol*. 2018;187:2642–2650. doi: 10.1093/aje/kwy181
29. Palacio A, Mansi R, Seo D, Suarez M, Garay S, Medina H, Tang F, Tamariz L. Social determinants of health score: does it help identify those at higher cardiovascular risk? *Am J Manag Care*. 2020;26:e312–e318. doi: 10.37765/ajmc.2020.88504
30. Chen R, Zhan Y, Pedersen N, Fall K, Valdimarsdóttir UA, Hägg S, Fang F. Marital status, telomere length and cardiovascular disease risk in a Swedish prospective cohort. *Heart*. 2020;106:267–272. doi: 10.1136/heartjnl-2019-315629
31. Xiao Q, Heiss G, Kucharska-Newton A, Bey G, Love SM, Whitsel EA. Life-course neighborhood socioeconomic status and cardiovascular events in Black and White adults in the Atherosclerosis Risk in Communities study. *Am J Epidemiol*. 2022;191:1470–1484. doi: 10.1093/aje/kwac070
32. Al Rifai M, Jia X, Pickett J, Hussain A, Navaneethan SD, Birtcher KK, Ballantyne C, Petersen LA, Virani SS. Social determinants of health and comorbidities among individuals with atherosclerotic cardiovascular disease: the Behavioral Risk Factor Surveillance System Survey. *Popul Health Manag*. 2022;25:39–45. doi: 10.1089/pop.2021.0084
33. Kyalwazi AN, Loccoh EC, Brewer LC, Ofili EO, Xu J, Song Y, Maddox KEJ, Yeh RW, Wadhera RK. Disparities in cardiovascular mortality between Black and White adults in the United States, 1999 to 2019. *Circulation*. 2022;146:211–228. doi: 10.1161/CIRCULATIONAHA.122.060199

34. Golaszewski NM, LaCroix AZ, Godino JG, Allison MA, Manson JE, King JJ, Weitlauf JC, Bea JW, Garcia L, Kroenke CH, et al. Evaluation of social isolation, loneliness, and cardiovascular disease among older women in the US. *JAMA Netw Open*. 2022;5:e2146461. doi: 10.1001/jamanetworkopen.2021.46461
35. Barger SD, Struve GC. Association of depression with 10-year and lifetime cardiovascular disease risk among US adults, National Health and Nutrition Examination Survey, 2005-2018. *Prev Chronic Dis*. 2022;19:E28. doi: 10.5888/pcd19.210418
36. Rossom RC, Hooker SA, O'Connor PJ, Crain AL, Sperl-Hillen JM. Cardiovascular risk for patients with and without schizophrenia, schizoaffective disorder, or bipolar disorder. *J Am Heart Assoc*. 2022;11:e021444. doi: 10.1161/JAHA.121.021444
37. Hooker SA, O'Connor PJ, Sperl-Hillen JM, Crain AL, Ohnsorg K, Kane S, Rossom R. Depression and cardiovascular risk in primary care patients. *J Psychosom Res*. 2022;158:110920. doi: 10.1016/j.jpsychores.2022.110920
38. Damen JA, Pajouheshnia R, Heus P, Moons KGM, Reitsma JB, Scholten R, Hooft L, Debray TPA. Performance of the Framingham risk models and pooled cohort equations for predicting 10-year risk of cardiovascular disease: a systematic review and meta-analysis. *BMC Med*. 2019;17:109. doi: 10.1186/s12916-019-1340-7
39. Welsh CE, Celis-Morales CA, Ho FK, Brown R, Mackay DF, Lyall DM, Anderson JJ, Pell JP, Gill JMR, Sattar N, et al. Grip strength and walking pace and cardiovascular disease risk prediction in 406,834 UK Biobank participants. *Mayo Clin Proc*. 2020;95:879–888. doi: 10.1016/j.mayocp.2019.12.032
40. Rodriguez F, Chung S, Blum MR, Coulet A, Basu S, Palaniappan LP. Atherosclerotic cardiovascular disease risk prediction in disaggregated Asian and Hispanic subgroups using electronic health records. *J Am Heart Assoc*. 2019;8:e011874. doi: 10.1161/JAHA.118.011874
41. SCORE2 Working Group and ESC Cardiovascular Risk Collaboration. SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. *Eur Heart J*. 2021;42:2439–2454. doi: 10.1093/eurheartj/ehab309
42. SCORE2-OP Working Group and ESC Cardiovascular Risk Collaboration. SCORE2-OP risk prediction algorithms: estimating incident cardiovascular event risk in older persons in four geographical risk regions. *Eur Heart J*. 2021;42:2455–2467. doi: 10.1093/eurheartj/ehab312
43. Cao J, Remaley AT, Guan W, Devaraj S, Tsai MY. Performance of novel low-density lipoprotein-cholesterol calculation methods in predicting clinical and subclinical atherosclerotic cardiovascular disease risk: the Multi-Ethnic Study of Atherosclerosis. *Atherosclerosis*. 2021;327:1–4. doi: 10.1016/j.atherosclerosis.2021.04.018
44. Pandey A, Mehta A, Paluch A, Ning H, Carnethon MR, Allen NB, Michos ED, Berry JD, Lloyd-Jones DM, Wilkins JT. Performance of the American Heart Association/American College of Cardiology Pooled Cohort Equations to estimate atherosclerotic cardiovascular disease risk by self-reported physical activity levels. *JAMA Cardiol*. 2021;6:690–696. doi: 10.1001/jamacardio.2021.0948
45. Mohan D, Mente A, Dehghan M, Rangarajan S, O'Donnell M, Hu W, Dagenais G, Wielgosz A, Lear S, Wei L, et al; PURE, ONTARGET, TRANSCEND, and ORIGIN Investigators. Associations of fish consumption with risk of cardiovascular disease and mortality among individuals with or without vascular disease from 58 countries. *JAMA Intern Med*. 2021;181:631–649. doi: 10.1001/jamainternmed.2021.0036
46. Saei Ghare Naz M, Sheidaei A, Aflatounian A, Azizi F, Ramezani Tehrani F. Does adding adverse pregnancy outcomes improve the Framingham cardiovascular risk score in women? Data from the Tehran Lipid and Glucose Study. *J Am Heart Assoc*. 2022;11:e022349. doi: 10.1161/JAHA.121.022349
47. Wang YX, Minguez-Alarcon L, Gaskins AJ, Wang L, Ding M, Missmer SA, Rich-Edwards JW, Manson JE, Chavarro JE. Pregnancy loss and risk of cardiovascular disease: the Nurses' Health Study II. *Eur Heart J*. 2022;43:190–199. doi: 10.1093/eurheartj/ehab737
48. Niiranen TJ, Kalesan B, Mitchell GF, Vasan RS. Relative contributions of pulse pressure and arterial stiffness to cardiovascular disease. *Hypertension*. 2019;73:712–717. doi: 10.1161/HYPERTENSIONAHA.118.12289
49. Han D, Berman DS, Miller RJH, Andreini D, Budoff MJ, Cademartiri F, Chinnaiyan K, Choi JH, Conte E, Marques H, et al. Association of cardiovascular disease risk factor burden with progression of coronary atherosclerosis assessed by serial coronary computed tomographic angiography. *JAMA Netw Open*. 2020;3:e2011444. doi: 10.1001/jamanetworkopen.2020.11444
50. Connors K, Flores-Torres MH, Stern D, Valdimarsdottir U, Rider JR, Lopez-Ridaura R, Kirschbaum C, Cantu-Brito C, Catzin-Kuhlmann A, Rodriguez BL, et al. Family member incarceration, psychological stress, and subclinical cardiovascular disease in Mexican women (2012-2016). *Am J Public Health*. 2020;110:S71–S77. doi: 10.2105/AJPH.2019.305397
51. Aiumtrakul N, Supasyndh O, Krittayaphong R, Phrommintikul A, Satirapoj B. Ankle-brachial index predicts renal outcomes and all-cause mortality in high cardiovascular risk population: a nationwide prospective cohort study in CORE project. *Int Urol Nephrol*. 2022;54:1641–1652. doi: 10.1007/s11255-021-03049-5
52. Shah S, Henry A, Roselli C, Lin H, Sveinbjornsson G, Fatemifar G, Hedman AK, Wilk JB, Morley MP, Chaffin MD, et al. Genome-wide association and mendelian randomisation analysis provide insights into the pathogenesis of heart failure. *Nat Commun*. 2020;11:163. doi: 10.1038/s41467-019-13690-5
53. Schneider CV, Schneider KM, Teumer A, Rudolph KL, Hartmann D, Rader DJ, Strnad P. Association of telomere length with risk of disease and mortality. *JAMA Intern Med*. 2022;182:291–300. doi: 10.1001/jamainternmed.2021.7804
54. Weale ME, Riveros-Mckay F, Selzam S, Seth P, Moore R, Tarran WA, Gradovich E, Giner-Delgado C, Palmer D, Wells D, et al. Validation of an integrated risk tool, including polygenic risk score, for atherosclerotic cardiovascular disease in multiple ethnicities and ancestries. *Am J Cardiol*. 2021;148:157–164. doi: 10.1016/j.amjcard.2021.02.032
55. Arbeev KG, Verhulst S, Steenstrup T, Kark JD, Bagley O, Kooperberg C, Reiner AP, Hwang SJ, Levy D, Fitzpatrick AL, et al. Association of leukocyte telomere length with mortality among adult participants in 3 longitudinal studies. *JAMA Netw Open*. 2020;3:e200023. doi: 10.1001/jamanetworkopen.2020.0023
56. Guasch-Ferre M, Liu X, Malik VS, Sun Q, Willett WC, Manson JE, Rexrode KM, Li Y, Hu FB, Bhupathiraju SN. Nut consumption and risk of cardiovascular disease. *J Am Coll Cardiol*. 2017;70:2519–2532. doi: 10.1016/j.jacc.2017.09.035
57. Gooding HC, Ning H, Gillman MW, Shay C, Allen N, Goff DC Jr, Lloyd-Jones D, Chiuve S. Application of a lifestyle-based tool to estimate premature cardiovascular disease events in young adults: the Coronary Artery Risk Development in Young Adults (CARDIA) study. *JAMA Intern Med*. 2017;177:1354–1360. doi: 10.1001/jamainternmed.2017.2922
58. Bress AP, Colantonio LD, Cooper RS, Kramer H, Booth JN 3rd, Odden MC, Bibbins-Domingo K, Shimbo D, Whelton PK, Levitan EB, et al. Potential cardiovascular disease events prevented with adoption of the 2017 American College of Cardiology/American Heart Association blood pressure guideline. *Circulation*. 2019;139:24–36. doi: 10.1161/CIRCULATIONAHA.118.035640
59. Pearson-Stuttard J, Bandosz P, Rehm CD, Penalvo J, Whitsel L, Gaziano T, Conrad Z, Wilde P, Micha R, Lloyd-Williams F, et al. Reducing US cardiovascular disease burden and disparities through national and targeted dietary policies: a modelling study. *PLoS Med*. 2017;14:e1002311. doi: 10.1371/journal.pmed.1002311
60. Macknin M, Stegmeier N, Thomas A, Worley S, Li L, Hazen SL, Tang WHW. Three healthy eating patterns and cardiovascular disease risk markers in 9 to 18 year olds with body mass index >95%: a randomized trial. *Clin Pediatr (Phila)*. 2021;60:474–484. doi: 10.1177/00099228211044841
61. Cong L, Ren Y, Hou T, Han X, Dong Y, Wang Y, Zhang Q, Liu R, Xu S, Wang L, et al. Use of cardiovascular drugs for primary and secondary prevention of cardiovascular disease among rural-dwelling older Chinese adults. *Front Pharmacol*. 2020;11:608136. doi: 10.3389/fphar.2020.608136
62. Walli-Attaei M, Joseph P, Rosengren A, Chow CK, Rangarajan S, Lear SA, AlHabib KF, Davletov K, Dans A, Lanas F, et al. Variations between women and men in risk factors, treatments, cardiovascular disease incidence, and death in 27 high-income, middle-income, and low-income countries (PURE): a prospective cohort study. *Lancet*. 2020;396:97–109. doi: 10.1016/S0140-6736(20)30543-2
63. Yao X, Shah ND, Gersh BJ, Lopez-Jimenez F, Noseworthy PA. Assessment of trends in statin therapy for secondary prevention of atherosclerotic cardiovascular disease in US adults from 2007 to 2016. *JAMA Netw Open*. 2020;3:e2025505. doi: 10.1001/jamanetworkopen.2020.25505
64. Centers for Disease Control and Prevention and National Center for Health Statistics. Multiple cause of death, CDC WONDER online database. Accessed April 1, 2023. https://wonder.cdc.gov/mcd-icd10.html
65. Gindi RM, Holmes JS, Arispe IE. *Health, United States, 2017: With Special Feature on Mortality*. National Center for Health Statistics; 2018.
66. Ritchey MD, Wall HK, Owens PL, Wright JS. Vital signs: state-level variation in nonfatal and fatal cardiovascular events targeted for prevention by

Million Hearts 2022. *MMWR Morb Mortal Wkly Rep*. 2018;67:974–982. doi: 10.15585/mmwr.mm6735a3
67. Centers for Disease Control and Prevention and National Center for Health Statistics. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death micro-data files. Accessed April 8, 2023. https://cdc.gov/nchs/nvss/mortality_public_use_data.htm
68. Xu J, Murphy SL, Kochanek KD, Arias E. Mortality in the United States, 2021. *NCHS Data Brief*. 2022;1–8.
69. Hagstrom E, Sorio Vilela F, Svensson MK, Hallberg S, Soreskog E, Villa G. Cardiovascular event rates after myocardial infarction or ischaemic stroke in patients with additional risk factors: a retrospective population-based cohort study. *Adv Ther*. 2021;38:4695–4708. doi: 10.1007/s12325-021-01852-1
70. Keeney T, Fox AB, Jette DU, Jette A. Functional trajectories of persons with cardiovascular disease in late life. *J Am Geriatr Soc*. 2019;67:37–42. doi: 10.1111/jgs.15584
71. Aggarwal G, Cheruiyot I, Aggarwal S, Wong J, Lippi G, Lavie CJ, Henry BM, Sanchis-Gomar F. Association of cardiovascular disease with coronavirus disease 2019 (COVID-19) severity: a meta-analysis. *Curr Probl Cardiol*. 2020;45:100617. doi: 10.1016/j.cpcardiol.2020.100617
72. Ssentongo P, Ssentongo AE, Heilbrunn ES, Ba DM, Chinchilli VM. Association of cardiovascular disease and 10 other pre-existing comorbidities with COVID-19 mortality: a systematic review and meta-analysis. *PLoS One*. 2020;15:e0238215. doi: 10.1371/journal.pone.0238215
73. Clarke TC, Schiller JS, Boersma P. Early release of selected estimates based on data from the 2019 National Health Interview Survey. 2020. Accessed April 4, 2023. https://cdc.gov/nchs/data/nhis/earlyrelease/EarlyRelease202009-508.pdf
74. Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project (HCUP). Accessed April 1, 2023. http://hcupnet.ahrq.gov/
75. Centers for Disease Control and Prevention and National Center for Health Statistics. National Ambulatory Medical Care Survey (NAMCS) public use data files. Accessed April 1, 2023. https://cdc.gov/nchs/ahcd/datasets_documentation_related.htm#data
76. Akhabue E, Rua M, Gandhi P, Kim JH, Cantor JC, Setoguchi S. Disparate cardiovascular hospitalization trends among young and middle-aged adults within and across race and ethnicity groups in four states in the United States. *J Am Heart Assoc*. 2023;12:e7978. doi: 10.1161/JAHA.122.027342
77. Agency for Healthcare Research and Quality. Medical Expenditure Panel Survey (MEPS): household component summary tables: medical conditions, United States. Accessed April 2, 2023. https://meps.ahrq.gov/mepsweb/
78. Meyers J, Hoog M, Mody R, Yu M, Davis K. The health care resource utilization and costs among patients with type 2 diabetes and either cardiovascular disease or cardiovascular risk factors: an analysis of a US Health insurance database. *Clin Ther*. 2021;43:1827–1842. doi: 10.1016/j.clinthera.2021.09.003
79. Global Burden of Disease Study and Institute for Health Metrics and Evaluation. University of Washington. Accessed August 2, 2023. http://ghdx.healthdata.org/.
80. World Health Organization. Cardiovascular diseases (CVDs). Accessed March 22, 2023. https://who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)
81. Stierman B, Afful J, Carroll M, Chen T, Davy O, Fink S, Fryar C, Gu Q, Hales C, Hughes J, et al. National Health and Nutrition Examination Survey 2017-March 2020 prepandemic data files: development of files and prevalence estimates for selected health outcomes. *National Health Statistics Reports*. 2021. Accessed April 1, 2023. https://stacks.cdc.gov/view/cdc/106273
82. World Health Organization. WHO mortality database. Accessed March 22, 2023. https://who.int/healthinfo/mortality_data/en/

# 15. STROKE (Cerebrovascular Diseases)

***ICD-9 430 to 438; ICD-10 I60 to I69. See Table 15-1 and Charts 15-1 through 15-17***

Click here to return to the Table of Contents

Click here to return to the Abbreviations

## Stroke Prevalence

## (See Table 15-1 and Chart 15-1)

- Stroke prevalence estimates may differ slightly between studies because each study selects and recruits a sample of participants to represent the target study population (eg, state, region, or country).
- An estimated 9.4 million Americans ≥20 years of age self-report having had a stroke (NHANES 2017–2020 data). Overall stroke prevalence during this period was an estimated 3.3% (Table 15-1).
- Prevalence of stroke in the United States increases with advancing age in both males and females (Chart 15-1).
- According to BRFSS[1] 2021 data (unpublished NHLBI tabulation), stroke prevalence in adults was 3.0% (median) in the United States, with the lowest prevalence in Vermont (1.9%) and the highest prevalence in Mississippi (4.9%).
- Projections show that by 2030 an additional 3.4 million US adults ≥18 years of age, representing 3.9% of the adult population, will have had a stroke, a 20.5% increase in prevalence from 2012.[2] The highest increase (29%) is projected to be in White Hispanic males.

## Stroke Incidence

## (See Table 15-1)

- Each year, ≈795 000 people experience a new or recurrent stroke (Table 15-1). Approximately 610 000 of these are first attacks and 185 000 are recurrent attacks (GCNKSS, NINDS, and NHLBI; GCNKSS and NINDS data for 1999 provided July 9, 2008; unpublished estimates compiled by the NHLBI).
- Of all strokes, 87% are ischemic, 10% are ICHs, and 3% are SAHs (GCNKSS, NINDS, 1999; unpublished NHLBI tabulation).
- According to the GBD Study 2019, ischemic strokes accounted for 62.4% of all global incident strokes in 2019 (7.63 [95% CI, 6.57–8.96] million), ICH for 27.9% (3.41 [95% CI, 2.97–3.91] million), and SAH for 9.7% (1.18 [95% CI, 1.01–1.39] million).[3]

### *Secular Trends*

- An analysis of data from the GBD Study 2019 found that from 1990 to 2019, the absolute number of incident strokes increased by 70.0% (95% CI, 67.0%–73.0%), and the age-standardized incidence rate for total stroke decreased by 17.0% (95% CI, 15.0%–18.0%).[3] The age-standardized incidence rate for ischemic stroke decreased by 10% (95% CI, 8.0%–12.0%) and ICH decreased by 29% (95% CI, 28.0%–30.0%) during the same period.
- A population-based incidence study conducted in Oxfordshire, England, from April 2002 to March 2018 found that between 2002 to 2010 and 2010 to 2018, stroke incidence increased significantly among subjects <55 years of age (IRR, 1.67 [95% CI, 1.31–2.14]) but fell significantly among those ≥55 years of age (IRR, 0.85 [95% CI, 0.78–0.92]; $P<0.001$ for difference).[4]
- A systematic review found among 50 studies in 20 countries that temporal trends in stroke incidence are diverging by age in high-income countries, with less favorable trends at younger versus older ages (pooled relative temporal rate ratio, 1.57 [95% CI, 1.42–1.74]).[5] The overall relative temporal rate ratio was consistent by sex (males, 1.46 [95% CI, 1.34–1.60]; females, 1.41 [95% CI, 1.28–1.55]) and by stroke subtype (ischemic, 1.62 [95% CI, 1.44–1.83]; ICH, 1.32 [95% CI, 0.91–1.92]; SAH, 1.54 [95% CI, 1.00–2.35]) but was greater in studies reporting trends solely after 2000 (1.51 [95% CI, 1.30–1.70]) versus solely before (1.18 [95% CI, 1.12–1.24]) and was highest in population-based studies in which the most recent reported period of ascertainment started after 2010 (1.87 [95% CI, 1.55–2.27]).
- In the multicenter ARIC study of Black and White adults, stroke incidence rates decreased by 32% (95% CI, 23%–40%) per 10 years during the 30-year period from 1987 to 2017 in adults ≥65 years of age. The decreases varied across age groups but were similar across sex and race.[6]
- Data from the Danish Stroke Registry and the Danish National Patient Registry showed that the incidence

The 2024 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2024. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

rate per 100 000 person-years in 2005 and 2018 of ischemic stroke (20.8 versus 21.9, respectively; average annual percentage change, −0.6 [95% CI, −1.5 to 0.3]) and ICH (2.2 versus 2.5, respectively; average annual percentage change, 0.6 [95% CI, −1.0 to 2.3]) remained steady in younger adults (18–49 years of age), but in older adults (>50 years of age), rates of ischemic stroke and ICH declined (−1.5 [95% CI, −1.9 to −1.1] and −1.2 [95% CI, −1.9 to −0.6], respectively), especially in those ≥70 years of age.[7] Comparing data from 1962 to 1967 and 1998 to 2005 shows that the relative incidence in older adults ≥55 years of age declined by 53% (HR, 0.47 [95% CI, 0.36–0.60]).[8]

- In a US nationwide study of mortality among Asian American individuals from 2003 to 2017, age-standardized cerebrovascular disease mortality declined by an average of 2.2%/y (95% CI, 1.1–3.2) among Asian American females and 2.4%/y (95% CI, 1.3–3.6) among Asian American males.[9] There was heterogeneity among Asian American ethnic subgroups. Average annual percent decline in cerebrovascular mortality was fastest among Japanese American individuals (decline of 3.1 %/y [95% CI, 2.0–4.2] among females and decline of 3.2%/y [95% CI, 2.0–4.2] among males), whereas no decline was observed among Asian Indian American or Vietnamese American females or males.

## Stroke Risk Factors

For prevalence and other information on any of these specific risk factors, refer to the specific risk factor chapters.

- In analyses using data from the GBD Study, 87% of the stroke risk could be attributed to modifiable risk factors such as HBP, obesity, hyperglycemia, hyperlipidemia, and renal dysfunction, and 47% could be attributed to behavioral risk factors such as smoking, sedentary lifestyle, and an unhealthy diet. Globally, 30% of the risk of stroke was attributable to air pollution.[10,11]
- The FINGER trial in 1259 adults 60 to 77 years of age found that a 2-year multidomain intervention with diet, physical and cognitive activity, and vascular monitoring compared with general health advice resulted in a reduced incidence of stroke (HR, 0.71 [95% CI, 0.51–0.99]).[12]

### *High BP*

***(See Chapter 8 [High Blood Pressure] for more information.)***

***(See Chart 15-2)***

- Among 430 977 adults 30 to 79 years of age in China with 5168 stroke deaths during a median follow-up of 10 years, stroke mortality rates per 100 000 person-years in BP groups were 39 in the normal BP, 71 in the prehypertension-low, 83 in the prehypertension-high, 283 in the isolated systolic hypertension, 82 in the isolated diastolic hypertension, and 375 in the systolic-diastolic hypertension groups. Compared with normal BP, multiadjusted HRs for stroke mortality were 1.20 (95% CI, 1.06–1.36) in the prehypertension-low, 1.53 (95% CI, 1.37–1.70) in the prehypertension-high, 2.52 (95% CI, 2.28–2.78) in the isolated systolic hypertension, 2.51 (95% CI, 1.94–3.21) in the isolated diastolic hypertension, and 5.60 (95% CI, 5.06–6.21) in the systolic-diastolic hypertension groups. For all BP categories relative to normal BP, HRs for hemorrhagic stroke mortality were larger than those for ischemic stroke mortality.[13]
- Among 33 357 adults in ALLHAT with 936 strokes during a median follow-up of 4.4 years, heat map plotting of stroke risk at all SBP and DBP combinations showed that stroke risk was lowest in the SBP/DBP range of <110/<60 mm Hg (HRs <0.90 relative to BP of 120/80 mm Hg) and stroke risk was highest in the SBP/DBP range of 170 to 190/85 to 100 mm Hg (HRs >2.00 relative to BP of 120/80 mm Hg; Chart 15-2).[14]
- In a meta-analysis of 66 trials of SBP-lowering interventions including 324 812 participants and 11 437 strokes over an average follow-up of 3.3 years, SBP lowering was associated with 21% lower odds (95% CI, 15%–26% lower) of stroke compared with control. In meta-analyses of stroke types, SBP lowering was associated with 14% lower odds (95% CI, 27% lower–2% higher) of ischemic stroke (6 trials), 28% lower odds (95% CI, 4%–46% lower) of hemorrhagic stroke (6 trials), and 28% lower odds (95% CI, 19%–39% lower) of fatal or disabling stroke (18 trials).[15]
- In a meta-analysis of randomized trials comparing more and less intensive BP targets that included 60 870 participants with an average 3.95 years of follow-up, more intensive BP control was associated with a lower risk of stroke (OR, 0.79 [95% CI, 0.67–0.93]).[16] The trials differed in the specific BP targets, and the average achieved SBP reduction in the more intensive treatment was 7.69 mm Hg (95% CI, 7.64–7.71 mm Hg).
- In a longitudinal cohort study of 11 848 adult participants undergoing 24-hour ambulatory BP assessment with a median follow-up of 13.7 years and 846 stroke events, higher mean pulse pressure was independently associated with stroke risk.[17] For participants ≤40 years of age, increased mean ambulatory pulse pressure was associated with a 3-fold higher risk of stroke (aHR per SD, 3.06 [95% CI, 1.03–9.09]).

- In a mendelian randomization study of adults 40 to 79 years of age in China, a 10–mm Hg increase in genetically predicted SBP was associated with an increased risk of ischemic stroke (HR, 1.37 [95% CI, 1.30–1.45]) and ICH (HR, 1.71 [95% CI, 1.58–1.87]).[18] Among adults in the United Kingdom, genetically predicted pulse pressure was associated with ischemic stroke in those ≥55 years of age (aOR per SD, 1.23 [95% CI, 1.13–1.34]) independently of genetically predicted mean arterial pressure.[19]
- Among adults ≥35 years of age recruited from rural areas of Fuxin County, Liaoning Province, China, ideal BP for stroke prevention varied by BMI: At BMI <24 kg/m$^2$, stroke risk was lowest in those with BP <130/80 mm Hg, whereas at BMI ≥24 kg/m$^2$, stroke risk was lowest in those with BP <120/80 mm Hg.[20] A 20–mm Hg increment in SBP was associated with 1.28 times the risk for stroke (95% CI, 1.22–1.34), and a 10–mm Hg increment in DBP was associated with 1.14 times the risk for stroke (95% CI, 1.09–1.19).
- In a meta-analysis of 56 513 patients undergoing intravenous thrombolysis for AIS (26 studies), elevated pretreatment (aOR, 1.08 [95% CI, 1.01–1.16]) and posttreatment (aOR, 1.13[95% CI, 1.01–1.25]) SBP levels were associated with increased risk of symptomatic ICH.[21] Pretreatment (aOR, 0.91 [95% CI, 0.84–0.98]) and posttreatment (aOR, 0.70 [95% CI, 0.57–0.87]) SBP values also were inversely related to lower likelihood of 3-month functional independence.

### *BP and Recurrent Stroke*

- In a meta-analysis of 10 studies including 13 944 stroke survivors and 1428 recurrent strokes during follow-up ranging from 1 to 5 years, hypertension was associated with 67% higher odds of recurrent stroke (95% CI, 45%–92%).[22] Among 17 916 patients in the PROFESS trial, every 10-point increment in SBP variability, defined as the SD across repeated measurements, was associated with 15% higher hazard (95% CI, 2%–32%) of recurrent stroke.[23]

## Diabetes

## (See Chapter 9 [Diabetes] for more information.)

- Prediabetes, defined as impaired glucose tolerance or impaired fasting glucose, is associated with a modestly increased risk of stroke. A meta-analysis of 53 prospective cohort studies including 1 611 339 participants, of which 18 studies reported the association between prediabetes and stroke, revealed that impaired glucose tolerance was associated with a 20% increased risk of stroke (aRR, 1.20 [95% CI, 1.00–1.45]).[24] Impaired fasting glucose, defined as FPG of 100 to 125 mg/dL, was associated increased stroke risk (aRR, 1.06 [95% CI, 1.01–1.11]).
- Diabetes is an independent risk factor for stroke recurrence; a meta-analysis of 27 studies involving 274 631 participants with prior ischemic stroke demonstrated that diabetes was an independent risk factor for stroke recurrence (pooled HR, 1.50 [95% CI, 1.36–1.65]).[25]
- In the GWTG-Stroke registry, diabetes was associated with a higher risk of adverse outcomes 3 years after ischemic stroke, including all-cause mortality (aHR, 1.24 [95% CI, 1.23–1.25]), all-cause hospital readmission (aHR, 1.22 [95% CI, 1.21–1.23]), a composite of mortality and cardiovascular readmission (aHR, 1.19 [95% CI, 1.18–1.20]), and ischemic stroke/TIA readmission (aHR, 1.18 [95% CI, 1.16–1.20]).[26]
- In a meta-analysis of 11 RCTs that included 56 161 patients with type 2 diabetes and 1835 cases of stroke, intensive blood glucose control did not reduce stroke risk compared with conventional glucose control (RR, 0.94 [95% CI, 0.84–1.06]).[27] An RCT of intensive or standard blood glucose control in patients with AIS with hyperglycemia (80% with diabetes) did not demonstrate a difference in favorable functional outcome (aRR, 0.97 [95% CI, 0.87–1.08]) at 90 days.[28] A meta-analysis of 19 RCTs with 155 027 participants with type 2 diabetes demonstrated that GLP1-RA treatment was associated with reduced stroke risk (RR, 0.84 [95% CI, 0.77–0.93]).[29]

## Disorders of Heart Rhythm

## (See Chapter 18 [Disorders of Heart Rhythm] for more information.)

### *Atrial Fibrillation*

- Because AF is often asymptomatic[30] and frequently undetected clinically,[31] the stroke risk attributed to AF is likely substantially underestimated. The 12-month prevalence of AF in patients with stroke attributed to large- or small-vessel disease was 12.1% in the STROKE-AF RCT using continuous cardiac monitoring versus 1.8% with usual care; median time to detection was 99 and 181 days, respectively.[32]
- In a meta-analysis of 50 studies, AF was detected in ≈24% (95% CI, 17%–31%) of patients with embolic stroke of undetermined source, depending on duration and type of monitoring used.[33]
- Important risk factors for stroke in the setting of AF include older age, hypertension, HF, diabetes, previous stroke or TIA, vascular disease, renal dysfunction,

low BMI, and female sex.[34–38] Biomarkers such as high levels of troponin, BNP, NT-proBNP, cystatin C, factor VIII antigen, interleukin-6, and growth differentiation factor-15 are associated with an increased risk of stroke or bleeding in AF after adjustment for traditional vascular risk factors.[39,40]

- In a meta-analysis of 26 studies of patients with AF and prior stroke (N= 23 054 patients), nonparoxysmal AF compared with paroxysmal AF was associated with a higher risk of recurrent stroke (OR, 1.47 [95% CI, 1.08–1.99]).[41]
- In a meta-analysis of 35 studies (N=2 458 010 patients), perioperative or postoperative AF was associated with an increased risk of early stroke (OR, 1.62 [95% CI, 1.47–1.80]) and later stroke (HR, 1.37 [95% CI, 1.07–1.77]). This risk was found in patients undergoing both noncardiac surgery (HR, 2.00 [95% CI, 1.70–2.35]) and cardiac surgery (HR, 1.20 [95% CI, 1.07–1.34]).[42]
- In a meta-analysis of 28 studies (N=2 612 816 patients), AF after noncardiac surgery was associated with a ≈3 fold increased risk of stroke at 1 month (OR, 2.82 [95% CI, 2.15–3.70]) and ≈4 fold increase in long-term risk of stroke (OR, 4.12 [95% CI, 3.32–35.11]).[43] For the choice of anticoagulant postoperatively, a study from the STS database of 26 522 patients with postcardiac surgery AF (36.8% on DOAC and 36.2% on vitamin K antagonist) showed no association between type of oral anticoagulant and 30-day outcomes (major bleeding, stroke/TIA, or mortality) but did show a half-day reduction in length of stay (B=—0.47 [95% CI, —0.62 to —0.33]).[44]
- In a meta-analysis of 21 national cohort studies including 9.7 million global participants eligible for oral anticoagulants, the prevalence of DOAC use increased from 0.00 (95% CI, 0.00–0.00) in 2010 to 0.45 (95% CI, 0.45–0.46) in 2018.[45] On the other hand, the prevalence of vitamin K antagonist use decreased from 0.42 (95% CI, 0.22–0.65) in 2010 to 0.32 (95% CI, 0.32–0.32) in 2018. Nine percent of participants in 2018 were treated with antiplatelet agents only.
- In an analysis of 2046 patients admitted with AIS who had AF, mean heart rate during the AIS period was not associated with stroke recurrence but was associated with higher mortality.[46]

### *Other Arrhythmias*

- In an analysis of inpatient and outpatient claims data from a 5% sample of all Medicare beneficiaries ≥66 years of age (2008–2014), atrial flutter was associated with a lower risk of stroke than AF.[47]
- In a meta-analysis of 5 studies (N=7545 patients), excessive supraventricular ectopic activity, defined as the presence of either ≥30 premature atrial contractions per hour or any runs of ≥20 premature atrial contractions, was associated with an increased risk of stroke (HR, 2.19 [95% CI, 1.24–4.02]).[48]
- In a French longitudinal cohort study of 1 692 157 patients who underwent 1:1 propensity score matching, isolated sinus node disease was associated with a lower risk of ischemic stroke compared with AF (HR, 0.77 [95% CI, 0.73–0.82]) but a higher risk compared with a control population (HR, 1.27 [95% CI, 1.19–1.35]).[49]

## High Blood Cholesterol and Other Lipids

## (See Chapter 7 [High Blood Cholesterol and Other Lipids] for more information.)

### *Total Cholesterol*

- In a meta-analysis of data from 61 cohorts, TC was weakly associated with risk of total stroke.[50] In the Prospective Studies Collaboration, an association between elevated TC and ischemic and total stroke mortality was present in early middle age (40–59 years) but not in older age.[51]
- Elevated TC is inversely associated with hemorrhagic stroke risk. In a meta-analysis of 23 prospective cohort and case-control studies, a 1-mmol/L higher TC concentration was associated with a 15% lower risk of hemorrhagic stroke (RR, 0.85 [95% CI, 0.80–0.91]).[52]

### *LDL Cholesterol*

- Evidence from RCTs, mendelian randomization analyses, and population-based cohort studies supports a direct and causal relationship between serum LDL-C and atherosclerotic ischemic stroke risk.[53]
  - A meta-analysis of LDL-C–lowering drug treatment trials has demonstrated that every 1–mmol/L (≈39–mg/dL) reduction in LDL-C is associated with a 20% lower risk of ischemic stroke (RR, 0.80 [95% CI, 0.76–0.84]) but a 17% increased risk of ICH (RR, 1.17 [95% CI, 1.03–1.32]).[54]
  - In an RCT that enrolled individuals with prior ischemic stroke/TIA and evident atherosclerosis, achieving an LDL-C <70 mg/dL (versus an LDL-C target range of 90–110 mg/dL) was associated with a lower risk of subsequent cardiovascular events (HR, 0.78 [95% CI, 0.61–0.98]) without increased risk of ICH.[55]
  - A meta-analysis of 39 primary and secondary prevention trials including 287 651 participants did not demonstrate an association between lipid-lowering therapy and ICH risk (OR, 1.12 [95% CI, 0.98–1.28]).[56] Another meta-analysis of 8 trials did not demonstrate a difference in the incidence of hemorrhagic stroke among those receiving

intensive lipid-lowering therapy (achieved LDL-C <55 mg/dL) and those receiving less intensive treatment (OR, 1.05 [95% CI, 0.85–1.31]).[57]
  - A mendelian randomization study demonstrated that every 1–mmol/L reduction in genetically predicted LDL-C was associated with a 25% reduced risk of ischemic stroke (RR, 0.75 [95% CI, 0.60–0.95]) but 13% increased risk of ICH (RR, 1.13 [95% CI, 0.91–1.40]).[54] Another mendelian randomization study demonstrated that genetically elevated LDL-C was associated with an increased risk of total ischemic stroke and large-artery atherosclerotic stroke but not other ischemic stroke subtypes.[58]

### *HDL Cholesterol*

- A meta-analysis of 62 prospective cohort studies including 900 501 participants and 25 678 strokes demonstrated that a 1–mmol/L increase in HDL-C level was associated with an 18% lower risk of total stroke (RR, 0.82 [95% CI, 0.76–0.89]); the RR for ischemic stroke was 0.75 (95% CI, 0.69–0.82) but was 1.21 (95% CI, 1.04–1.42) for ICH.[59] Genetic predisposition to higher HDL-C has been associated with lower risk of small-vessel ischemic stroke in mendelian randomization analyses.[58,60]

### *Triglycerides*

- In a population-based cohort study of 5 688 055 Korean young adults (20–39 years of age) with a median follow-up of 7.1 years, serum triglyceride concentration was associated with an increased risk of stroke (HR, 2.53 [95% CI, 2.34–2.73]).[61]
- Low triglyceride levels have been associated with an increased risk of hemorrhagic stroke. In the WHS, compared with females in the highest quartile of triglyceride levels, those in the lowest quartile had an increased risk of hemorrhagic stroke (RR, 2.00 [95% CI, 1.18–3.39]).[62]
- In an RCT of 8179 participants in 11 countries with established CVD or diabetes, other vascular risk factors, and elevated serum triglycerides despite the use of statin therapy, icosapent ethyl treatment reduced nonfatal stroke risk compared with placebo (HR, 0.71 [95% CI, 0.54–0.94]).[63]

### *Smoking/Tobacco Use*

### *(See Chapter 3 [Smoking/Tobacco Use] for more information.)*

- Current smoking is associated with an increased prevalence of MRI-defined subclinical brain infarcts.[64]
- A meta-analysis of 141 cohort studies showed that low cigarette consumption (≈1 cigarette/d) carries a risk of developing stroke up to 50% of the risk associated with high cigarette consumption (≈20 cigarettes/d).[65] This is much higher than what would be predicted from a linear or log-linear dose-response relationship between smoking and risk of stroke.[65]
- Exposure to secondhand smoke, also called passive smoking or secondhand tobacco smoke, is a risk factor for stroke.
  - Meta-analyses have estimated a pooled RR of 1.25 for exposure to spousal smoking (or nearest equivalent) and risk of stroke. A nonlinear dose-response relationship between exposure to secondhand smoke and stroke risk was also reported (RR increased from 1.16 [95% CI, 1.06–1.27] for 5 cigarettes/d to 1.56 [95% CI, 1.25–1.96] for 40 cigarettes/d].[66]
  - A study using NHANES data sampled from 1988 to 1994 and 1999 to 2012 found that individuals with a prior stroke have greater odds of having been exposed to secondhand smoke (OR, 1.46 [95% CI, 1.05–2.03]), and secondhand smoke exposure was associated with a 2-fold increase in mortality among stroke survivors compared with stroke survivors without the exposure (AAMR, 96.4±20.8 per 100 person-years versus 56.7±4.8 per 100 person-years; $P$=0.026).[67]
- In a meta-analysis of studies from Europe, North America, and Asia, adult ever users of smokeless tobacco had a higher risk of fatal stroke (OR, 1.39 [95% CI, 1.29–1.49]).[68]
- The FINRISK study found a strong association between current smoking and SAH compared with nonsmoking (HR, 2.77 [95% CI, 2.22–3.46]) and reported a dose-dependent and cumulative association with SAH risk that was highest in females who were heavy smokers.[69]
- In a systematic review of efficacy of smoking-cessation pharmacotherapy after stroke (n=2 trials and n=6 observational studies), cessation rates ranged from 33% to 66% with pharmacological therapy combined with behavioral interventions and 15% to 46% with pharmacological therapy without behavioral interventions.[70]
- In a meta-analysis of 18 studies and 17 982 adult participants with CHD who were smoking at the time of diagnosis, smoking cessation was associated with a lower risk of cardiovascular death (HR, 0.61 [95% CI, 0.49–0.75]).[71] A secondary analysis including 9 studies and 11 352 participants showed that smoking cessation was associated with a lower risk of nonfatal stroke (HR, 0.70 [95% CI, 0.53–0.90]).
- In a cross-sectional study from 2016 to 2018 of the US CDC BRFSS surveys (N=6 867 786 stroke survivors), the estimated prevalence of e-cigarette use among stroke survivors in the United States was 13.5% (95% CI, 11.8%–15.3%).[72]

### Physical Inactivity

**(See Chapter 4 [Physical Activity and Sedentary Behavior] for more information.)**

- The GBD Study 2019 estimated that low physical inactivity accounted for 1.7% of stroke-related disability globally (95% CI, 0.3%–4.5%) and 2.9% in high-income countries (95% CI, 0.5%–8.0%).[3]
- In a case-control study of NHANES participants, self-reported recent moderate-intensity activity (OR, 0.8 [95% CI, 0.7–0.9]), vigorous-intensity activity (OR, 0.6 [95% CI, 0.5–0.8]), and muscle-strengthening exercises (OR, 0.6 [95% CI, 0.5–0.8]) were associated with lower odds of stroke.[73]
- A prospective study among 437 318 participants in China found that physical inactivity was associated with an increased risk of incident total stroke (aHR, 1.52 [95% CI, 1.37–1.70]), ischemic stroke (aHR, 1.49 [95% CI, 1.33–1.67]), and hemorrhagic stroke (aHR, 1.83 [95% CI, 1.30–2.59]).[74]
- In the REGARDS study, sedentary time was independently associated with higher stroke risk (HR per 1 h/d increase in sedentary time, 1.14 [95% CI, 1.02–1.28]) independently of PA levels.[75] Light-intensity PA associated with reduced risk of incident stroke (HR per 1–h/d increase, 0.86 [95% CI, 0.77–0.97]).
- In a systematic review of 7 observational studies that included 41 800 stroke survivors, prestroke PA was associated with lower stroke severity at hospital admission.[76]
- In a longitudinal cohort study of 3472 stroke survivors, prestroke physical inactivity was associated with higher odds of dependency for activities of daily living 3 months after stroke (OR, 2.30 [95% CI, 1.89–2.80]).[77]

### Cardiorespiratory Fitness

- The REGARDS study (≥45 years of age) reported a race-specific association between cardiorespiratory fitness and incident stroke. White participants in the highest tertile of cardiorespiratory fitness had a 46% lower risk of ischemic stroke (95% CI, 31%–57%) compared with White participants in the lowest tertile of cardiorespiratory fitness but not hemorrhagic stroke (HR, 0.67 [95% CI, 0.33–1.36]). These associations were not present in Black participants (ischemic stroke: HR, 1.00 [95% CI, 0.74–1.37]; hemorrhagic stroke: HR, 1.98 [95% CI, 0.87–4.52]).[78]
- The Oslo Ischemia Cohort Study assessed change in cardiorespiratory fitness levels, assessed by a bicycle electrocardiographic test, between baseline and >7 years from the baseline examination with follow-up over 23.6 years (N=1403). Middle-aged Norwegian males (40–59 years of age) who became fit (above median) from unfit (below median) between the 2 examinations had 66% lower risk (95% CI, 33%–83%) of incident stroke compared with those who became unfit from fit. Those males who became unfit from fit had 2.35 times (95% CI, 1.49–3.63) greater risk of incident stroke compared with those who were continuously fit.[79]
- In the UK Biobank cohort study (N=66 438; 40–69 years of age), cardiorespiratory fitness was inversely associated with ischemic stroke (HR, 0.71 [95% CI, 0.57–0.89]) but not with hemorrhagic stroke (HR, 0.96 [95% CI, 0.68–0.1.53]).[80]

### Nutrition

**(See Chapter 5 [Nutrition] for more information.)**

- Diet quality:
  - Among 7841 adults in the Guizhou Population Health Cohort Study in China with 142 incident ischemic strokes over a mean follow-up of 6.6 years, the least favorable quartile of diet quality (assessed by Chinese Diet Balance Index) compared with the most favorable was associated with 3.31 times the hazard of ischemic stroke (95% CI, 1.57–6.97), and inadequate dietary variety was associated with 5.40 times the hazard of ischemic stroke (95% CI, 1.70–17.2), adjusted for sociodemographic, behavioral, and clinical risk factors.[81]
  - Among 26 547 adults in the Malmö Diet and Cancer Study in Sweden with 2339 incident ischemic strokes over a median follow-up of 21.2 years, high diet quality by Swedish nutrition recommendations was associated with 17% lower hazard of ischemic stroke (95% CI, 3%–28% lower), adjusted for established risk factors and comorbidities.[82]
  - Among 4701 young adults in the CARDIA study in the United States with 80 incident strokes over a median follow-up of 32 years, each 1-SD increment in diet quality assessed by the A Priori Diet Quality Score was associated with 30% lower hazard of incident stroke (95% CI, 1%–50% lower).[83]
- Vegetarian diet: In a meta-analysis of 12 cohort studies that included 770 867 participants with 14 419 incident stroke cases, vegetarians had a 10% lower RR of stroke compared with nonvegetarians (RR, 0.90 [95% CI, 0.77–1.05]).[84] A significant association was not found between vegetarian diet and the outcome of ischemic and hemorrhagic stroke.
- Fruits and vegetables:
  - In a study based on GBD Study 2017 data for China, the association of low fruit intake with stroke mortality was stronger for males than for females and stronger for older adults than for younger adults.[85] The age-standardized stroke

mortality attributed to low fruit intake was 6% lower for males and 41% lower for females in 2017 (versus 1992).
  - Among 87 177 adults in Japan with 4091 incident strokes over a median follow-up of 13.1 years, higher intake of flavonoid-rich fruits (such as citrus, strawberries, and grapes) was associated with 30% lower hazard of stroke among females (95% CI, 16%–42% lower) but not among males (7% lower hazard [95% CI, 21% lower–9% higher]).[86]
  - In a meta-analysis of 6 cohort studies, the highest level of green leafy vegetable intake was associated with 7% lower hazard of total stroke (95% CI, 3%–10% lower), 8% lower hazard of ischemic stroke (95% CI, 4%–12% lower), and 5% lower hazard of hemorrhagic stroke (95% CI, 14%–4% higher); heterogeneity of cohort-specific results was moderate ($I^2$=36%).[87]
  - In a Bayesian meta-regression analysis of 12 cohort studies, increasing vegetable consumption from none to a minimum risk exposure level (306–372 g/d) was associated with a 23.2% (95% CI, 16.4%–29.4%) reduction in ischemic stroke risk and 15.9% (95% CI, 1.7%–28.1%) reduction in hemorrhagic stroke risk.[88]
- Fiber: A meta-analysis comprising 185 cohort studies with 58 clinical trials revealed that high fiber intake (highest quantile) is associated with 22% (95% CI, 12%–31%) lower risk of incident stroke compared with the lowest quantile of fiber intake.[89]
- Coffee:
  - In a meta-analysis of 21 studies including >2.4 million individuals, the highest category of coffee consumption was associated with 13% (95% CI, 6%–20%) lower stroke risk compared with the lowest category of coffee consumption; heterogeneity of cohort-specific results was moderate ($I^2$=32%). Dose-response meta-analysis suggested a U-shaped relationship, with 3 to 4 cups of coffee/d associated with the lowest risk: 21% lower stroke risk compared with abstaining from coffee.[90]
  - Among UK Biobank participants (N=468 629) with a median follow-up of 11 years, light to moderate coffee drinking (0.5 to 3 cups of coffee/d) was associated with a 21% reduced hazard of incident stroke (aHR, 0.79 [95% CI, 0.63–0.99]) after adjustment for cardiovascular risk factors.[91]
- Milk:
  - Among 110 585 adults in the Japan Collaborative Cohort, daily milk consumption was associated with 20% (95% credible interval, 7%–31%) lower stroke mortality among males but not among females (5% lower mortality [95% CI, 20% lower–17% higher]).[92]
  - In a meta-analysis of 3 studies including 163 128 adults and 3691 ischemic strokes, the highest category of milk intake was associated with 12% lower risk of ischemic stroke (2%–21% lower; $I^2$=0%) compared with the lowest category.[93]
- ASBs: The FHS (N=2888; >45 years of age) showed that those who consumed ≥1 artificially sweetened soft drinks per day (eg, diet cola) had 1.97 times (95% CI, 1.1–3.55) and 2.34 times (95% CI, 1.24–4.45) the risk of total and ischemic stroke, respectively, compared with those who consumed 0 artificially sweetened soft drinks per week.[94] In an analysis of 52 754 participants in the WHI, consumption of ≥1 daily servings of ASB was associated with a higher risk of stroke (aHR, 1.24 [95% CI, 1.04–1.48]).[95]
- Omega-3 fatty acids:
  - In the Danish Diet, Cancer and Health cohort study (N=57 053), there was no association between omega-3 fatty acids intake (highest versus lowest quantile) and ischemic stroke (HR, 1.06 [95% CI, 0.93–1.21]) during an average of 13.5 years of follow-up.[96]
  - In the VITAL RCT in the United States (N=25 871), those participants (males ≥50 years of age, females ≥55 years of age) who consumed an omega-3 fatty acid supplement 1 g/d (EPA 460 mg plus DHA 380 mg) for an average of 5.3 years had a stroke risk similar to that of individuals not taking omega-3 supplements (RR, 1.04 [95% CI, 0.83–1.31]).[97]
  - However, in the US Million Veteran Program, omega-3 fatty acid supplement use was associated with 12% (95% CI, 5%–19%) lower risk of nonfatal ischemic stroke over 3.3 years of follow-up, although fish intake was not associated with stroke risk.[98]
- Vitamin D: In a meta-analysis of 20 observational cohort studies (n=217 235), the highest category of vitamin D intake was associated with 25% (95% CI, 2%–43%) lower stroke risk than the lowest category of vitamin D intake; optimal vitamin D intake for low stroke risk was ≈12 µg/d.[99] However, in a meta-analysis of 22 RCTs (N=83 200), vitamin D supplementation did not affect stroke risk (RR, 0.97 [95% CI, 0.90–1.03]).[100]
- Saturated fats: In a meta-analysis of 12 studies (N=462 268), each 10–g/d increment in saturated fat intake was associated with 6% (95% CI, 2%–11%) lower stroke risk.[101]

### *Kidney and Liver Disease*

#### *(See Chapter 12 [Kidney Disease] for more information.)*

- A meta-analysis of 38 studies comprising 1 735 390 participants (n=26 405 stroke events) showed that

any level of proteinuria was associated with greater stroke risk even after adjustment for cardiovascular risk factors (aRR, 1.72 [95% CI, 1.51–1.95]).[102] The association did not substantially attenuate with further adjustment for hypertension.

- In a study from the multicenter Japan Stroke Data Bank including 10 392 adult participants with an acute stroke occurring between October 2016 and December 2019, lower eGFR was associated with high risk of cardioembolic stroke (aOR per 1-SD decrease in eGFR, 1.20 [95% CI, 1.13–1.28]) and lower risk of small-vessel occlusion stroke (aOR per 1-SD decrease in eGFR, 0.89 [95% CI, 0.84–0.94]).[103] In addition, eGFR <45 mL·min$^{-1}$·1.73 m$^{-2}$ (versus eGFR ≥60 mL·min$^{-1}$·1.73 m$^{-2}$) and proteinuria (versus no proteinuria) were associated with increased risk of an unfavorable functional outcome, defined as a modified Rankin Scale score of 3 to 6 at discharge, after cardioembolic stroke (OR, 1.30 [95% CI, 1.01–1.69] and 3.18 [95% CI, 2.03–4.98], respectively) and small-vessel occlusion (OR, 1.44 [95% CI, 1.01–2.07] and 2.08 [95% CI, 1.08–3.98], respectively).
- A meta-analysis of 12 studies found that a urine ACR of >30 mg/mmol was associated with an increased risk of stroke (RR, 1.67 [95% CI, 1.49–1.86]).[104]
- Among 232 236 patients in the GWTG-Stroke registry, admission eGFR was inversely associated with mortality and poor functional outcomes. After adjustment for potential confounders, lower eGFR was associated with increased mortality, with the highest mortality among those with eGFR <15 mL·min$^{-1}$·1.73 m$^{-2}$ without dialysis (OR, 2.52 [95% CI, 2.07–3.07]) compared with those with eGFR ≥60 mL·min$^{-1}$·1.73 m$^{-2}$. Lower eGFR was also associated with decreased likelihood of being discharged home.[105]
- In a retrospective observational cohort study (N=85 116 patients with incident nonvalvular AF), stroke rates increased from 1.04 events per 100 person-years in stage 1 CKD to 3.72 in stage 4 to 5 CKD.[106]
- In CRIC, a prospective cohort study of 1778 females and 2161 males with CKD, no significant sex differences in the risk of stroke were found (aHR, 0.83 [95% CI, 0.54–1.28]).[107] Notably, the mean eGFR was 43.9±17.4 mL·min$^{-1}$·1.73 m$^{-2}$ in females (22% had an eGFR <30 mL·min$^{-1}$·1.73 m$^{-2}$) and 45.7±16.4 mL·min$^{-1}$·1.73 m$^{-2}$ in males (18% had an eGFR <30 mL·min$^{-1}$·1.73 m$^{-2}$).
- In the Q-Cohort Study (N=3045 participants; median follow-up time, 8.8 years), a multicenter cohort study of patients on maintenance hemodialysis from Japan, a 10-unit decrease in the geriatric nutritional risk index (calculated from serum albumin and BMI) was associated with an increased risk of ischemic stroke (aHR, 1.49 [95% CI, 1.05–2.12]) and hemorrhagic stroke (aHR, 1.89 [95% CI, 1.1–3.2]) after adjustment for potential confounders.[108]
- In the ARIC study cohort (N=12 588 participants; median follow-up time, 24.2 years), those in the top quartile of concentration of the liver enzyme γ-glutamyl transpeptidase compared with those in the lowest quartile were at increased risk of stroke after adjustment for age, sex, and race (aHR, 1.94 [95% CI, 1.64–2.30] for all incident stroke; aHR, 2.01 [95% CI, 1.68–2.41] for ischemic stroke).[109] There was a dose-response association ($P_{\text{linear trend}}$<0.001).
- In a case-cohort analysis in the REGARDS cohort, advanced liver fibrosis was classified with the use of validated cutoffs of the Fibrosis-4 score and NAFLD Fibrosis Score.[110] Advanced liver fibrosis was associated with stroke in females (aHR, 3.51 [95% CI, 1.00–12.34]) but not males (aHR, 0.70 [95% CI, 0.16–3.16]; $P_{\text{interaction}}$=0.098).

### *Stroke After Procedures and Surgeries*

- In-hospital stroke rates after TAVR declined from 2.2% in 2012 to 1.6% in 2019.[111]
- In a registry of 123 186 patients, the use of embolic protection devices for TAVR increased over time, reaching 13% of TAVR procedures in 2019.[112] However, embolic protection device use was not associated with a lower risk of in-hospital stroke in the primary instrumental variable analysis (aRR, 0.90 [95% CI, 0.58–1.13]). This was confirmed in the recent PROTECTED TAVR RCT of 3000 participants randomized to an embolic protection device during TAVR, in which the incidence of the primary outcome, stroke within 72 hours after TAVR or before discharge, did not differ between groups.[113]
- In a study from the STS National Adult Cardiac Surgery Database, the incidence of postoperative stroke after type A aortic dissection repair was 13%.[114] Axillary cannulation (OR, 0.60 [95% CI, 0.49–0.73]) and retrograde cerebral perfusion (OR, 0.75 (95% CI, 0.61–0.93]) were associated with lower risk of postoperative stroke.
- In a nationwide prospective cohort study from Denmark (N=78 096 elderly patients undergoing hip fracture surgery), patients with a higher $CHA_2DS_2$-VASc score had a higher risk of ischemic stroke among patients with and without AF.[115]
- In the PRECOMBAT trial evaluating the long-term outcomes of PCI with drug-eluting stents compared with CABG for unprotected left main CAD, the 10-year incidence of ischemic stroke was not significantly different (HR, 0.71 [95% CI, 0.22–2.23]; incidence rate, 1.9% in the PCI arm [n=300] and 2.2% in the CABG arm [n=300]).[116]

### Risk Factor Issues Specific to Females

- In a meta-analysis of 11 studies of stroke incidence published between 1990 and January 2017, the pooled crude rate of pregnancy-related stroke was 30.0 per 100 000 pregnancies (95% CI, 18.8–47.9). The crude rates per 100 000 pregnancies were 18.3 (95% CI, 11.9–28.2) for antenatal/perinatal stroke and 14.7 (95% CI, 8.3–26.1) for postpartum stroke.[117]
- Among 80 191 parous females in the WHI Observational Study, those who reported breastfeeding for at least 1 month had a 23% lower risk of stroke than those who never breastfed (HR, 0.77 [95% CI, 0.70–0.83]). The strength of the association increased with increasing breastfeeding duration (1–6 months: HR, 0.81 [95% CI, 0.74–0.90]; 7–12 months: HR, 0.75 [95% CI, 0.66–0.85]; ≥13 months: HR, 0.74 [95% CI, 0.65–0.83]; $P_{trend}$<0.01). The strongest association was observed among NH Black females (HR, 0.54 [95% CI, 0.37–0.71]).[118]
- In a systematic review and meta-analysis of 78 studies including >10 million participants, any HDP, including gestational hypertension, preeclampsia, or eclampsia, was associated with a greater risk of ischemic stroke; late menopause (55 years of age) and gestational hypertension were associated with a greater risk of hemorrhagic stroke; and oophorectomy, HDP, PTB, and stillbirth were associated with a greater risk of any stroke.[119]
- In a systematic review and meta-analysis of 16 cohort studies and 2 case-control studies including 7.8 million participants, females who had a miscarriage or stillbirth had a higher risk of stroke (HR, 1.07 [95% CI, 1.00–1.14] and 1.38 [95% CI, 1.11–1.71], respectively). This increased with each additional miscarriage and stillbirth.[120]
- In an analysis from the FHS of 1435 females with at least 1 pregnancy before menopause, hysterectomy, or 45 years of age, females with a history of preeclampsia had a higher risk of stroke in later life compared with females without a history of preeclampsia after adjustment for time-varying covariates (RR, 3.79 [95% CI, 1.24–11.60]).[121]
- In a prospective cohort study in Japan (N=74 928 adults), weight gain during midlife was associated with an increased risk of stroke in females (aHR, 1.61 [95% CI, 1.36–1.92] for weight gain ≥5 kg) but not in males.[122]
- In a population-based matched cohort study in the United Kingdom (n=56 090 females with endometriosis and 223 669 matched control subjects without endometriosis), females with endometriosis had a 19% increased risk of cerebrovascular disease (aHR, 1.19 [95% CI, 1.04–1.36]) compared with females without endometriosis.[123]
- In a case-control analysis of data from the Longitudinal Health Insurance Database 2000 of the Taiwan National Health Research Institutes, among 24 955 females 15 to 49 years of age with dysmenorrhea, nonsteroidal anti-inflammatory drug use and duration of use were associated with increased incidence of stroke. The aHR for nonsteroidal anti-inflammatory drug use was 1.47 (95% CI, 0.93–2.32).[124] The aHR for nonsteroidal anti-inflammatory drug use ≥24 d/mo was 2.29 (95% CI, 1.36–3.84).
- In a retrospective cohort study in the Taiwan National Health Insurance Research Database, among females 40 to 65 years of age treated with postmenopausal hormone therapy, the incidence of ischemic stroke was 1.17-fold higher in females treated with conjugated equine estrogen than in those treated with estradiol (4.24 per 1000 person-years versus 3.61 per 1000 person-years; aHR, 1.23 [95% CI, 1.05–1.44]).[125]
- Among people living with HIV, females had a higher incidence of stroke or TIA than males, especially at younger ages.[126] Compared with females without HIV, females living with HIV had a 2-fold higher incidence of ischemic stroke.[127]
- In a record linkage study among 487 767 primiparous females 15 to 44 years of age with singleton pregnancies giving birth in New South Wales, Australia, from 2003 to 2015, a history of stroke before pregnancy was associated with early-term delivery (37–38 weeks; RR, 1.49 [95% CI, 1.17–1.90]) and a prelabor caesarean section (RR, 2.83 [95% CI, 2.20–3.63]).[128] There were no differences in other APOs for females with a history of stroke.

### SDB and Sleep Duration

### (See Chapter 13 [Sleep] for more information.)

- SDB is associated with stroke risk. In a meta-analysis including 16 cohort studies (N=24 308 individuals), severe OSA was associated with a doubling in stroke risk (RR, 2.15 [95% CI, 1.42–3.24]). Severe OSA was independently associated with stroke risk among males, but not females, in stratified analyses. Neither mild nor moderate OSA was associated with stroke risk.[129]
- OSA may be particularly associated with stroke occurring at the time of waking up (wake-up stroke). In a meta-analysis of 5 studies (N=591 patients), patients with wake-up stroke had a higher AHI than those with non–wake-up stroke, and there was an increased incidence of severe OSA in those with wake-up stroke (OR, 3.18 [95% CI, 1.27–7.93]).[130]
- OSA is also common after stroke.[131] In a 2017 meta-analysis that included 43 studies, the prevalence of OSA (AHI >10) after stroke and TIA ranged from 24% to 92%, with a pooled estimate of 59%.[132] The

proportion of patients with cerebrovascular disease with severe OSA (AHI >30) ranged from 8% to 64%.

- In a 2019 meta-analysis of 89 studies (N=7096 patients; 54 studies performed within 1 month of stroke, 23 at 1–3 months, and 12 after 3 months), the prevalence after stroke of SDB with AHI >5 episodes/h was 71% (95% CI, 66.6%–74.8%) and with AHI >30 episodes/h was 30% (95% CI, 24.4%–35.5%).[133] Severity and prevalence of SDB were similar at all time periods after stroke.
- In the BASIC project, Mexican American people had a higher prevalence of poststroke SDB, defined as an AHI ≥10, than NH White people after adjustment for confounders (PR, 1.21 [95% CI, 1.01–1.46]).[131]
- In a meta-analysis of 75 studies including 8670 patients with stroke, the prevalence of sleep apnea was nominally higher in those with hemorrhagic (82.7% [95% CI, 64.4%–92.7%]) compared with patients with ischemic stroke (67.5% [95% CI, 63.2%–71.5%]; *P*=0.098) and in those with supratentorial (64.4% [95% CI, 56.7%–71.4%]) compared with infratentorial (56.5% [95% CI, 42.2%–60.0%]; *P*=0.171) stroke.[134]
- Sleep duration also may be associated with stroke risk. In a meta-analysis of 14 prospective cohort studies, long sleep, defined mostly as self-reported sleep ≥8 to 9 h/night, was associated with incident stroke (aHR, 1.46 [95% CI, 1.26–1.69]) after adjustment for demographics, vascular risk factors, and comorbidities.[135]
- Among 4785 Chinese adults >65 years of age in the 2011 CHARLS, short and long sleep durations were not associated with stroke risk in those who reported good general health status.[136] In individuals who reported poor health status, compared with normal sleep duration (7–8 h/d), short sleep duration (aOR, 2.11 [95% CI, 1.30–3.44]) and long sleep duration (aOR, 1.86, [95% CI, 1.08–3.21]) were associated with increased stroke risk.
- In a mendelian randomization analysis using the UK Biobank data (N=446 118 participants), short sleep was associated with an increased risk of cardioembolic stroke (OR, 1.33 [95% CI, 1.11–1.60]), and long sleep increased the risk of large-artery stroke (OR, 1.41 [95% CI, 1.02–1.95]), but associations were not significant after correction for multiple comparisons.[137]
- In a mendelian randomization study including 40 585 stroke cases and 406 111 controls and using 36 SNPs associated with daytime sleepiness as instrumental variables, daytime sleepiness was associated with large-artery stroke (OR, 6.75 [95% CI, 1.49–30.57]) but not with all stroke, all ischemic stroke, cardioembolic stroke, or small-artery stroke.[138]

### *Psychosocial Factors*

- In the INTERSTROKE case-control study of 26 919 participants from 32 countries, participants with psychological distress had a >2-fold (OR, 2.20 [95% CI, 1.78–2.72]) greater odds of having a stroke than control participants.[139] Another INTERSTROKE analysis found an increased odds of acute stroke in people with depressive symptoms compared with those without depressive symptoms (OR, 1.46 [95% CI, 1.34–1.58]), and the odds of stroke increased as the number of depressive symptoms increased.[140]
- History of depression and persistent depressive symptoms increases the risk of incident stroke. The association was even stronger in Black participants without diabetes (HR, 2.64 [95% CI, 1.48–4.72]).[141]
- In a prospective cohort study in New South Wales (N=221 677 participants; average follow-up, 4.7 years), high psychological distress was associated with increased risk of fatal and nonfatal stroke in females (HR 1.56 [95% CI, 1.26–1.93]) and males (HR, 1.19 [95% CI, 0.96–1.48]) compared with a low level of psychological distress.[142] Among 20 688 adults with hypertension in the China Stroke Primary Prevention Trial, those who reported high levels of psychological stress had 1.40 times the risk of first stroke (95% CI, 1.01–1.94) and 1.45 times the risk of first ischemic stroke (95% CI, 1.01–2.09) compared with those who reported low levels of psychological stress.[143]
- The presence of depressive symptoms, assessed by the 4-item Center for Epidemiological Studies Depression scale, was associated with incident stroke in both Black and White participants in the population-based REGARDS cohort study.[144] Participants with scores of 1 to 3 (aHR, 1.27 [95% CI, 1.11–1.43]) and scores ≥4 (aHR, 1.25 [95% CI, 1.03–1.51]) had increased stroke risk compared with participants without depressive symptoms, with no differential effect by race.
- Among 13 930 patients with ischemic stroke and 28 026 control subjects in the NINDS Stroke Genetics Network, each 1-SD increase in the Psychiatric Genomics Consortium PRS for major depressive disorder was associated with a 3% increase in the odds of ischemic stroke (OR, 1.03 [95% CI, 1.00–1.05]) for those of European ancestry and an 8% increase (OR, 1.08 [95% CI, 1.04–1.13]) for those of African ancestry.[145] The risk score was associated with increased odds of small-artery occlusion in both ancestry samples, cardioembolic stroke in those of European ancestry, and large-artery atherosclerosis in those of African ancestry.
- Among 1 068 117 older adults in the Information System for Research in Primary Care of Catalonia, antidepressant medication use was associated with increased risk for stroke (current users: HR, 1.04

[95% CI, 1.02–1.06]; recent users: HR, 3.34 [95% CI, 3.27–3.41]; and past users: HR, 2.06 [95% CI, 2.02–2.10]) compared with antidepressant nonusers.[146]

- In the UK Biobank cohort study (N=479 054; mean follow-up, 7.1 years), social isolation (HR, 1.39 [95% CI, 1.25–1.54]) and loneliness (HR, 1.36 [95% CI, 1.20–1.55]) were associated with a higher risk of incident stroke in analyses adjusted for demographic characteristics. However, after adjustment for biological factors, health behaviors, depressive symptoms, socioeconomic factors, and chronic diseases, these relationships were no longer statistically significant. In fully adjusted analyses, social isolation, but not loneliness, was associated with increased risk of mortality after stroke (HR, 1.32 [95% CI, 1.08–1.61]).[147]
- Among 7108 CHARLS participants followed up for 8 years, those with depressive symptoms but no chronic diseases had 1.66 times the risk of incident stroke (95% CI, 0.95–2.90), those with depressive symptoms and 1 chronic disease had 1.94 times the risk of incident stroke (95% CI, 1.17–3.24), and those with depressive symptoms and at least 2 chronic diseases had 3.00 times the risk of incident stroke (95% CI, 1.85–4.88) compared with those with no depressive symptoms and no chronic diseases.[148]

## Social Determinants of Health/Health Equity

### Sex

- In the United States in 2019, females accounted for 57.1% of stroke deaths.[149]
- Females have a higher lifetime risk of stroke than males. In the FHS, lifetime risk of stroke among those 55 to 75 years of age was 1 in 5 for females (95% CI, 20%–21%) and ≈1 in 6 for males (95% CI, 14%–17%).[150]
- In the GCNKSS, sex-specific ischemic stroke incidence rates between 1993 to 1994 and 2015 declined significantly for both males and females. In males, there was a decline from 282 (95% CI, 263–301) to 211 (95% CI, 198–225) per 100 000. In females, the decline was from 229 (95% CI, 215–242) to 174 (95% CI, 163–185) per 100 000. This trend was not observed for ICH or SAH.[151]
- Age-specific incidence rates are substantially lower in females than males in younger and middle-aged groups, but these differences narrow so that in the oldest age groups, incidence rates in females are approximately equal to or even higher than those in males.[151,152]
- A systematic review conducted between January 2008 and July 2021 looked at sex differences in ischemic strokes among young adults (18–45 years of age).[153] Overall, in young adults ≤35 years of age, the estimated effect size favored more ischemic strokes in females (IRR, 1.44 [95% CI, 1.18–1.76]; $I^2$=82%) and a nonsignificant sex difference in young adults 35 to 45 years of age (IRR, 1.08 [95% CI, 0.85–1.38]; $I^2$=95%).
- Racial and ethnic disparities in stroke risk may persist or even increase in elderly females from underrepresented races and ethnicities.[63] In NOMAS, among 3298 stroke-free participants followed up through 2019, Black and Hispanic females ≥70 years of age had a higher risk of stroke compared with White females after adjustment for age, sex, education, and insurance status (Black females/White females: HR, 1.76 [95% CI, 1.10–2.80]; Hispanic females/White females: HR, 1.77 [95% CI, 1.04–3.00]).[154] This increased risk was not present among elderly Black or Hispanic males compared with White males.

### Race and Ethnicity

- A cohort study compared Black and White participants in the SPRINT trial with the same groups in the observational ARIC study to assess whether clinical trial participation mitigated disparities in stroke risk.[155] The risk of stroke between self-reported White participants in SPRINT and ARIC was not significantly different (inverse propensity–weighted HR 0.78 [0.52-1.19]). Black ARIC participants were twice as likely to have a stroke as White ARIC participants (inverse propensity–weighted HR, 1.96 [95% CI, 1.41–2.71]), but Black SPRINT participants did not have higher stroke risk compared with self-reported White SPRINT or White ARIC participants (inverse propensity–weighted HR, 0.99 [95% CI, 0.68–1.77] and 0.95 [95% CI, 0.57–1.59], respectively). Black SPRINT participants in the intensive BP control group had a lower risk of stroke compared with Black ARIC participants (inverse propensity–weighted HR, 0.39 [95% CI, 0.20–0.75]). The authors concluded that the absence of the racial disparity in stroke incidence in SPRINT indicated that aspects of the disparity are modifiable.
- A retrospective cohort of Black and White participants in the ARIC, MESA, and REGARDS studies (1983–2019) compared the performance of stroke-specific algorithms with PCEs developed for ASCVD for the prediction of new-onset stroke.[156] The study looked at 62 482 participants who were at least 45 years of age and free of stroke or TIA. Significant differences in discrimination were observed by race: C indexes were 0.76 for all 3 models in White females versus 0.69 in Black females (all $P$<0.001) and between 0.71 and 0.72 in White males and between 0.64 and 0.66 in Black males (all $P$>0.001). All algorithms exhibited worse discrimination in Black individuals than in White individuals, suggesting a need

to expand the pool of risk factors and to improve modeling techniques to address observed racial disparities and improve model performance.

- In a study of NH White and Black females from the WHI (N=126 018, 9% Black females) followed up through 2010, Black females had a greater risk of total stroke than White females (age-adjusted HR, 1.47 [95% CI, 1.33–1.63]).[157] Adjustment for socioeconomic factors and stroke risk factors attenuated this association, although the higher risk for Black females remained statistically significant in those 50 to <60 years of age (HR, 1.76 [95% CI, 1.09–2.83]).
- In the ARIC study, stroke incidence rates per decade (from 1987–2017) showed similar declines over time in White and Black individuals (see the Secular Trends section).[6]
- In an analysis of pooled SHS and ARIC data, there were 242 stroke events (7.6%) among 3182 American Indian participants without prior stroke followed up from 1988 to 2008; there were 613 stroke events (5.9%) among 10 413 White participants from 1987 to 2011. American Indian participants had higher stroke rates in unadjusted analyses. Results were attenuated after adjustment for vascular risk factors, which may be on the causal pathway for this association.[158]
- Black people are at higher risk for dementia than White people within 5 years of ischemic stroke. In an analysis of South Carolina data from 2000 to 2012 (n=68 758 individuals with a diagnosis of ischemic stroke), Black race increased risk for 5 categories of dementia after incident stroke (HR, 1.37 for AD to HR, 1.95 for vascular dementia).[159]
- A retrospective study of 34 596 patients admitted to 43 hospitals from January 2016 to September 2020 assessed racial disparities in mechanical thrombectomy in 26 640 NH White individuals (77.0%) and 7956 Black individuals (23.0%) and found that Black individuals with stroke underwent mechanical thrombectomy less frequently than White individuals in part because of longer times from last known well to hospital arrival and a lower rate of documented acute large-vessel occlusion (see Organization of Stroke Care section).[160]
- In a retrospective analysis of the BRFSS 2016, Black (OR, 1.58 [95% CI, 1.54–1.63]) and Hispanic (OR, 2.30 [95% CI, 2.19–2.42]) individuals more frequently reported worsening confusion or memory loss that interfered with day-to-day activities than White individuals.[161]

## TIA: Prevalence, Incidence, Racial and Ethnic Disparities, and Prognosis

- TIAs confer a substantial short-term risk of stroke, hospitalization for CVD events, and death. There is a 1.2% risk of stroke at 2 days and 7.4% risk of stroke at 90 days after TIA.[162]
- Among 14 059 participants in the FHS followed up from 1948 to 2017, the incidence of TIA was 1.19 per 1000 person-years. In those with a TIA (median follow-up, 8.86 years), 29.5% had a stroke with a median time to stroke of 1.64 years (IQR, 0.07–6.6 years). Compared with age- and sex-matched control subjects without TIA, participants who experienced a TIA were at a higher risk of stroke (aHR, 4.37 [95% CI, 3.30–5.71]). This association was unaltered when the analysis was limited to the last epoch (2000–2017).
- In the Oxford Vascular Study, acute lesions on MRI were identified in 13% of participants with TIA.[163] In age- and sex-adjusted analyses, these participants had a higher risk of recurrent ischemic stroke compared with individuals with TIA and a negative MRI (HR, 2.54 [95% CI, 1.21–5.34]; *P*=0.014).
- In a substudy of the SpecTRA multicenter cohort of participants with transient neurological symptoms, MRI diffusion-weighted imaging, performed within 7 days of an event, identified a lesion in 35.1% of participants.[164] Among participants with focal symptoms, increased duration of symptoms (up to 24 hours) was directionally proportional to the probability of identifying a lesion (ranging from 30% at <1-hour duration to 72% at 24 hours). This relationship was not present among those with mixed or nonfocal symptoms, in whom the predicted probability of a lesion was 35%. In a meta-analysis of 68 studies from 1971 to 2019, the estimated risk of subsequent ischemic stroke after a TIA was 2.4% (95% CI, 1.8%–3.2%) within 2 days, 3.8% (95% CI, 2.5%–5.4%) within 7 days, 4.1% (95% CI, 2.4%–6.3%) within 30 days, and 4.7% (95% CI, 3.3%–6.4%) within 90 days.[165] However, when studies were categorized according to date of publication (before 1999, 1999–2007, after 2007), the risk of subsequent ischemic stroke appears to have slightly declined. Among patients with TIA enrolled in the POINT trial, 188 of 1964 patients (9.6%) enrolled with TIA had a modified Rankin Scale score <1 (some disability) at 90 days.[166] In multivariable analysis, age, subsequent ischemic stroke, serious adverse events, and major bleeding were significantly associated with disability in TIA.

## Recurrent Stroke: Incidence, Race and Ethnicity, and Risk

- A meta-analysis of 13 cohorts with 59 919 participants found that MetS was associated with higher risk of recurrent stroke (RR, 1.46 [95% CI, 1.07–1.97]).[167]

- The IPSS compared outcomes after PCAIS and anterior circulation arterial ischemic stroke in neonates and children with AIS up to 18 years of age.[168] Those investigators found that recurrent ischemic events were more frequent in PCAIS than anterior circulation arterial ischemic stroke (30% versus 22%; *P*=0.02) despite similar rates of secondary preventive antithrombotic treatment. Multivariable logistic regression analysis found PCAIS (OR, 1.69 [95% CI, 1.08–2.65]; *P*=0.02) and cervicocephalic artery dissections (OR, 2.39 [95% CI, 1.36–4.22]; *P*=0.003) to be risk factors for recurrent ischemic events.
- Clinical features associated with recurrent stroke among participants enrolled in the RE-SPECT ESUS trial were assessed.[169] A total of 384 of 5390 participants had recurrent stroke (annual rate, 4.5%) over a median follow-up of 19 months. Multivariable models revealed that stroke or TIA before the index event (HR, 2.27 [95% CI, 1.83–2.82]), creatinine clearance <50 mL/min (HR, 1.69 [95% CI, 1.23–2.32]), male sex (HR, 1.60 [95% CI, 1.27–2.02]), and $CHA_2DS_2$-VASc score of 4 (HR, 1.55 [95% CI, 1.15–2.08] and HR, 1.66 [95% CI, 1.21–2.26] for scores ≥5) versus $CHA_2DS_2$-VASc scores of 2 to 3 were independent predictors for recurrent stroke.
- A post hoc cohort study was conducted using data from the CNSR from 2007 to 2018 and included patients with ischemic stroke who were enrolled in CNSR in phases I or III within 7 days of symptom onset.[170] Over 10 years, the adjusted cumulative incidence of recurrent stroke within 12 months decreased from 15.5% (95% CI, 14.8%–16.2%) to 12.5% (95% CI, 11.9%–13.1%; *P*<0.001). Although the stroke recurrence rate in China decreased significantly, ≈12.5% of patients still experienced stroke recurrence within 12 months.
- Among 128 789 Medicare beneficiaries from 1999 to 2013, the incidence of recurrent stroke per 1000 person-years was 108 (95% CI, 106–111) for White people and 154 (95% CI, 147–162) for Black people. Mortality after recurrence was 16% (95% CI, 15%–18%) for White people and 21% (95% CI, 21%–22%) for Black people. Compared with White people, Black people had higher risk of 1-year recurrent stroke (aHR, 1.36 [95% CI, 1.29–1.44]).[171]
- In a meta-analysis of publications through September 2017, MRI findings of multiple lesions (pooled RR, 1.7 [95% CI, 1.5–2.0]), multiple-stage lesions (pooled RR, 4.1 [95% CI, 3.1–5.5]), multiple-territory lesions (pooled RR, 2.9 [95% CI, 2.0–4.2]), prior infarcts (pooled RR, 1.5 [95% CI, 1.2–1.9]), and isolated cortical lesions (pooled RR, 2.2 [95% CI, 1.5–3.2]) were associated with increased risk of ischemic stroke recurrence. A history of stroke or TIA was also associated with higher risk (pooled RR, 2.5 [95% CI, 2.1–3.1]). Risk of recurrence was lower for small- versus large-vessel stroke (pooled RR, 0.3 [95% CI, 0.1–0.7]) and for stroke resulting from an undetermined cause versus large-artery atherosclerosis (pooled RR, 0.5 [95% CI, 0.2–1.1]).[172]
- A meta-analysis of 104 studies with 71 298 patients with ischemic stroke found that moderate to severe WMH burden was associated with increased risk of any recurrent stroke (RR, 1.65 [95% CI, 1.36–2.01]) and recurrent ischemic stroke (RR, 1.90 [95% CI, 1.26–2.88]).[173]
- A study among 7101 patients with ischemic strokes followed up for 1 year found a significant association between WMH volume and recurrent strokes. This association by WMH quartile was stronger for recurrent hemorrhagic stroke (HR, 1, 7.32, 14.12, and 33.52) than for ischemic recurrence (HR, 1, 1.03, 1.37, and 1.61). However, the absolute incidence of ischemic stroke recurrence remained higher by WMH quartile (3.8%/y, 4.5%/y, 6.3%/y, and 8.2%/y) compared with hemorrhagic recurrence (0.1%/y, 0.4%/y, 0.6%/y, and 1.3%/y).[174]
- In a nationwide cohort study of Danish patients with first ischemic stroke treated with intravenous tPA, time from symptom onset to treatment was associated with long-term recurrent stroke risk.[175] Compared with those treated within 90 minutes, the risk was increased for those treated at 91 to 180 minutes (HR, 1.25 [95% CI, 1.06–1.48]) and for those treated at 181 to 270 minutes (HR, 1.35 [95% CI, 1.12–1.61]).
- In a study in China (N=9022), adherence to guideline-based secondary stroke prevention conferred a lower risk of recurrent stroke (HR, 0.85 [95% CI, 0.74–0.99]) at 12 months compared with low or no adherence.[176]
- Data from 2015 to 2019 in 1458 hospitals in China found that an increase of 10 μg/m$^3$ in PM1 was associated with a 1.64% increment in stroke recurrence.[177]
- In a nationwide Danish registry study of individuals after stroke from 2003 to 2012 (n=60 503 strokes), income was inversely related to long-term, but not short-term, mortality for all causes of death.[178] There was a 5.7% absolute difference (*P*<0.05) in mortality between the lowest- and highest-income groups at 5 years after stroke.
- Employment status was linked to outcomes in a study of 377 symptomatic patients with stroke from the Jisei stroke registry in Tokyo. Patients with regular employment compared with those with nonregular employment were more likely to have a hyperacute stroke on Monday in reference to Sunday (OR, 2.56 [95% CI, 1.00–6.54]; *P*=0.049) but were also more likely to have a favorable outcome defined as a

modified Rankin Score of 0 to 2 at 3 months (OR, 2.89 [95% CI, 1.38–6.05]; *P*=0.005).[179]

- In the WHO MONICA-psychological program, among a random sample from a Russian/Siberian population 25 to 64 years of age, a social network index was associated with stroke risk. During 16 years of follow-up, the risk of stroke in people with a low level of social network was 3.4 times higher for males (95% CI, 1.28–5.46) and 2.3 times higher for females (95% CI, 1.18–4.49).[180]

## Genetics and Family History

- Ischemic stroke is heritable, although heritability estimates vary by ischemic stroke subtype.[181] A study of n=3752 patients with ischemic strokes and n=5972 control subjects estimated ischemic stroke heritability to be 37.9%. Estimated heritability was higher for large-vessel disease (40.3%) and lower for small-vessel disease (16.1%).
- Rare monogenic causes of stroke include Fabry disease, sickle cell disease, homocystinuria, Marfan syndrome, vascular Ehlers-Danlos syndrome (type IV), pseudoxanthoma elasticum, retinal vasculopathy with cerebral leukodystrophy and systemic manifestations, and mitochondrial myopathy, encephalopathy, and lactic acidosis.[182]
- The largest multiethnic GWAS of stroke conducted to date reported 32 genetic loci for any stroke or stroke subtypes.[183] These loci point to a major role of cardiac mechanisms beyond established sources of cardioembolism. Approximately half of the stroke genetic loci share genetic associations with other vascular traits, most notably BP. The identified loci were also enriched for targets of antithrombotic drugs, including alteplase and cilostazol.
- Because previous multiethnic stroke GWASs were conducted primarily in European ancestral populations, GWASs in populations with proportionately greater representation of non-European participants also have been conducted.[184] The largest effort to date in 5 ancestries (33% non-European) with n=110 182 cases and n=1 503 898 controls identified 61 novel independent loci for stroke and stroke subtypes. Putative causal genes included *SH3PXD2A*, *FURIN*, *GRK5*, and *NOS3*, and lead variant effect sizes were highly correlated across ancestral populations. Cross-ancestry and ancestry-specific GRSs predicted ischemic stroke in African, East Asian, and European populations independently of risk factors.
- Some stroke genetic loci may be subtype specific.[183] For example, *EDNRA* and *LINC01492* were associated exclusively with large-artery stroke. However, shared genetic influences between stroke subtypes were also evident. For example, *SH2B3* showed shared influence on large-artery and small-vessel stroke and *ABO* on large-artery and cardioembolic stroke; *PMF1-SEMA4A* has been associated with both nonlobar ICH and ischemic stroke.
- A GWAS of ICH suggests that 15% of this heritability is attributable to genetic variants in the *APOE* gene and 29% is attributable to non-*APOE* genetic variants.[185] Other genes strongly implicated in ICH are *PMF1* and *SLC25A44*, which have been linked to ICH with small-vessel disease.[186,187]
- A multiethnic GWAS of SAH in 10 754 cases and 306 882 controls of European and East Asian ancestry identified 17 risk loci, 11 of which were not previously reported.[188]
- An initial GWAS of small-vessel stroke from the International Stroke Consortium (n=4203 cases and n=50 728 controls) identified a novel association with a region on chromosome 16q24.2.[189] A follow-up study that included n=7338 cases and n=254 798 controls identified 5 loci in European or transethnic meta-analysis (*ICA1L-WDR12-CARF-NBEAL1*, *ULK4*,*SPI1-SLC39A13-PSMC3-RAPSN*,*ZCCHC14*, and *ZBTB14-EPB41L3*).[190] By extending analyses to simultaneously consider cerebral white matter hyperintensities and small-vessel stroke, multitrait GWAS identified an additional 7 loci (*SLC25A44-PMF1-BGLAP*, *LOX-ZNF474-LOC100505841*, *FOXF2-FOXQ1*, *VTA1-GPR126*, *SH3PXD2A*, *HTRA1-ARMS2*, and *COL4A2*). Two of these loci (*COL4A2* and *HTRA1*) are implicated in monogenic forms of small-vessel stroke.
- GWASs of early-onset ischemic stroke also are emerging. One study of participants 18 to 59 years of age (n=16 730 cases and n=599 237 controls from 48 studies) identified 2 independent variants at *ABO*, a known stroke locus.[191] Low-frequency genetic variants (ie, allele frequency <5%) also may contribute to risk of large- and small-vessel stroke. *GUCY1A3*, for example, with a minor allele frequency in the lead SNP of 1.5%, was associated with large-vessel stroke.[192] The gene encodes the α1-subunit of soluble guanylyl cyclase, which plays a role in both nitric oxide–induced vasodilation and platelet inhibition and has been associated with early MI. Low-frequency coding variants also may affect ischemic stroke risk, including variants at *ABO*, *TPTE*, *MEP1A*, and *DDX31*.[193] However, the rarity of these variants has made replication challenging.
- Genetically determined higher levels of monocyte chemoattractant protein-1/chemokine (C-C motif) ligand 2 concentrations were associated with high risk of any stroke, including associations with large-artery stroke, ischemic stroke, and cardioembolic stroke, but not small-vessel stroke or

ICH. These results implicate inflammation in stroke pathogenesis.[194]
- Genetic determinants of coagulation factors, including factor XI and factor VII, have been implicated in the pathogenesis of ischemic stroke.[195,196]
- Genetic correlation analyses suggest genetic overlaps between ischemic stroke and PA, cardiometabolic factors, smoking, and lung function. Genetic predisposition to higher concentration of small LDL particles was associated with risk of large-artery stroke (OR, 1.31 [95% CI, 1.09–1.56]; $P$=0.003).[197]

## Awareness

- Awareness of stroke symptoms and signs among US adults remains suboptimal but improved in NHIS from 2009 to 2014. In 2014, 68.3% of survey respondents were able to recognize 5 common stroke symptoms, and 66.2% demonstrated knowledge of all 5 stroke symptoms and the importance of calling 9-1-1.[198]
- In the 357 participants who completed the South Asian Health Awareness About Stroke program from 2014 to 2017, those ≤60 years of age had a 2.9-point greater increase in score on educational questionnaires than those >60 years of age ($P$<0.0001) after a culturally specific educational presentation on stroke awareness.[199]
- A study of a community-partnered intervention among seniors from underrepresented races and ethnicities found that participants would respond to only half of presented stroke symptoms by immediately calling 9-1-1 (49% intervention, 54% control at baseline). This rate increased to 68% among intervention participants with no change for control subjects.[200]
- Knowledge of stroke risk factors and symptoms is limited in children; stroke knowledge is lowest for those living in communities with greater economic need and sociodemographic distress and lower school performance.[201]

## Stroke Mortality

## (See Table 15-1 and Charts 15-3 through 15-7)

- In 2021 (unpublished NHLBI tabulations using CDC WONDER[202] and the NVSS[203]):
  - On average, someone died of a stroke every 3 minutes 14 seconds.
  - Stroke accounted for ≈1 of every 21 deaths in the United States.
  - When considered separately from other CVDs, stroke ranks fifth among all causes of death, behind diseases of the heart, cancer, COVID-19, and unintentional injuries/accidents.
  - The number of deaths with stroke as an underlying cause was 162 890 (Table 15-1); the age-adjusted death rate for stroke as an underlying cause of death was 41.1 per 100 000, whereas the age-adjusted rate for any mention of stroke as a cause of death was 74.9 per 100 000.
  - Approximately 66% of stroke deaths occurred outside of an acute care hospital.
  - More females than males die of stroke each year because of the higher prevalence of elderly females compared with males. Females accounted for 56.5% of US stroke deaths in 2021.
- Conclusions about changes in stroke death rates from 2011 to 2021 are as follows[202]:
  - The age-adjusted stroke death rate increased 8.4% (from 37.9 per 100 000 to 41.1 per 100 000), whereas the actual number of stroke deaths increased 26.3% (from 128 932 to 162 890 deaths).
  - Age-adjusted stroke death rates increased 9.5% for males and 8.1% for females.
  - Crude stroke death rates increased among people 25 to 34 years of age (7.7%; from 1.3 to 1.4 per 100 000), 35 to 44 years of age (19.0%; from 4.2 to 5.0 per 100 000), 45 to 54 years of age (10.2%; from 12.8 to 14.1 per 100 000), 55 to 64 years of age (16.3%; from 29.4 to 34.2 per 100 000), 65 to 74 years of age (7.5%; from 78.2 to 84.1 per 100 000), and >85 years of age (17.7%; from 943.7 to 1111.1 per 100 000). In comparison, the crude stroke death rates declined among those 75 to 84 years of age (−3.7%; 285.4 to 274.8 per 100 000). There has been a recent flattening of or increase in death rates among most age groups (Charts 15-3 and 15-4).
- There are substantial geographic disparities in stroke mortality, with higher rates in the southeastern United States known as the Stroke Belt (2015–2017; Chart 15-5). This area is usually defined to include the 8 southern states of North Carolina, South Carolina, Georgia, Tennessee, Mississippi, Alabama, Louisiana, and Arkansas. Historically, the overall average stroke mortality has been ≈30% higher in the Stroke Belt than in the rest of the nation and ≈40% higher in the Stroke Buckle (North Carolina, South Carolina, and Georgia).[204]
- Based on pooled data from several large studies, the probability of death within 1 or 5 years after a stroke was highest in individuals ≥75 years of age (Charts 15-6 and 15-7).

### *Racial and Ethnic Disparities*

### *See Charts 15-6 through 15-8*

- In 2021, NH Black males and females had higher age-adjusted death rates for stroke than NH White,

NH Asian, NH American Indian or Alaska Native, and Hispanic males and females in the United States (Chart 15-8).

- Age-adjusted stroke death rates increased among all racial and ethnic groups; however, in 2021, rates remained higher among NH Black people (59.6 per 100 000; change since 2018, 12.5%) than among NH White people (39.8 per 100 000; change since 2018, 10.6%), NH Asian people (32.6 per 100 000; change since 2018, 11.6%), NH American Indian or Alaska Native people (34.6 per 100 000; change since 2018, 12.7%), and Hispanic people (36.1 per 100 000; change since 2018, 12.8%).[202]
- The probability of death within 1 year of a stroke was lowest in Black males 45 to 64 years of age (Chart 15-6). The probability of death within 5 years of a stroke was lowest for White males 45 to 64 years of age (Chart 15-7).
- Based on US national death statistics from 1990 to 2009, stroke mortality rates among American Indian and Alaska Native people were higher than among White people. In federally recognized tribal reservations, off-reservation trust land, and adjacent areas, the stroke mortality rate ratio for American Indian and Alaska Native males compared with White males was 1.20 (95% CI, 1.14–1.25). In those same areas, the rate ratio for American Indian and Alaska Native females was 1.19 (95% CI, 1.15–1.24). Stroke mortality rate ratios for American Indian/Alaska Native people versus White people varied by region with the lowest in the Southwest (0.93 for both sexes combined) and the highest in Alaska (1.51 for both sexes combined). Starting in 2001, rates among American Indian/Alaska Native people decreased in all regions.[205]
- Data from the ARIC study (1987–2011; 4 US cities) showed that the cumulative all-cause mortality rate after a stroke was 10.5% at 30 days, 21.2% at 1 year, 39.8% at 5 years, and 58.4% at the end of 24 years of follow-up. Mortality rates were higher after an incident hemorrhagic stroke (67.9%) than after ischemic stroke (57.4%). Age-adjusted mortality after an incident stroke decreased over time (absolute decrease, 8.1 deaths per 100 strokes after 10 years), which was attributed mainly to the decrease in mortality among those ≤65 years of age (absolute decrease of 14.2 deaths per 100 strokes after 10 years).[6]
- Projections of stroke mortality from 2012 to 2030 differ on the basis of the factors included in the forecasting.[206] Conventional projections that incorporate only expected population growth and aging reveal that the number of stroke deaths in 2030 may increase by ≈50% compared with the number of stroke deaths in 2012. However, if previous stroke mortality trends are also incorporated into the forecasting, the number of stroke deaths among the entire population is projected to remain stable through 2030, with potential increases among the population ≥65 years of age. Moreover, the trend-based projection method reveals that the disparity in stroke deaths among NH Black people compared with NH White people could increase from an RR of 1.10 (95% CI, 1.08–1.13) in 2012 to 1.30 (95% CI, 0.45–2.44) in 2030.[206]

## Complications and Recovery

## (See Chart 15-9)

- Recurrent stroke is common (Chart 15-9).

### *Rehabilitation and Readmission*

#### *Disability*

- In 125 548 Medicare fee-for-service beneficiaries discharged from inpatient rehabilitation facilities after stroke, individuals who had a paid caregiver before their stroke had a lower odds of being discharged with potential to recover to full independence after discharge than those who lived with a caregiver or family (OR for walking, 0.59 [95% CI, 0.51–0.69]).[207]
- In the Swedish Stroke Register (Riksstroke) of 11 775 patients with first ischemic stroke who were functionally independent before stroke, the number of chronic comorbidities was associated with a poor outcome (dead or dependent; modified Rankin Scale score ≥3) at 12 months[208]: no comorbidity, 24.8%; 1 comorbidity, 34.7%; 2 to 3 comorbid conditions, 45.2%; and ≥4 comorbid conditions, 59.4%. At 5 years, these proportions were 37.7%, 50.3%, 64.3%, and 81.7%, respectively. There were substantial negative effects of dementia, kidney disease, and HF.
- In a meta-analysis of 22 studies including 5125 participants, the prevalence of lateropulsion (pusher syndrome) after stroke was 55.1% (95% CI, 35.9%–74.2%).[209] This decreased from 52.8% (95% CI, 40.7%–65%) in the acute phase to 37% (95% CI, 26.3%–47.7%) in the early subacute phase and 22.8% (95% CI, 0%–46.3%) in the late subacute phase.
- In a meta-analysis of 55 studies, 56.7% (95% CI, 48.3%–65.1%) of people returned to work after stroke at 1 year and 66.7% (95% CI, 60.2%–73.2%) at 2 years in population-based studies.[210]

### *Comorbid Complications*

- In a systematic review of 47 studies (N=139 432 patients; mean age, 68.3 years; mean NIHSS score, 8.2), the pooled frequency of poststroke pneumonia was 12.3% (95% CI, 11%–13.6%). The frequency was lower in stroke units (8% [95% CI, 7.1%–9%]) than other locations ($P_{interaction}$=0.001). The

frequency of poststroke urinary tract infection was 7.9% (95% CI, 6.7%–9.3%) and of any poststroke infection was 21% (95% CI, 13%–29.3%).[211]

- In a meta-analysis that included 7 studies from multiple continents, the incidence density of late-onset poststroke seizure (ie, seizure occurring at least 14 days after a stroke) was 1.12 (95% CI, 0.95–1.32) per 100 person-years.[212]
- In a meta-analysis of 9 studies (7 countries), reduced motor function in the upper limb (OR, 2.81 [95% CI, 1.40–5.61]), diabetes (OR, 2.09 [95% CI, 1.16–3.78]), and a history of shoulder pain (OR, 2.78 [95% CI, 1.29–5.97]) were identified as significant risk factors for the development of poststroke shoulder pain within the first year after stroke.[213]
- In a meta-analysis of 26 366 participants from 42 studies, the prevalence of poststroke dysphagia was 42%.[214] Poststroke dysphagia was associated with high risk of pneumonia (OR, 4.08 [95% CI, 2.13–7.79]) and mortality (OR, 4.07 [95% CI, 2.17–7.63]). Factors associated with increased risk of poststroke dysphagia include hemorrhagic stroke type (OR, 1.52 [95% CI, 1.13–2.07]), prior stroke (OR, 1.40 [95% CI, 1.18–1.67]), severe stroke (OR, 1.38 [95% CI, 1.17–1.61]), female sex (OR, 1.25 [95% CI, 1.09–1.43]), and diabetes (OR, 1.24 [95% CI, 1.02–1.51]). In CHS, among 509 participants with recovery data, those in the lowest quintiles of prestroke walking speed and grip strength had approximately twice the risk of poststroke decline in both cognition (aOR, 2.00 [95% CI, 1.18–3.39] for walking speed; aOR, 1.86 [95% CI, 1.05–3.32] for grip strength) and activities of daily living (aOR, 2.19 [95% CI, 1.33–3.62] for walking speed; OR, 1.74 [95% CI, 1.01–3.02] for grip strength).[215] Inflammatory biomarkers were associated with an increased risk of poststroke cognitive decline among males (aOR, 1.48 [95% CI, 1.14–1.92] per doubling of CRP; aOR, 2.02 [95% CI, 1.28–3.20] per doubling of IL-6), and frailty was associated with a 3-fold increase in risk of decline in activities of daily living among females (aOR, 3.21 [95% CI, 1.27–8.13]).
- Among 938 patients with ischemic stroke in the Spanish Stroke-Chip study, 19 patients (2%) had acute decompensated HF, and a 3-biomarker panel including vascular adhesion protein-1 >5.67, NT-proBNP >4.98, and d-dimer >5.38 predicted this outcome with a sensitivity of 89.5% and specificity of 71.7%.[216] Eighty-six patients (9.1%) had respiratory tract infections, and a panel of interleukin-6 >3.97, von Willebrand factor >3.67, and d-dimer >4.58 predicted respiratory tract infection with sensitivity of 82.6% and specificity of 59.8%. The addition of the panel to clinical predictors significantly improved AUCs of the receiver-operating characteristic curves for both outcomes.

### *Depression*

- In a retrospective cohort study among US Medicare beneficiaries admitted for ischemic stroke from July 1, 2016, to December 31, 2017, females (n=90 474) were 20% more likely to develop poststroke depression over 1.5 years of follow-up than males (n=84 427) in adjusted models (HR, 1.20 [95% CI, 1.17–1.23]).[217]
- In a secondary analysis of a randomized, multicenter, placebo-controlled trial among 308 patients with spontaneous intracranial hemorrhage who completed the Center for Epidemiologic Studies Depression Scale, poststroke depression occurred in 36% of patients at 180 days.[218] Correlates of depression included female sex (aOR, 1.93, [95% CI, 1.07–3.48]), Hispanic ethnicity (aOR, 3.05 [95% CI, 1.19–7.85]), intraventricular hemorrhage (aOR, 1.88 [95% CI, 1.02–3.45]), right-sided lesions (aOR, 3.00 [95% CI, 1.43–6.29]), impaired cognition at day 30 (aOR, 2.50 [95% CI, 1.13–5.54]), and not being at home at day 30 (aOR, 3.17 [95% CI, 1.05–9.57]).
- Poststroke depression is associated with higher mortality. Among 15 prospective cohort studies (N=250 294 participants), poststroke depression was associated with an increased all-cause mortality (HR, 1.59 [95% CI, 1.30–1.96]).[219]
- In a secondary analysis of the AFFINITY trial including 1221 participants recruited within 2 weeks of stroke and randomized to fluoxetine or placebo, 36.6% of participants developed depression in the year after their stroke (17.9% had early, 7.4% had late, and 11.4% had persistent depression).[220] Increased stroke severity, defined as doubling of the measured NIHSS, was associated with increased risk of early (RR, 2.08 [95% CI, 1.65–2.62]), late (RR, 1.53 [95% CI, 1.14–2.06]), and persistent (RR, 2.50 [95% CI, 1.89–3.32]) depression. In addition, history of depression and having a partner were associated with increased risk of persistent depression (RR, 6.28 [95% CI, 2.88–13.71] and 3.94 [95% CI, 2.42–6.41], respectively).

## Functional Impairment

Functional and cognitive impairment and dementia are common after stroke, with the incidence increasing with duration of follow-up.

- Stroke accelerates natural age-related functional decline. In the CHS, 382 of 5888 participants (6.5%) had ischemic stroke during follow-up with ≥1 disability assessment afterward. The annual increase in disability more than tripled after stroke (0.15 additional Barthel index points per year [95% CI, 0.004–0.30]). It is notable that the disability index did not change significantly after MI (0.02 additional points per year [95% CI, −0.07 to 0.11]).[221]

- In secondary analysis of the AFFINITY RCT evaluating the use of fluoxetine after stroke, improvement in the modified Rankin Scale was observed in 95% of participants at 12 months.[222] Functional recovery was associated with younger age (<70 years of age at time of stroke); absence of prestroke history of diabetes, CHD, or ischemic stroke; prestroke history of depression, relationship with a partner, living with others, independence, or paid employment; absence of fluoxetine intervention; ischemic stroke (versus hemorrhagic stroke); and lower baseline NIHSS and Patient Health Questionnaire-9 scores.

### *Cognitive Impairment and Dementia*

- In a study among 4 centers in Shanghai (N=383 patients with AIS), the prevalence of cognitive impairment (Montreal Cognitive Assessment Scale score <22) was 49.6% at 2 weeks and 34.2% at 6 months.[223] Age, lower level of education, higher glucose level, and severe stroke were correlates of poststroke cognitive impairment, and LDL-C level was associated with higher cognitive scores. The DREAM-LDL score had an area under the receiver-operating curve of 0.93 for predicting cognitive impairment at 6 months.
- Among 109 patients with ischemic stroke, NIHSS score (β=−0.54 [95% CI, −0.99 to −0.89]) and preexisting leukoaraiosis severity (β=−1.45 [95% CI, −2.86 to −0.03]) independently predicted functional independence, primarily through an effect on cognitive rather than motor scores.[224]
- In a multicenter cohort study of 912 patients with lacunar stokes and 425 control subjects, vascular cognitive impairment was identified in 38.8% of patients with lacunar strokes versus 13.4% of control subjects.[225] Factors associated with vascular cognitive impairment include diabetes (aOR, 1.98 [95% CI, 1.40–2.80]) and higher BMI (aOR, 1.03 [95% CI, 1.00–1.05]). On the other hand, years of full-time education was found to be associated with lower risk of vascular cognitive impairment (aOR, 0.92 [95% CI, 0.86–0.99]).

## Stroke in Children

- On the basis of pathogenic differences, pediatric strokes are typically classified as either perinatal (occurring at ≤28 days of life and including in utero strokes) or (later) childhood. Presumed perinatal strokes are diagnosed in children with no symptoms in the newborn period who present with hemiparesis or other neurological symptoms later in infancy.
- Reported incidence was higher in newborns than in older children (1/3500 live births/y versus 1–2/100 000 live births/y) with a ratio of ≈6 times higher.[226] A multicenter prospective study in Beijing included all the live births from 17 representative maternal delivery hospitals from March 1, 2019, to February 29, 2020.[227] A total of 27 cases were identified, and the incidence of perinatal stroke in Beijing was 1 in 2660 live births, including 1 in 5985 for ischemic stroke and 1 in 4788 for hemorrhagic stroke.

### *Risk Factors*

- A case-control study of 40 patients with perinatal arterial ischemic stroke matched to 80 controls found that emergency cesarean section (OR, 13.79 [95% CI, 3.51–54.13]), primiparity (OR, 11.74 [95% CI, 3.28–42.02]), birth asphyxia (OR, 40.55 [95% CI, 3.08–532.94]), and Apgar score of 7 after 5 minutes (OR, 13.75 [95% CI, 1.03–364.03]) were significantly associated with perinatal arterial ischemic stroke in multivariate analysis.[228]
- A recent review of ischemic stroke in childhood found that the main risk factors in children >28 days of age were nonatherosclerotic arteriopathies (53%), cardiac disorders (31%), and prothrombotic states (13%). These risk factors accounted for most of the cases with variations by geographic area and age.[229]A recent review of the role of infection and inflammation in the pathogenesis of perinatal arterial ischemic stroke infections found that in neonates, chorioamnionitis and intrauterine inflammation were common risk factors for AIS.[230] The review found that in infants and children, even minor childhood infections were associated with subsequent increased risk for AIS. A retrospective study found that the strongest association between infection and AIS was during the 3-day period after the medical visit for infection (OR, 12.1 [95% CI, 2.5–57]; *P*=0.002); a multicenter prospective study found that an association between clinical infection and childhood AIS infection in the prior week conferred a 6.5-fold increased risk of AIS (95% CI, 3.3–13; *P*<0.0001). The review also found that postinfectious inflammatory mechanisms after infections with herpesviruses may lead to focal cerebral arteriopathy. The authors emphasized that other agents such as parvovirus B19, dengue virus, and SARS-CoV-2 have recently been implicated as other potential triggers.
- A multicenter prospective study in Beijing that included all the live births from 17 representative maternal delivery hospitals from March 1, 2019, to February 29, 2020, found that the risk factors include primiparity, placental or uterine abruption/acute chorioamnionitis, intrauterine distress, asphyxia, and severe infection.[227]
- In an analysis of data from the IPSS from 2003 to 2014 (N=2127 children with AIS), 725 (34%) had arteriopathy.[231] Subtypes of arteriopathy were

dissection (27%), moyamoya (25%), focal cerebral arteriopathy inflammatory subtype (15%), diffuse cerebral vasculitis (15%), and nonspecific arteriopathy (19%). In a separate analysis of the IPSS, among 2768 cases of AIS, 1931 (70%) were located in the anterior circulation, 507 (18%) in the posterior circulation, and 330 (12%) in both territories.[168] Cervicocephalic arterial dissections were significantly more frequent in posterior circulation strokes (20%) than in anterior circulation strokes (8.5%), whereas cardioembolism was less frequent in posterior circulation strokes (19% versus 32%; $P<0.001$). Case fatality was equal in both groups (2.9%), but survivors of posterior circulation childhood stroke were more likely to have a normal neurological examination at hospital discharge (29% versus 21%; $P=0.002$). A systematic review was conducted to find literature on cases with neurofibromatosis type 1–associated Moyamoya syndrome.[232] At total of 152 literature cases of children ≤18 years of age (median age of moyamoya syndrome diagnosis, 6 years [IQR, 3–10.8 years]) were identified. Stroke or TIA was present at diagnosis in 46%. TIA and stroke were more common in children <4 years of age compared with those ≥4 years of age (61% versus 40%; $P=0.02$) and in patients with bilateral versus unilateral moyamoya syndrome (62% versus 34%; $P=0.001$). The authors suggest that there is an aggressive form of moyamoya syndrome in children with neurofibromatosis type 1 before 4 years of age and that early screening should be considered to facilitate early detection and treatment of cerebral arteriopathy.

- In a study of 66 infants with perinatal hemorrhagic stroke, 66.7% were in preterm infants compared with 33.3% in term infants. Respiratory insufficiency, perinatal asphyxia, respiratory distress syndrome, neonatal sepsis, use of invasive mechanical ventilation, use of noninvasive mechanical ventilation, and prolonged hospitalization were more common in preterm infants than term infants ($P<0.05$), whereas mucosal bleeding, primiparity, and multiple lobe involvement were more common in term infants ($P<0.05$).[233]
- A population-based controlled study suggested a minimal association between perinatal stroke and thrombophilia[234]; therefore, routine testing is not recommended in very young children.

### Complications

- Among 355 children with stroke followed up prospectively as part of a multicenter study with a median follow-up of 2 years, the cumulative stroke recurrence rate was 6.8% (95% CI, 4.6%–10%) at 1 month and 12% (95% CI, 8.5%–15%) at 1 year.[235] The sole predictor of recurrence was the presence of an arteriopathy, which increased the risk of recurrence 5-fold compared with an idiopathic AIS (HR, 5.0 [95% CI, 1.8–14]).
- IPSS compared risk factors, clinical presentation and outcomes after PCAIS and anterior circulation arterial ischemic stroke in neonates and children with AIS up to 18 years of age.[168] Those investigators found that PCAIS was less frequent in neonates compared with children (8.8% versus 22%; $P<0.001$) and that recurrent ischemic events were more frequent in PCAIS than anterior circulation arterial ischemic stroke (30% versus 22%; $P=0.02$) despite similar rates of secondary preventive antithrombotic treatment (see Recurrent Stroke: Incidence, Race and Ethnicity, and Risk section).
- A retrospective study of data from the Alberta Perinatal Stroke Program Edmonton database compared patients with perinatal arterial ischemic stroke who developed infantile spasms (n=9) with a seizure-free control group (perinatal arterial ischemic stroke only; n=16). A greater proportion of patients with perinatal arterial ischemic stroke who developed infantile spasms had injury to deep cerebral structures (67%) than patients with perinatal arterial ischemic stroke only (25%). Infarct size was significantly associated with infantile spasm development as determined by modified pediatric ASPECTS ($P=0.002$).[236]
- A retrospective review of records of 83 children first diagnosed with AIS and hemorrhagic stroke at the Pediatric Department, Chiang Mai University Hospital between January 1, 2009, and December 31, 2018, was conducted.[237] Fifty-one patients with AIS (56%) and 32 with hemorrhagic stroke (35.2%) were identified with a median age at onset of 6.9 years for AIS and 5.3 years for hemorrhagic stroke. The mortality rate was higher in hemorrhagic stroke compared with AIS (16.6 [95% CI, 8.9–30.8] versus 1.1 [95% CI, 0.3–4.6] per 100 person-years). Thirty children (36.1%) developed epilepsy during the follow-up (median duration, 26 months). Recurrent stroke occurred in 1 child with AIS and 1 child with hemorrhagic stroke. Neurological deficits were seen in 70% of childhood AIS during the follow-up.

### Cost

- In a study of 111 pediatric stroke cases admitted to a single US children's hospital, the median 1-year direct cost of a childhood stroke (inpatient and outpatient) was ≈$50 000, with a maximum approaching $1 000 000. More severe neurological impairment after a childhood stroke correlated with higher direct costs of a stroke at 1 year and poorer quality of life in all domains.[238]
- A prospective study at 4 centers in the United States and Canada found that the median 1-year

out-of-pocket cost incurred by the family of a child with a stroke was $4354 (maximum, $38 666), which exceeded the median American household cash savings of $3650 at the time of the study and represented 6.8% of the family's annual income.[239]

## Stroke in Young Adults and in Midlife

- Approximately 10% of strokes occur in individuals 18 to 50 years of age.[240]
- A population-based incidence study conducted in Oxfordshire, England, from April 2002 to March 2018 found that from 2002 through 2010 to 2010 through 2018, stroke incidence increased significantly among subjects <55 years of age (IRR, 1.67 [95% CI, 1.31–2.14]) but fell significantly among those 55 years of age or older (IRR, 0.85 [95% CI, 0.78–0.92]; $P<0.001$ for difference).[4] This significant increase in those <55 years of age was independent of sex, stroke severity, pathological subtype, and changes in investigation.
- A systematic review of studies reporting stroke incidence in high-income countries at younger ages (usually <45, <55, or <60 years of age) during at least 2 time periods found among 50 studies in 20 countries that temporal trends in stroke incidence are diverging by age in high-income countries, with less favorable trends at younger versus older ages (pooled relative temporal rate ratio, 1.57 [95% CI, 1.42–1.74]; see the Secular Trends section).[5]
- In the NIS, hospitalizations for AIS increased significantly for both males and females and for certain racial and ethnic groups among younger adults 18 to 54 years of age.[241] From 1995 to 2011 through 2012, hospitalization rates almost doubled for males 18 to 34 years of age (from 11.2 to 18.0 per 10 000 hospitalizations) and 35 to 44 years of age (from 37.7 to 68.2 per 10 000 hospitalizations). Hospitalization rates for ICH and SAH remained stable, however, except for declines among males and NH Black people 45 to 54 years of age with SAH.
- A systematic review was conducted between January 2008 to July 2021 for sex differences in ischemic strokes among young adults (18–45 years of age).[153] Females <35 years of age were 1.44 times as likely to experience incident ischemic stroke than males <35 years of age (95% CI, 1.18–1.76). Female and males 35 to 45 years of age were about equally likely to experience incident ischemic stroke (IRR for females versus males, 1.08 [95% CI, 0.85–1.38]).
- Data from the Danish Stroke Registry and the Danish National Patient Registry showed that the incidence rate per 100 000 person-years of ischemic stroke was steady from 2015 to 2018 in younger adults (20.8 in 2005 versus 21.9 in 2018; average annual percentage change, −0.6 [95% CI, −1.5 to 0.3]).[7]
- Stroke incidence may differ by sex among younger adults. In the GCNKSS, incidence in males 20 to 44 years of age increased from 15 to 31 per 100 000 ($P<0.05$) in the interval from 1993 and 1994 to 2015; the incidence in females remained stable, from 20 to 26 per 100 000 ($P>0.05$).[151] In the REGARDS cohort, middle-aged females 45 to 64 years of age had lower risk of stroke than males (White females/males: IRR, 0.68 [95% CI, 0.49–0.94]; Black females/males: IRR, 0.72 [95% CI, 0.52–0.99]).[242]

### *Risk Factors*

- A pooled analysis of consecutive patients with ischemic stroke 18 to 50 years of age looked at differences in prevalence of risk factors and causes of ischemic stroke between different ethnic and racial groups, geographic regions, and countries with different income levels.[243] A total of 17 663 patients from 32 cohorts in 29 countries were included. Hypertension and diabetes were most prevalent in Black (hypertension, 52.1%; diabetes, 20.7%) and Asian (hypertension 46.1%, diabetes, 20.9%) individuals. Large-vessel atherosclerosis and small-vessel disease were more frequently the cause of stroke in high-income countries (both $P<0.001$), whereas "other determined strokes/undetermined strokes" were higher in low- and middle-income countries (both $P<0.001$). Patients in low- and middle-income countries were younger, had less vascular risk factors, and more often died within 3 months compared with those from high-income countries (OR, 2.49 [95% CI, 1.42–4.36]).
- The distribution of risk factors according to IPSS classification in patients with cryptogenic and noncryptogenic stroke according to the TOAST and ASCOD classification was assessed among 1322 patients 18 to 49 years of age with first-ever, imaging-confirmed ischemic stroke between 2013 and 2021 (median age 44.2 years and 52.7% males).[244] Of these, 333 (25.2%) had a cryptogenic stroke according to the TOAST classification. Additional classification using the ASCOD criteria reduced the number patients with cryptogenic stroke to 260 (19.7%). When risk factors according to the IPSS were considered, the number of patients with no potential cause or risk factor for stroke reduced to 10 (0.8%).
- A prospective multicenter study of young adults 18 to 55 years of age in Argentina found that among 269 patients with ischemic stroke, 25.7% had no vascular risk factors, 26.3% had 1 vascular risk factor, and 48% had ≥2 vascular risk factors. Males had significantly higher sedentarism, arterial

hypertension, obesity, alcohol consumption, and diabetes compared with females.[245]

### Long-Term Outcomes

- In a county-level study, stroke mortality rates among US adults 35 to 64 years of age increased from 14.7 per 100 000 in 2010 to 15.4 per 100 000 in 2016.[246] Rates decreased among older adults ≥65 years of age from 299.3 per 100 000 in 2010 to 271.4 per 100 000 in 2016.
- In the Young ESUS Longitudinal Cohort Study conducted in 41 stroke research centers in 13 countries, a total of 535 consecutive patients ≤50 years of age (mean±SD age, 40.4±7.3 years; 297 [56%] male) with a diagnosis of embolic stroke of undetermined source were enrolled.[247] The recurrent ischemic stroke and death rate was 2.19 per 100 patient-years, and the ischemic stroke recurrence rate was 1.9 per 100 patient-years. Of the recurrent strokes, 9 (64%) were embolic stroke of undetermined source, 2 (14%) were cardioembolic, and 3 (21%) were of other determined cause. Multivariate analysis found that history of stroke or TIA (HR, 5.3 [95% CI, 1.8–15]), presence of diabetes (HR, 4.4 [95% CI, 1.5–13]), and history of CAD (HR, 10 [95% CI, 4.8–22]) were associated with recurrent ischemic stroke.

## Organization of Stroke Care

- The RACECAT trial assessed 1401 patients with suspected acute large-vessel occlusion stroke in Catalonia, Spain, between March 2017 and June 2020.[248] Those investigators compared transportation to a thrombectomy-capable center (n=688) with transportation to the closest local stroke center (n=713) and assessed disability at 90 days based on the modified Rankin Scale. Compared with patients first transported to local stroke centers, patients directly transported to thrombectomy-capable centers had significantly lower odds of receiving tPA (229/482 [47.5%] versus 282/467 [60.4%]; OR, 0.59 [95% CI, 0.45–0.76]) and significantly higher odds of receiving thrombectomy (235/482 [48.8%] versus 184/467 [39.4%]; OR, 1.46 [95% CI, 1.13–1.89]). Mortality at 90 days in the safety population was not significantly different between groups (188/688 [27.3%] versus 194/713 [27.2%]; aHR, 0.97 [95% CI, 0.79–1.18]). There was no significant difference in 90-day neurological outcomes between transportation to a local stroke center versus a thrombectomy-capable referral center in patients with suspected large-vessel occlusion stroke.
- Within a large telestroke network, of 234 patients who met the inclusion criteria, 51% were transferred for mechanical thrombectomy by ambulance and 49% by helicopter; 27% underwent thrombectomy. The median actual transfer time was 132 minutes (IQR, 103–165 minutes). Longer transfer time was associated with lower rates of thrombectomy, and transfer at night rather than during the day was associated with significantly longer delay. Metrics and protocols for more efficient transfer, especially at night, could shorten transfer times.[249]
- In a multinational survey of neurointerventionalists, general anesthesia was the most frequently used anesthesia protocol for endovascular therapy (42%), and 52% used a preprepared endovascular therapy kit.[250] A retrospective study assessed the role of noninvasive vascular imaging at referral centers in outcomes, including endovascular therapy, using data from a population-based registry in Catalonia (CICAT registry) from 2016 to 2020. Patients with vascular imaging and without vascular imaging were compared. A total of 5128 patients with ischemic stroke were admitted at referral centers: 59.8% had vascular imaging; 35.5% were transferred to a CSC; and 11.7% received endovascular therapy. Among patients with severe stroke (NIHSS score >16) at referral centers, multivariate analysis adjusted for sex found that lower age (OR, 0.981 [95% CI, 0.971–0.992]; $P<0.001$), thrombolytic treatment (OR, 1.824 [95% CI, 1.353–2.458]; $P<0.001$), and vascular imaging (OR, 1.48 [95% CI, 1.12–1.96]; $P=0.006$) were independent factors associated with endovascular therapy.[251]
- A retrospective study using data from the Chinese Stroke Center Alliance (August 2015–August 2019) looked at regional discrepancy of adherence to guideline-recommended stroke interventions for the Stroke Belt division (North versus South) and the economic development division (East versus Middle versus West).[252] It was determined that the overall quality of care in the non–Stroke Belt regions was higher than that in the Stroke Belt regions. Stroke care performance measures differed across regions, along the Stroke Belt division, and along the economic development division.
- Among hospitals participating in GWTG-Stroke from 2013 to 2015, rates of defect-free care were high for both CSCs (94.6%) and primary stroke centers (94.0%). For ED admissions, CSCs had higher rates of intravenous tPA (14.3% versus 10.3%) and endovascular thrombectomy (4.1% versus 1.0%). Door-to-tPA time was shorter for CSCs (median, 52 minutes versus 61 minutes; adjusted risk ratio, 0.92 [95% CI, 0.89–0.95]), and a greater proportion of patients at CSCs had times to tPA that were ≤60 minutes (79.7% versus 65.1%; aOR, 1.48 [95% CI, 1.25–1.75]). CSCs had in-hospital mortality rates that were higher for both ED admissions (4.6% versus 3.8%; aOR, 1.14 [95% CI, 1.01–1.29]) and

transfers (7.7% versus 6.8%; aOR, 1.17 [95% CI, 1.05–1.32]).[253]

- Adequate transition of care behaviors were assessed in 550 participants with ischemic stroke (2018–2021) in the Transition of Care Stroke Disparities Study who were discharged home or to rehabilitation and had a modified Rankin Scale score of 0 to 3.[254] Using a summary metric of adequate transition of care behavior, investigators determined that 1 in 3 patients did not attain 30-day adequate transition of care behaviors. Participants with successful adequate transition of care were more likely to live with a spouse (60% versus 47%; $P$=0.01), feel close to ≥3 individuals (84% versus 71%; $P$<0.01), be employed full-time (42% versus 31%; $P$=0.02), have history of dyslipidemia (45% versus 34%; $P$=0.02), and have thrombectomy (15% versus 8%; $P$=0.02) but less likely to have a history of smoking (17% versus 32%; $P$<0.001), CAD (14% versus 21%; $P$=0.04), and HF (3% versus 11%; $P$<0.01).

## Hospital Discharges and Ambulatory Care Visits (See Table 15-1)

- In 2020, there were 855 280 inpatient discharges from short-stay hospitals with stroke as the principal diagnosis (HCUP, unpublished NHLBI tabulation; Table 15-1).
- In 2020, there were 835 233 ED visits with stroke as the principal diagnosis (HCUP;[255] unpublished NHLBI tabulation). In 2019, physician office visits for a first-listed diagnosis of stroke totaled 2 782 000 (NAMCS,[256] unpublished NHLBI tabulation).
- Age-specific AIS hospitalization rates from 2000 to 2010 decreased for individuals 65 to 84 years of age (−28.5%) and ≥85 years of age (−22.1%) but increased for individuals 25 to 44 years of age (43.8%) and 45 to 64 years of age (4.7%). Age-adjusted AIS hospitalization rates were lower in females, and females had a greater rate of decrease from 2000 to 2010 than males (−22.1% versus −17.8%, respectively).[257]
- An analysis of the NIS 2011 to 2012 for AIS found that after risk adjustment, all underrepresented racial and ethnic groups except Native American people had a significantly higher likelihood of length of stay ≥4 days than White people.[258]

## Operations and Procedures

- In the HCUP 2013 to 2016 Nationwide Readmissions Database (n=925 363 AIS admissions before the endovascular era [January 2013–January 2015] and n=857 347 during the endovascular era [February 2015–December 2016]), the proportion of patients receiving intravenous thrombolysis increased from 7.8% to 8.4% and the proportion receiving endovascular therapy doubled from 1.3% to 2.6%.[259] Length of stay declined from 6.8 to 5.7 days in the endovascular era, but total charges increased ($56 691 versus $53 878).
- In an analysis of NIS 2014 to 2016, among 376 956 patients with AIS, 6230 (1.54%) underwent endovascular thrombectomy, of whom 1547 (24.83%) were ≥80 years of age.[260] The rate of endovascular thrombectomy in patients ≥80 years of age doubled from 0.83% in 2014 to 1.83% by 2016, 1 year after the publication of studies demonstrating the efficacy of endovascular thrombectomy for patients with large-vessel occlusion. The rate of discharge to home or an acute rehabilitation center was significantly lower in patients ≥80 years of age (9%) than in younger patients (26%; $P$<0.001).
- In an individual patient–level meta-analysis of 7 cohort studies, a 10-point increase in mean SBP levels during the first 24 hours after endovascular thrombectomy was associated with a lower functional improvement (aOR, 0.88 [95% CI, 0.84–0.93]), modified Rankin Scale score ≤2 (aOR, 0.87 [95% CI, 0.82–0.93]), and higher all-cause mortality (aOR, 1.15 [95% CI, 1.06–1.23]) at 3 months.[261] However, a recent RCT of 821 patients in China who underwent successful endovascular thrombectomy comparing intensive BP control (target <120 mm Hg) with less intensive BP control (target, 140–180 mm Hg) was stopped prematurely because of safety concerns. Patients in the more intensive BP control arm had a higher incidence of poor functional outcome and early neurological deterioration.[262] Based on large-scale cohort studies and meta-analyses, a Markov model suggested that for individuals ≥80 years of age who are functionally independent at baseline, intravenous thrombolysis with tPA improved QALYs by only 0.83 QALY; for patients with baseline disability, intravenous thrombolysis yielded only an additional 0.27 QALY over endovascular thrombectomy.[263]

### *CEA Compared With CAS for Stroke Prevention*

- In 2020, an estimated 104 000 inpatient CEA and CAS procedures were performed in the United States. CEA is the most frequently performed surgical procedure to prevent stroke (HCUP;[255] unpublished NHLBI tabulation).
- In a meta-analysis of 7118 patients with asymptomatic carotid artery stenosis from 7 RCTs comparing CEA and CAS, there was no significant difference in the perioperative composite outcome that included stroke, death, or MI.[264] However, CAS was associated with an increased risk of perioperative nondisabling stroke (OR, 1.62 [95% CI, 1.16–2.24]) but

not perioperative disabling stroke or death. There was no significant difference in the long-term composite outcome of stroke, death, or MI.

- In a study from the NCDR Carotid Artery Revascularization and Endarterectomy and Peripheral Vascular Intervention registries (N=58 423 patients undergoing CEA or CAS), presence of contralateral carotid occlusion was associated with an increased risk of the composite outcome of death, stroke, and MI after CEA (aOR, 1.69 [95% CI, 1.27–2.30]) and no increase after CAS (aOR, 0.94 [95% CI, 0.72–1.22]).[265]
- Transcarotid artery revascularization with cerebral flow reversal is an emerging treatment option for carotid artery stenosis in patients at high risk for traditional endarterectomy. In a propensity-matched analysis of 342 CEAs and 109 transcarotid artery revascularizations performed between January 2011 and July 2018, transcarotid artery revascularization was associated with an increased incidence of intraoperative hypertension (adjusted coefficient, 1.41 [95% CI, 0.53–2.29]) and decreased reverse flow/clamp time and estimated blood loss. In the perioperative period, there were no differences between transcarotid artery revascularization and CEA with respect to MI, stroke, and all-cause mortality.[266]

## Cost

## (See Table 15-1)

- In 2019 to 2020 (average annual; MEPS,[267] unpublished NHLBI tabulation):
  - The direct and indirect cost of stroke in the United States was $56.2 billion (Table 15-1).
  - The estimated direct medical cost of stroke was $34.5 billion. This includes hospital outpatient or office-based health care professional visits, hospital inpatient stays, ED visits, prescribed medicines, and home health care.
- The mean expense per patient for direct care for any type of service (including hospital inpatient stays, outpatient and office-based visits, ED visits, prescribed medicines, and home health care) in the United States was estimated at $8923 (unpublished NHLBI tabulation using MEPS).[267]
- Among Medicare beneficiaries >65 years of age in the US nationwide GWTG-Stroke Registry linked to Medicare claims data (2011–2014), in those with minor stroke (NIHSS score ≤5) or high-risk TIA (n=62 518 patients from 1471 hospitals), the mean Medicare payment for the index hospitalization was $7951, and the cumulative all-cause inpatient Medicare spending per patient (with or without any subsequent admission) was $1451 at 30 days and $8105 at 1 year.[268]
- In an analysis of trends in physician reimbursement from 2000 to 2019, after adjustment for inflation, the average reimbursement for stroke (*ICD-10* I60–I63) procedures decreased by an average of 0.43%/y (11.2% from 2000–2019).[269] The adjusted reimbursement rate for telestroke codes decreased by 12.1% from 2010 to 2019, and from 2005 to 2019, the reimbursement for alteplase rose by 163.98% (average of +7.3%/y).
- Between 2015 and 2035, total direct medical stroke-related costs are projected to more than double, from $36.7 billion to $94.3 billion, with much of the projected increase in costs arising from those ≥80 years of age.[270]
- The total cost of stroke in 2035 (in 2015 dollars) is projected to be $81.1 billion for NH White people, $32.2 billion for NH Black people, and $16.0 billion for Hispanic people.[270]

## Global Burden of Stroke

### *Prevalence*

### *(See Charts 15-10 through 15-13)*

Based on 204 countries and territories in 2021[271]:

- Globally, there were 93.81 (95% UI, 89.40–99.87) million prevalent cases of all stroke subtypes in 2021. The age-standardized prevalence rate decreased by 1.33% (95% UI, −3.54% to 0.97%) from 2010 to 2021.
- Age-standardized stroke prevalence rates were highest in sub-Saharan Africa and East, Southeast, and Central Asia. Rates were the lowest in Australasia (Chart 15-10).
- The global prevalence of ischemic stroke was 69.93 (95% UI, 65.59–74.91) million cases in 2021. There was an increase of 1.08% (95% UI, −1.69% to 4.11%) in the age-standardized prevalence rate from 2010 to 2021.
- Age-standardized prevalence of ischemic stroke was highest in southern sub-Saharan Africa, followed by western sub-Saharan Africa and East and Central Asia (Chart 15-11).
- The global prevalence of ICH was 16.61 (95% UI, 15.24–18.29) million cases in 2021. There was a decrease of 9.39% (95% UI, −11.22% to −7.28%) in the age-standardized prevalence rate from 2010 to 2021.
- The prevalence of ICH was highest in western sub-Saharan Africa, Southeast Asia, Oceania, and high-income Asia Pacific (Chart 15-12).
- The global prevalence of SAH was 7.85 (95% UI, 7.19–8.42) million cases in 2021. There was a decrease of 4.08% (95% UI, −5.89% to −2.11%) in the age-standardized prevalence rate from 2010 to 2021.

- Age-standardized prevalence of SAH was highest in high-income Asia Pacific and Andean Latin America (Chart 15-13).

### *Mortality*

#### *(See Charts 15-14 through 15-17)*

Based on 204 countries and territories in 2021[271]:

- The number of deaths due to stroke in 2021 was 7.44 (95% UI, 6.76–8.01) million, and the age-standardized mortality rate decreased 17.39% (95% UI, −22.35% to −12.04%) since 2010.
- Age-standardized mortality due to stroke was highest in Oceania and Southeast and Central Asia. Rates were lowest in Australasia and Western Europe (Chart 15-14).
- Globally, the number of deaths due to ischemic stroke in 2021 was 3.71 (95% UI, 3.34–4.01) million. The age-standardized mortality rate decreased 15.83% (95% UI, −20.51% to −10.44%) from 2010.
- Age-standardized mortality due to ischemic stroke was highest in Central Asia and Eastern Europe. Mortality was lowest in Australasia (Chart 15-15).
- Globally, the number of deaths due to ICH in 2021 was 3.38 (95% UI, 3.13–3.64) million. The age-standardized mortality rate decreased 19.13% (95% UI, −24.81% to −12.64%) from 2010.
- Age-standardized ICH mortality was highest in Oceania, followed by Southeast Asia and central and eastern sub-Saharan Africa (Chart 15-16).
- Globally, the number of deaths due to SAH in 2021 was 0.36 (95% UI, 0.32–0.41) million. The age-standardized mortality rate decreased 16.92% (95% UI, −24.52% to −10.08%) from 2010.
- Age-standardized mortality estimated for SAH was highest in Oceania followed by Andean Latin America and Southeast and Central Asia in 2021 (Chart 15-17).

## COVID-19 and Stroke

- A review by the World Stroke Organization on the global impact of the COVID-19 pandemic on stroke care found the following[272]:
  - Stroke occurs in ≈1.4% of patients hospitalized with COVID-19 infection, with these patients showing an excess of large-vessel occlusion and increased mortality.
  - Stroke presentations fell during the pandemic, with newer data suggesting that total stroke mortality may have risen with increased stroke deaths at home and in care homes.
  - Strategies/guidelines were developed to adapt stroke services worldwide and to protect health care workers. Adaptations included increasing use of telemedicine for all aspects of stroke care.
  - The pandemic exacerbated already marked global inequalities in stroke incidence and mortality.
- A recent review looked at stroke and cerebrovascular disease as a complication of the SARS-CoV-2 infection and outlined the main clinical and radiological characteristics of cerebrovascular complications of vaccinations, with a focus on vaccine-induced immune thrombotic thrombocytopenia.[273] The review found that the risk of stroke and other outcomes of interest (thrombocytopenia, VTE, arterial thrombosis, cerebral venous sinus thrombosis, and MI) after a SARS-CoV-2 infection was significantly higher than after vaccination with either the Oxford-AstraZeneca or the Pfizer vaccine.
- A retrospective observational study using data from the Italian stroke network during a period of high incidence of COVID-19 assessed whether the in-hospital rerouting and the switch from a drip-and-ship to a mothership model (direct transport of all patients with suspected stroke to the hub) could ensure an adequate volume of acute treatments. The study looked at the volume of stroke cases managed in the ED and reperfusion therapies. Data from March 2020 were compared with data from March 2019. A decrease of 28% in confirmed stroke cases managed in the ED, a negative correlation between stroke cases in the ED and COVID-19 progression ($r_s$=−0.390, $P$=0.030), and a similar number of treatments in March 2020 and March 2019 were found. The adoption of the mothership model did not delay alteplase infusion (median call-to-needle time, $P$=0.126; median door-to-needle time, $P$=0.142) but did lead to a significant reduction in median call-to-groin time ($P$=0.018) and door-to-groin time ($P$=0.010).[274]
- A retrospective nationwide survey across 542 primary stroke centers in Japan assessed the impact of the COVID-19 pandemic (during 2020) on the volumes of annual stroke admissions compared with those before the pandemic (during 2019). The number of patients with stroke declined from 2019 to 2020, with a reduction of 2.51% (95% CI, −2.58% to −2.44%).[275] The reductions were 1.92% (95% CI, −2.00% to −1.85%; 127 979 to 125 522) for ischemic stroke, 3.88% (95% CI, −4.07% to −3.70%; 41 906 to 40 278) for ICH, and 4.58% (95% CI, −4.95% to −4.23%; 13 020 to 12 424) for SAH. The annual decline in the admission volume was mainly in the 5 areas with the largest number of infected people per million population (4.72% [95% CI, −4.92% to −4.53%]).
- A retrospective review of patients with a discharge diagnosis of AIS from the GWTG database from 2 CSCs in New York was performed from January 1, 2019, to July 1, 2020, comparing the pre–COVID-19 (January/February), peak COVID-19 (March/

April), and post–COVID-19 time periods. Stroke volumes were found to be significantly lower during the peak COVID-19 period in 2020 compared with 2019 (absolute decline, 49.5%; $P<0.001$). Patients were more likely to present after 24 hours from last known well during the 2020 peak COVID-19 period ($P=0.03$), but there was not a significant difference in the rate of treatment with either tPA or mechanical thrombectomy during the peak COVID-19 period. Relative treatment rates increased during the 2020 post–COVID-19 period to 11.4% ($P=0.01$).[276]

- A cohort study using the French national database of hospital admissions extracted data on all hospitalizations in France with at least 1 stroke diagnosis between January 1, 2019, and June 30, 2020.[277] Stroke hospitalizations dropped from March 10, 2020 (slope gradient, −11.70) and began to rise again from March 22 (slope gradient, 2.090) to May 7, representing a total decrease of 18.42%. The percentage change was −15.63%, −25.19%, and −18.62% for ischemic strokes, TIAs, and hemorrhagic strokes, respectively. Overall stroke hospitalizations in France experienced a decline during the first lockdown period, which could not be explained by a sudden change in stroke incidence and thus is likely to be a direct or indirect result of the COVID-19 pandemic.
- A cohort study of patients with COVID-19 admitted to Yale–New Haven Health between January 3, 2020, and August 28, 2020, with and without AIS and a subcohort of hospitalized patients with COVID-19 demonstrating a neurological symptom with and without AIS was conducted. A total of 1827 patients were included (AIS, n=44; no AIS, n=1783). Among all hospitalized patients with COVID-19, history of stroke and platelet count >200×1000/μL at hospital presentation were independent predictors of AIS (derivation AUC, 0.89; validation AUC, 0.82), regardless of COVID-19 severity. In the subcohort of patients with a neurological symptom (n=827), the risk of AIS was significantly higher among patients with a history of stroke who were <60 years of age (derivation AUC, 0.83; validation AUC, 0.81). In an ischemic stroke control cohort without COVID-19 (n=168), patients with AIS were significantly older and less likely to have had a prior stroke.[278]
- A systematic review looked at the clinical features and etiological characteristics of patients with ischemic stroke with COVID-19 infection. Data from 14 articles including 93 patients were assessed. Median age was 65 years (IQR, 55–75 years); 75% were male; stroke occurred after a median of 6 days from COVID-19 infection diagnosis; and patients had a median NIHSS score of 19. Cryptogenic strokes were more frequent (51.8%), followed by cardioembolic strokes (26.5%). A significant association was observed between the etiological classification and the interval between the COVID-19 diagnosis and the cerebrovascular event ($P_{trend}=0.039$). The clinical severity of stroke was significantly associated with the severity grade of COVID-19 infection ($P_{trend}=0.03$).[279]

**Table 15-1. Stroke in the United States**

| Population group | Prevalence, 2017–2020, ≥20 y of age | New and recurrent attacks, 1999, all ages | Mortality, 2021, all ages* | Hospital discharges, 2020, all ages | Cost, 2019–2020 |
|---|---|---|---|---|---|
| Both sexes | 9 400 000 (3.3% [95% CI, 2.8%–3.8%]) | 795 000 | 162 890 | 855 280 | $56.2 Billion |
| Males | 4 000 000 (2.9%) | 370 000 (46.5%)† | 70 852 (43.5%)† | | … |
| Females | 5 400 000 (3.6%) | 425 000 (53.5%)† | 92 038 (56.5%)† | | … |
| NH White males | 2.7% | 325 000‡ | 50 219 | … | … |
| NH White females | 3.6% | 365 000 ‡ | 67 590 | … | … |
| NH Black males | 4.8% | 45 000‡ | 10 428 | … | … |
| NH Black females | 5.4% | 60 000‡ | 12 409 | … | … |
| Hispanic males | 2.5% | … | 6433 | … | … |
| Hispanic females | 2.5% | … | 7343 | … | … |
| NH Asian males | 1.8% | … | 2848§ | … | … |
| NH Asian females | 1.5% | … | 3580§ | … | … |
| NH American Indian or Alaska Native | … | … | 799 | … | … |
| NH Native Hawaiian or Other Pacific Islander | … | … | 247 | … | … |

CIs have been added for overall prevalence estimates in key chapters. CIs have not been included in this table for all subcategories of prevalence for ease of reading.

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.[280]

COVID-19 indicates coronavirus disease 2019; ellipses (…), data not available; NH, non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

*Mortality for Hispanic, American Indian or Alaska Native, and Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting Hispanic origin or race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native, Asian and Pacific Islander, and Hispanic decedents, as well as undercounts of these groups in censuses.

†These percentages represent the portion of total stroke incidence or mortality that applies to males versus females.

‡Estimates include Hispanic and NH people. Estimates for White people include other non-Black races.

§Includes Chinese, Filipino, Japanese, and other Asian people.

Sources: Prevalence: Unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using NHANES.[281] Percentages for racial and ethnic groups are age adjusted for Americans ≥20 years of age. Age-specific percentages are extrapolated to the 2020 US population. Incidence: Greater Cincinnati/Northern Kentucky Stroke Study and National Institutes of Neurological Disorders and Stroke data for 1999 provided on July 9, 2008. US estimates compiled by NHLBI. See also Kissela et al.[282] Data include children. Mortality (for underlying cause of stroke): Unpublished NHLBI tabulation using National Vital Statistics System.[203] These data represent underlying cause of death only. Hospital discharges (with a principal diagnosis of stroke): Unpublished NHLBI tabulation using Healthcare Cost and Utilization Project.[255] Data include those inpatients discharged alive, dead, or status unknown. Cost: Unpublished NHLBI tabulation using Medical Expenditure Panel Survey.[267] Data include estimated direct and indirect costs for 2019 to 2020 (average annual).

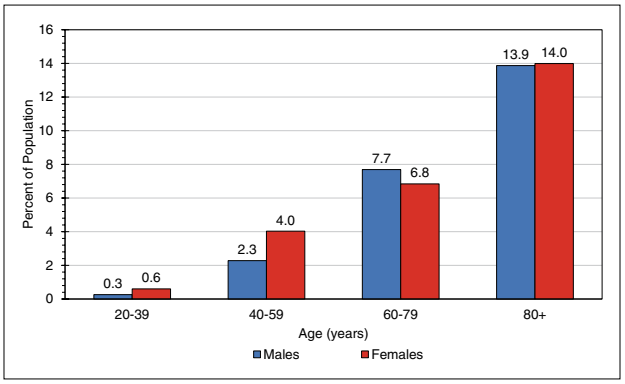



**Chart 15-1. Prevalence of stroke, by age and sex, United States (NHANES, 2017–2020).**
NHANES indicates National Health and Nutrition Examination Survey.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.[281]

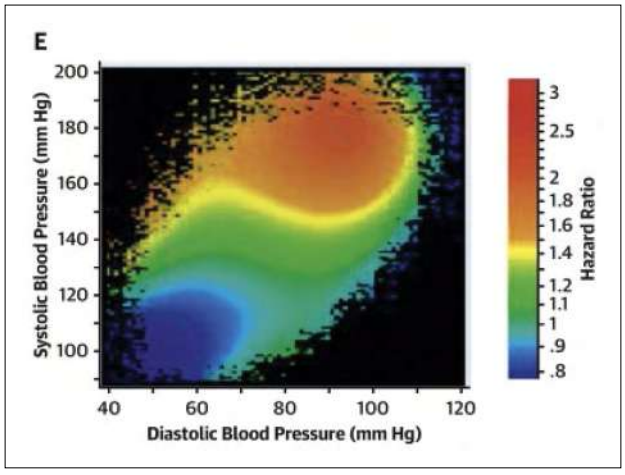



**Chart 15-2. Heat map of stroke risk at all combinations of SBP and DBP observed in ALLHAT.**
ALLHAT indicates Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; DBP, diastolic blood pressure; and SBP, systolic blood pressure.
Source: Reprinted from Itoga et al.[14] Copyright © 2021, with permission from American College of Cardiology Foundation.

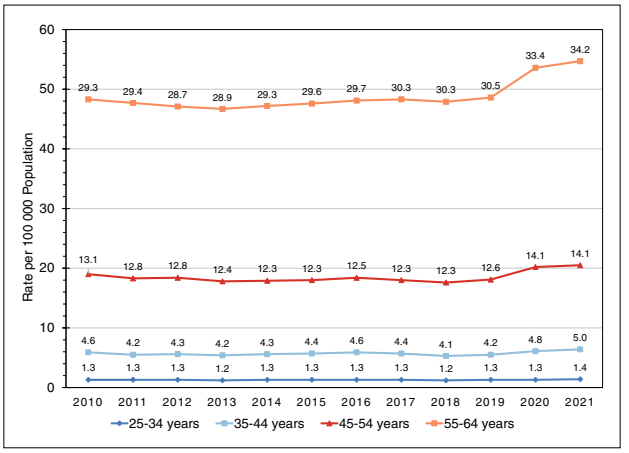



**Chart 15-3. Crude stroke mortality rates among young US adults (25–64 years of age), 2010 to 2021.**
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research.[202]

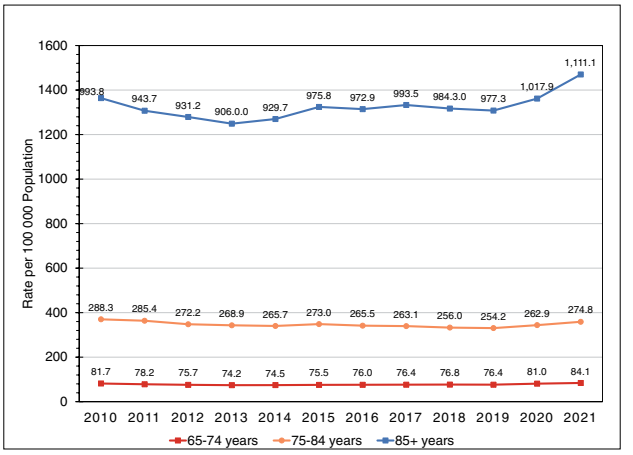



**Chart 15-4. Crude stroke mortality rates among older US adults (≥65 years of age), 2010 to 2021.**
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research.[202]

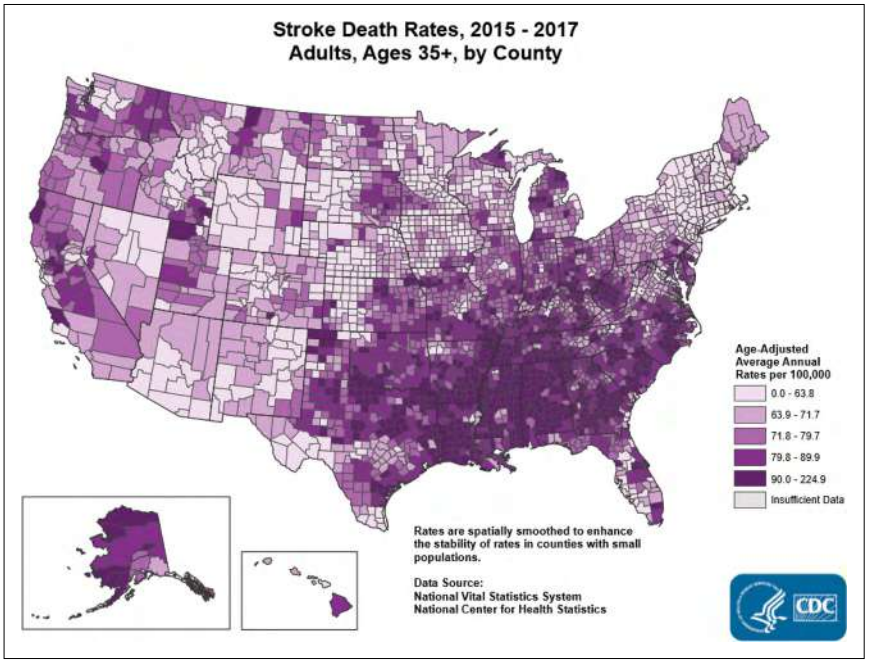



**Chart 15-5. Stroke death rates, 2015 through 2017, among adults ≥35 years of age, by US county.**
Rates are spatially smoothed to enhance the stability of rates in counties with small populations. *ICD-10* codes for stroke: I60 through I69.
CDC indicates Centers for Disease Control and Prevention; and *ICD-10*, *International Classification of Diseases*, *10th Revision.*
Source: Reprinted from National Vital Statistics System.[283]

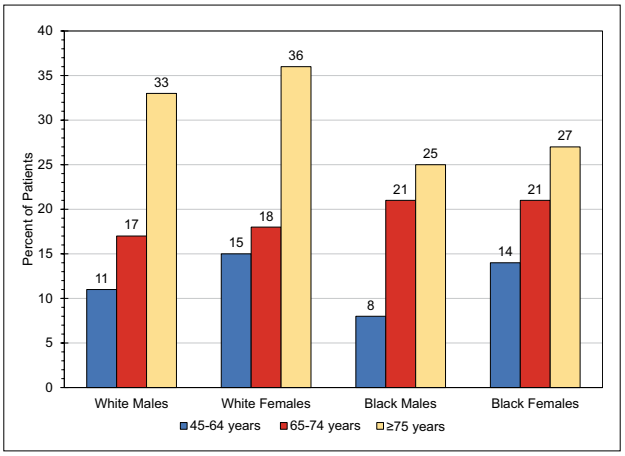



**Chart 15-6. Probability of death within 1 year after first stroke, United States, 1995 to 2011.***

*Data years 1986 to 2011 for those who were 45 to 64 years of age because of the small number of events.

Source: Unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using pooled data from the Framingham Heart Study, Atherosclerosis Risk in Communities Study, Cardiovascular Health Study, Multi-Ethnic Study of Atherosclerosis, Coronary Artery Risk Development in Young Adults, and Jackson Heart Study of the NHLBI.

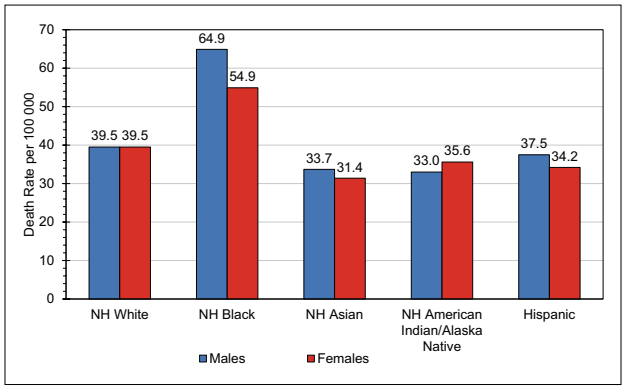



**Chart 15-8. Age-adjusted death rates for stroke, by sex and race and ethnicity, United States, 2021.**

Death rates for the American Indian or Alaska Native and Asian or Pacific Islander populations are known to be underestimated. Stroke includes *ICD-10* codes I60 through I69 (cerebrovascular disease). *ICD-10* indicates *International Classification of Diseases, 10th Revision*; and NH, non-Hispanic.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research.[202]

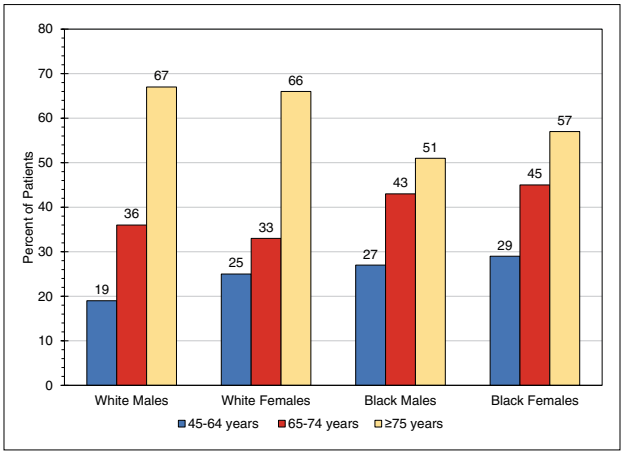



**Chart 15-7. Probability of death within 5 years after first stroke, United States, 1995 to 2011.***

*Data years 1986 to 2011 for those who were 45 to 64 years of age because of the small number of events.

Source: Unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using pooled data from the Framingham Heart Study, Atherosclerosis Risk in Communities Study, Cardiovascular Health Study, Multi-Ethnic Study of Atherosclerosis, Coronary Artery Risk Development in Young Adults, and Jackson Heart Study of the NHLBI.

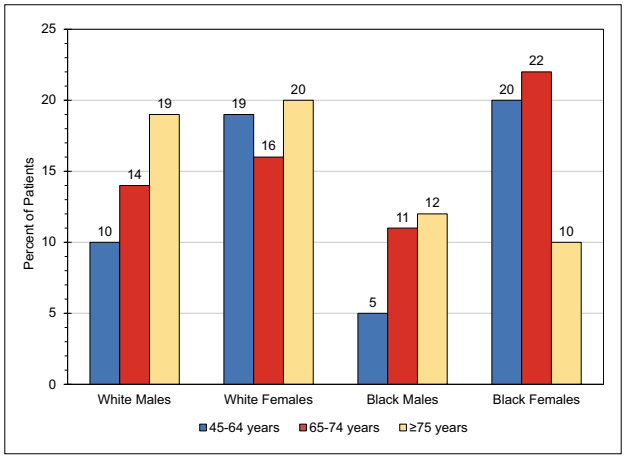



**Chart 15-9. Probability of recurrent stroke in 5 years after first stroke, United States, 1995 to 2011.***

*Data years 1986 to 2011 for those who were 45 to 64 years of age because of the small number of events.

Source: Unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using pooled data from the Framingham Heart Study, Atherosclerosis Risk in Communities Study, Cardiovascular Health Study, Multi-Ethnic Study of Atherosclerosis, Coronary Artery Risk Development in Young Adults, and Jackson Heart Study of the NHLBI.

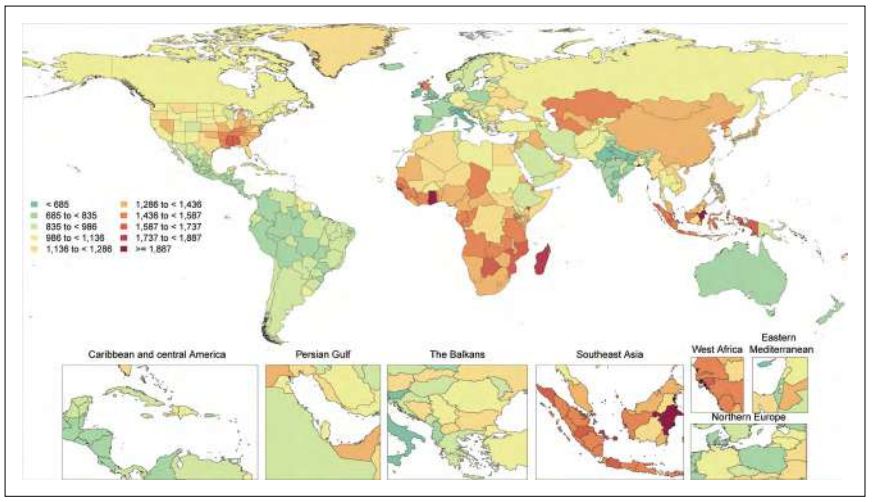



**Chart 15-10. Age-standardized global prevalence rates of total stroke (all subtypes) per 100 000, both sexes, 2021.**
During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.
GBD indicates Global Burden of Disease.
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[271]

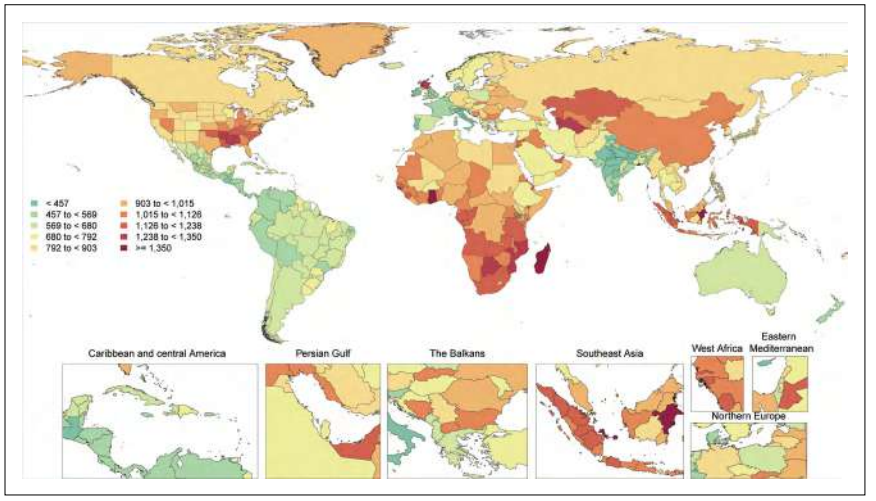



**Chart 15-11. Age-standardized global prevalence rates of ischemic stroke per 100 000, both sexes, 2021.**
During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.
GBD indicates Global Burden of Disease.
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[271]

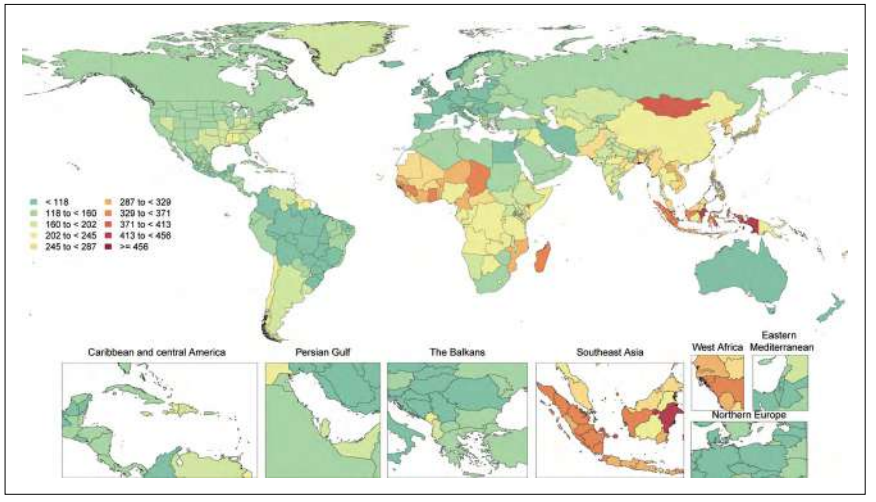



**Chart 15-12. Age-standardized global prevalence rates of ICH per 100 000, both sexes, 2021.**
During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.
GBD indicates Global Burden of Disease; and ICH, intracerebral hemorrhage.
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[271]



 *Circulation*. 2024;149:e347–e913. DOI: 10.1161/CIR.0000000000001209

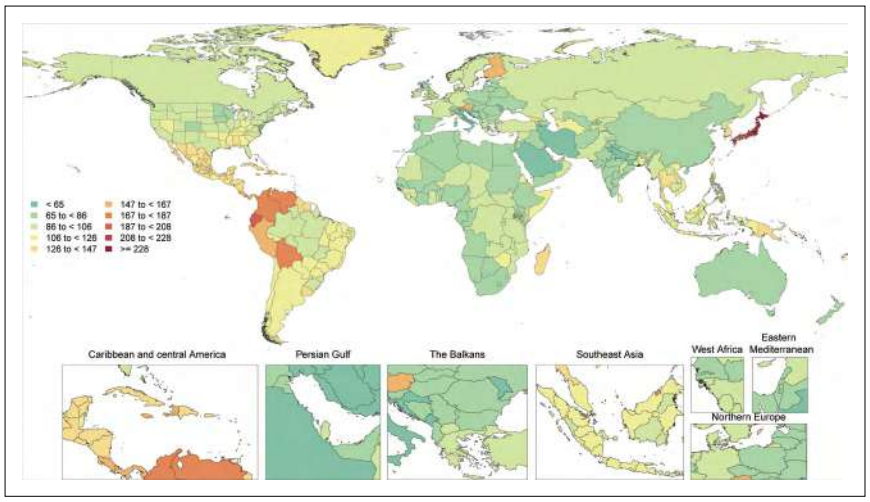



**Chart 15-13. Age-standardized global prevalence rates of SAH per 100 000, both sexes, 2021.**
During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.
GBD indicates Global Burden of Disease; and SAH, subarachnoid hemorrhage.
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[271]

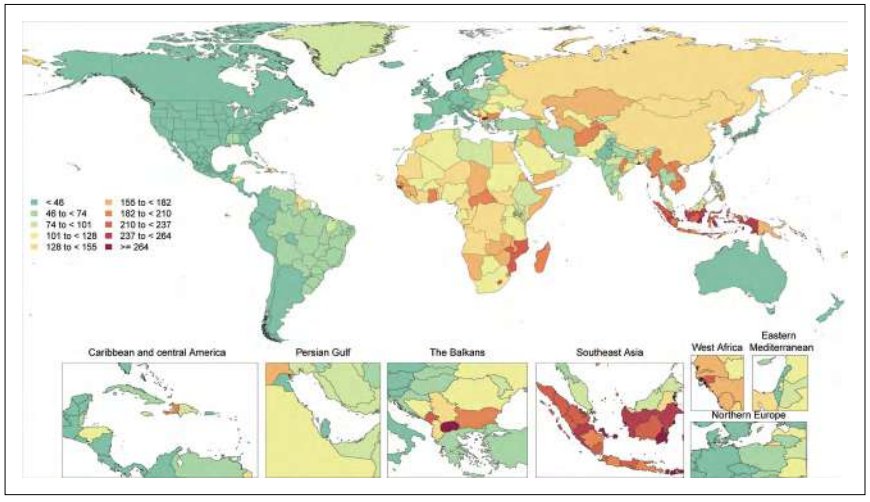



**Chart 15-14. Age-standardized global mortality rates of total stroke (all subtypes) per 100 000, both sexes, 2021.**
During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.
GBD indicates Global Burden of Disease.
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[271]

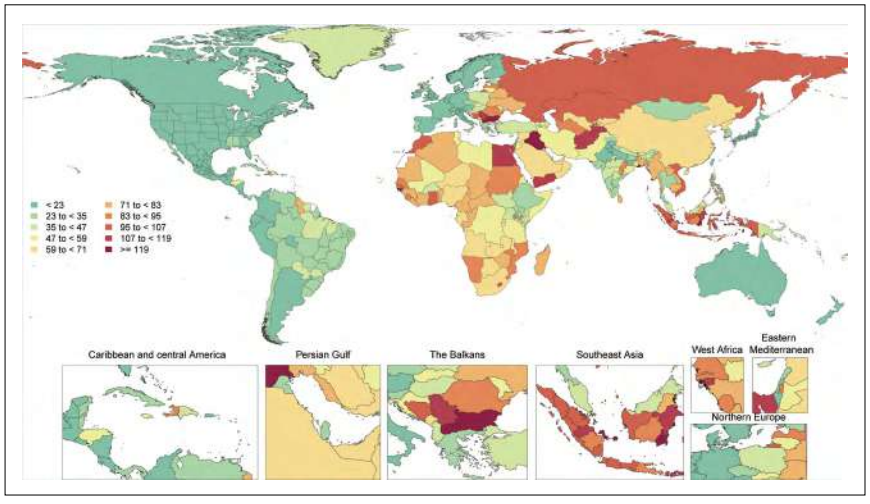



**Chart 15-15. Age-standardized global mortality rates of ischemic stroke per 100 000, both sexes, 2021.**
During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.
GBD indicates Global Burden of Disease.
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[271]

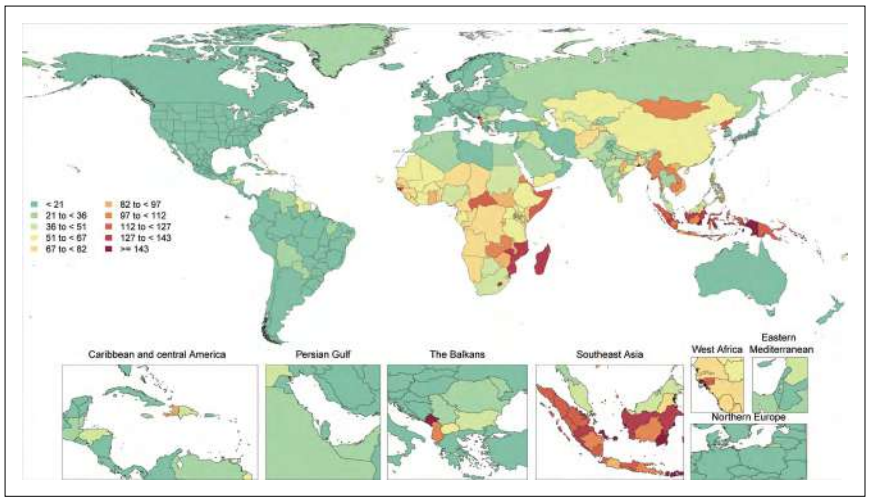



**Chart 15-16. Age-standardized global mortality rates of ICH per 100 000, both sexes, 2021.**
During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.
GBD indicates Global Burden of Disease; and ICH; intracerebral hemorrhage.
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[271]

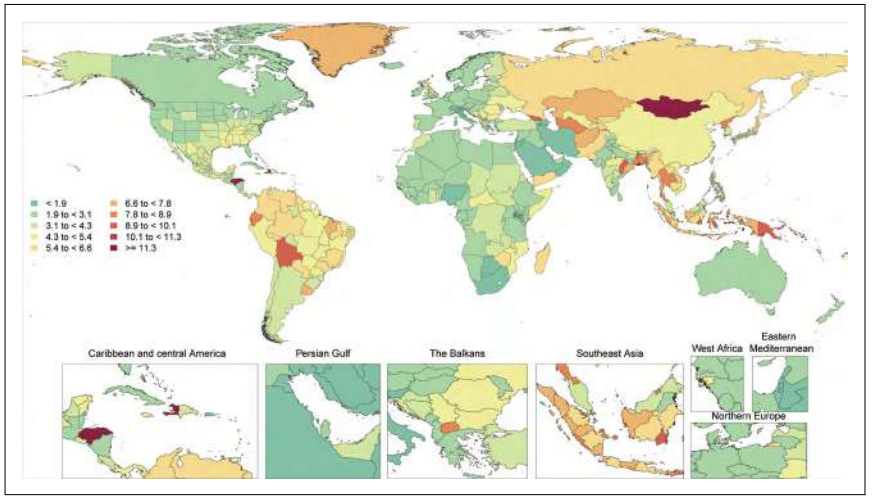



**Chart 15-17. Age-standardized global mortality rates of SAH per 100 000, both sexes, 2021.**
During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.
GBD indicates Global Burden of Disease; and SAH, subarachnoid hemorrhage.
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[271]

## REFERENCES


1. Centers for Disease Control and Prevention and National Center for Chronic Disease Prevention and Health Promotion. Behavioral Risk Factor Surveillance System (BRFSS): BRFSS Prevalence & Trends Data. Accessed March 27, 2023. https://cdc.gov/brfss/brfssprevalence/
2. Ovbiagele B, Goldstein LB, Higashida RT, Howard VJ, Johnston SC, Khavjou OA, Lackland DT, Lichtman JH, Mohl S, Sacco RL, et al; on behalf of the American Heart Association Advocacy Coordinating Committee and Stroke Council. Forecasting the future of stroke in the United States: a policy statement from the American Heart Association and American Stroke Association [published correction appears in *Stroke*. 2015;46:e179]. *Stroke*. 2013;44:2361–2375. doi: 10.1161/STR.0b013e31829734f2
3. GBD 2019 Stroke Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol*. 2021;20:795–820. doi: 10.1016/S1474-4422(21)00252-0
4. Li L, Scott CA, Rothwell PM. Association of younger vs older ages with changes in incidence of stroke and other vascular events, 2002-2018. *JAMA*. 2022;328:563–574. doi: 10.1001/jama.2022.12759
5. Scott CA, Li L, Rothwell PM. Diverging temporal trends in stroke incidence in younger vs older people: a systematic review and meta-analysis. *JAMA Neurol*. 2022;79:1036–1048. doi: 10.1001/jamaneurol.2022.1520
6. Koton S, Sang Y, Schneider ALC, Rosamond WD, Gottesman RF, Coresh J. Trends in stroke incidence rates in older US adults: an update from the Atherosclerosis Risk in Communities (ARIC) Cohort Study. *JAMA Neurol*. 2019;77:109–113. doi: 10.1001/jamaneurol.2019.3258
7. Skajaa N, Adelborg K, Horvath-Puho E, Rothman KJ, Henderson VW, Casper Thygesen L, Sorensen HT. Nationwide trends in incidence and mortality of stroke among younger and older adults in Denmark. *Neurology*. 2021;96:e1711–e1723. doi: 10.1212/WNL.0000000000011636
8. Aparicio HJ, Himali JJ, Satizabal CL, Pase MP, Romero JR, Kase CS, Beiser AS, Seshadri S. Temporal trends in ischemic stroke incidence in younger adults in the Framingham study. *Stroke*. 2019;50:1558–1560. doi: 10.1161/STROKEAHA.119.025171
9. Shah NS, Xi K, Kapphahn KI, Srinivasan M, Au T, Sathye V, Vishal V, Zhang H, Palaniappan LP. Cardiovascular and cerebrovascular disease mortality in Asian American subgroups. *Circ Cardiovasc Qual Outcomes*. 2022;15:e008651. doi: 10.1161/CIRCOUTCOMES.121.008651
10. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. 2020;396:1204–1222. doi: 10.1016/S0140-6736(20)30925-9
11. GBD 2019 Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. 2020;396:1223–1249. doi: 10.1016/S0140-6736(20)30752-2
12. Lehtisalo J, Rusanen M, Solomon A, Antikainen R, Laatikainen T, Peltonen M, Strandberg T, Tuomilehto J, Soininen H, Kivipelto M, et al. Effect of a multi-domain lifestyle intervention on cardiovascular risk in older people: the FINGER trial. *Eur Heart J*. 2022;43:2054–2061. doi: 10.1093/eurheartj/ehab922
13. Guo J, Lv J, Guo Y, Bian Z, Zheng B, Wu M, Yang L, Chen Y, Su J, Zhang J, et al; China Kadoorie Biobank Collaborative Group. Association between

blood pressure categories and cardiovascular disease mortality in China. *PLoS One*. 2021;16:e0255373. doi: 10.1371/journal.pone.0255373
14. Itoga NK, Tawfik DS, Montez-Rath ME, Chang TI. Contributions of systolic and diastolic blood pressures to cardiovascular outcomes in the ALLHAT study. *J Am Coll Cardiol*. 2021;78:1671–1678. doi: 10.1016/j.jacc.2021.08.035
15. Zhong XL, Dong Y, Xu W, Huang YY, Wang HF, Zhang TS, Sun L, Tan L, Dong Q, Yu JT. Role of blood pressure management in stroke prevention: a systematic review and network meta-analysis of 93 randomized controlled trials. *J Stroke*. 2021;23:1–11. doi: 10.5853/jos.2020.02698
16. Reboldi G, Angeli F, Gentile G, Verdecchia P. Benefits of more intensive versus less intensive blood pressure control: updated trial sequential analysis. *Eur J Intern Med*. 2022;101:49–55. doi: 10.1016/j.ejim.2022.03.032
17. Gavish B, Bursztyn M, Thijs L, Wei DM, Melgarejo JD, Zhang ZY, Boggia J, Hansen TW, Asayama K, Ohkubo T, et al; International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcome Investigators. Predictive power of 24-h ambulatory pulse pressure and its components for mortality and cardiovascular outcomes in 11848 participants recruited from 13 populations. *J Hypertens*. 2022;40:2245–2255. doi: 10.1097/HJH.0000000000003258
18. Clarke R, Wright N, Walters R, Gan W, Guo Y, Millwood IY, Yang L, Chen Y, Lewington S, Lv J, et al; China Kadoorie Biobank Collaborative Group. Genetically predicted differences in systolic blood pressure and risk of cardiovascular and noncardiovascular diseases: a mendelian randomization study in Chinese adults. *Hypertension*. 2023;80:566–576. doi: 10.1161/HYPERTENSIONAHA.122.20120
19. Georgakis MK, Gill D, Malik R, Protogerou AD, Webb AJS, Dichgans M. Genetically predicted blood pressure across the lifespan: differential effects of mean and pulse pressure on stroke risk. *Hypertension (dallas, tex: 1979)*. 2020;76:953–961. doi: 10.1161/HYPERTENSIONAHA.120.15136
20. Zheng L, Xie Y, Zheng J, Guo R, Wang Y, Dai Y, Sun Z, Xing L, Zhang X, Sun Y. Associations between ideal blood pressure based on different BMI categories and stroke incidence. *J Hypertens*. 2020;38:1271–1277. doi: 10.1097/HJH.0000000000002404
21. Malhotra K, Ahmed N, Filippatou A, Katsanos AH, Goyal N, Tsioufis K, Manios E, Pikilidou M, Schellinger PD, Alexandrov AW, et al. Association of elevated blood pressure levels with outcomes in acute ischemic stroke patients treated with intravenous thrombolysis: a systematic review and meta-analysis. *J Stroke*. 2019;21:78–90. doi: 10.5853/jos.2018.02369
22. Zheng S, Yao B. Impact of risk factors for recurrence after the first ischemic stroke in adults: a systematic review and meta-analysis. *J Clin Neurosci*. 2019;60:24–30. doi: 10.1016/j.jocn.2018.10.026
23. de Havenon A, Fino NF, Johnson B, Wong KH, Majersik JJ, Tirschwell D, Rost N. Blood pressure variability and cardiovascular outcomes in patients with prior stroke: a secondary analysis of PRoFESS. *Stroke*. 2019;50:3170–3176. doi: 10.1161/STROKEAHA.119.026293
24. Huang Y, Cai X, Mai W, Li M, Hu Y. Association between prediabetes and risk of cardiovascular disease and all cause mortality: systematic review and meta-analysis. *BMJ*. 2016;355:i5953. doi: 10.1136/bmj.i5953
25. Zhang L, Li X, Wolfe CDA, O'Connell MDL, Wang Y. Diabetes as an independent risk factor for stroke recurrence in ischemic stroke patients: an updated meta-analysis. *Neuroepidemiology*. 2021;55:427–435. doi: 10.1159/000519327
26. Echouffo-Tcheugui JB, Xu H, Matsouaka RA, Xian Y, Schwamm LH, Smith EE, Bhatt DL, Hernandez AF, Heidenreich PA, Fonarow GC. Diabetes and long-term outcomes of ischaemic stroke: findings from Get With The Guidelines-Stroke. *Eur Heart J*. 2018;39:2376–2386. doi: 10.1093/eurheartj/ehy036
27. Fang H, Zhou Y, YJ T, Du H, YX S, LY Z. Effects of intensive glucose lowering in treatment of type 2 diabetes mellitus on cardiovascular outcomes: a meta-analysis of data from 58,160 patients in 13 randomized controlled trials. *Int J Cardiol*. 2016;218:50–58. doi: 10.1016/j.ijcard.2016.04.163
28. Johnston KC, Bruno A, Pauls Q, Hall CE, Barrett KM, Barsan W, Fansler A, Van de Bruinhorst K, Janis S, Durkalski-Mauldin VL; Neurological Emergencies Treatment Trials Network and the SHINE Trial Investigators. Intensive vs standard treatment of hyperglycemia and functional outcome in patients with acute ischemic stroke: the SHINE randomized clinical trial. *JAMA*. 2019;322:326–335. doi: 10.1001/jama.2019.9346
29. Li J, Ji C, Zhang W, Lan L, Ge W. Effect of new glucose-lowering drugs on stroke in patients with type 2 diabetes: a systematic review and Meta-analysis. *J Diabetes Complications*. 2023;37:108362. doi: 10.1016/j.jdiacomp.2022.108362
30. Strickberger SA, Ip J, Saksena S, Curry K, Bahnson TD, Ziegler PD. Relationship between atrial tachyarrhythmias and symptoms. *Heart Rhythm*. 2005;2:125–131. doi: 10.1016/j.hrthm.2004.10.042
31. Tayal AH, Tian M, Kelly KM, Jones SC, Wright DG, Singh D, Jarouse J, Brillman J, Murali S, Gupta R. Atrial fibrillation detected by mobile cardiac outpatient telemetry in cryptogenic TIA or stroke. *Neurology*. 2008;71:1696–1701. doi: 10.1212/01.wnl.0000325059.86313.31
32. Bernstein RA, Kamel H, Granger CB, Piccini JP, Sethi PP, Katz JM, Vives CA, Ziegler PD, Franco NC, Schwamm LH; STROKE-AF Investigators. Effect of long-term continuous cardiac monitoring vs usual care on detection of atrial fibrillation in patients with stroke attributed to large- or small-vessel disease: the STROKE-AF randomized clinical trial. *JAMA*. 2021;325:2169–2177. doi: 10.1001/jama.2021.6470
33. Sposato LA, Cipriano LE, Saposnik G, Ruiz Vargas E, Riccio PM, Hachinski V. Diagnosis of atrial fibrillation after stroke and transient ischaemic attack: a systematic review and meta-analysis. *Lancet Neurol*. 2015;14:377–387. doi: 10.1016/S1474-4422(15)70027-X
34. Okumura K, Tomita H, Nakai M, Kodani E, Akao M, Suzuki S, Hayashi K, Sawano M, Goya M, Yamashita T, et al; J-RISK AF Research Group. Risk factors associated with ischemic stroke in Japanese patients with nonvalvular atrial fibrillation. *JAMA Netw Open*. 2020;3:e202881. doi: 10.1001/jamanetworkopen.2020.2881
35. Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. *JAMA*. 2015;313:603–615. doi: 10.1001/jama.2014.18574
36. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on Atrial Fibrillation. *Chest*. 2010;137:263–272. doi: 10.1378/chest.09-1584
37. Olesen JB, Lip GY, Hansen ML, Hansen PR, Tolstrup JS, Lindhardsen J, Selmer C, Ahlehoff O, Olsen AM, Gislason GH, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. *BMJ*. 2011;342:d124. doi: 10.1136/bmj.d124
38. Piccini JP, Stevens SR, Chang Y, Singer DE, Lokhnygina Y, Go AS, Patel MR, Mahaffey KW, Halperin JL, Breithardt G, et al; ROCKET AF Steering Committee and Investigators. Renal dysfunction as a predictor of stroke and systemic embolism in patients with nonvalvular atrial fibrillation: validation of the R(2)CHADS(2) index in the ROCKET AF (Rivaroxaban Once-daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) and ATRIA (AnTicoagulation and Risk factors In Atrial fibrillation) study cohorts. *Circulation*. 2013;127:224–232. doi: 10.1161/CIRCULATIONAHA.112.107128
39. Oyama K, Giugliano RP, Berg DD, Ruff CT, Jarolim P, Tang M, Murphy SA, Lanz HJ, Grosso MA, Antman EM, et al. Serial assessment of biomarkers and the risk of stroke or systemic embolism and bleeding in patients with atrial fibrillation in the ENGAGE AF-TIMI 48 trial. *Eur Heart J*. 2021;42:1698–1706. doi: 10.1093/eurheartj/ehab141
40. Singleton MJ, Yuan Y, Dawood FZ, Howard G, Judd SE, Zakai NA, Howard VJ, Herrington DM, Soliman EZ, Cushman M. Multiple blood biomarkers and stroke risk in atrial fibrillation: the REGARDS Study. *J Am Heart Assoc*. 2021;10:e020157. doi: 10.1161/JAHA.120.020157
41. Mentel A, Quinn TJ, Cameron AC, Lees KR, Abdul-Rahim AH. The impact of atrial fibrillation type on the risks of thromboembolic recurrence, mortality and major haemorrhage in patients with previous stroke: a systematic review and meta-analysis of observational studies. *Eur Stroke J*. 2020;5:155–168. doi: 10.1177/2396987319896674
42. Lin MH, Kamel H, Singer DE, Wu YL, Lee M, Ovbiagele B. Perioperative/postoperative atrial fibrillation and risk of subsequent stroke and/or mortality. *Stroke*. 2019;50:1364–1371. doi: 10.1161/STROKEAHA.118.023921
43. AlTurki A, Marafi M, Proietti R, Cardinale D, Blackwell R, Dorian P, Bessissow A, Vieira L, Greiss I, Essebag V, et al. Major adverse cardiovascular events associated with postoperative atrial fibrillation after noncardiac surgery: a systematic review and meta-analysis. *Circ Arrhythm Electrophysiol*. 2020;13:e007437. doi: 10.1161/CIRCEP.119.007437
44. Nauffal V, Trinquart L, Osho A, Sundt TM, Lubitz SA, Ellinor PT. Non-vitamin K antagonist oral anticoagulant vs warfarin for post cardiac surgery atrial fibrillation. *Ann Thorac Surg*. 2021;112:1392–1401. doi: 10.1016/j.athoracsur.2020.12.031
45. Grymonprez M, Simoens C, Steurbaut S, De Backer TL, Lahousse L. Worldwide trends in oral anticoagulant use in patients with atrial fibrillation from 2010 to 2018: a systematic review and meta-analysis. *Europace*. 2022;24:887–898. doi: 10.1093/europace/euab303
46. Lee KJ, Kim BJ, Han MK, Kim JT, Choi KH, Shin DI, Yeo MJ, Cha JK, Kim DH, Nah HW, et al; CRCS-K (Clinical Research Collaboration for Stroke in Korea) Investigators. Effect of heart rate on stroke recurrence and mortality

in acute ischemic stroke with atrial fibrillation. *Stroke*. 2020;51:162–169. doi: 10.1161/STROKEAHA.119.026847
47. Al-Kawaz M, Omran SS, Parikh NS, Elkind MSV, Soliman EZ, Kamel H. Comparative risks of ischemic stroke in atrial flutter versus atrial fibrillation. *J Stroke Cerebrovasc Dis*. 2018;27:839–844. doi: 10.1016/j.jstrokecerebrovasdis.2017.10.025
48. Meng L, Tsiaousis G, He J, Tse G, Antoniadis AP, Korantzopoulos P, Letsas KP, Baranchuk A, Qi W, Zhang Z, et al. Excessive supraventricular ectopic activity and adverse cardiovascular outcomes: a systematic review and meta-analysis. *Curr Atheroscler Rep*. 2020;22:14. doi: 10.1007/s11883-020-0832-4
49. Bodin A, Bisson A, Gaborit C, Herbert J, Clementy N, Babuty D, Lip GYH, Fauchier L. Ischemic stroke in patients with sinus node disease, atrial fibrillation, and other cardiac conditions. *Stroke*. 2020;51:1674–1681. doi: 10.1161/STROKEAHA.120.029048
50. Peters SA, Singhateh Y, Mackay D, Huxley RR, Woodward M. Total cholesterol as a risk factor for coronary heart disease and stroke in women compared with men: a systematic review and meta-analysis. *Atherosclerosis*. 2016;248:123–131. doi: 10.1016/j.atherosclerosis.2016.03.016
51. Lewington S, Whitlock G, Clarke R, Sherliker P, Emberson J, Halsey J, Qizilbash N, Peto R, Collins R; Prospective Studies Collaboration. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. *Lancet*. 2007;370:1829–1839. doi: 10.1016/S0140-6736(07)61778-4
52. Wang X, Dong Y, Qi X, Huang C, Hou L. Cholesterol levels and risk of hemorrhagic stroke: a systematic review and meta-analysis. *Stroke*. 2013;44:1833–1839. doi: 10.1161/STROKEAHA.113.001326
53. Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, Hegele RA, Krauss RM, Raal FJ, Schunkert H, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease, 1: evidence from genetic, epidemiologic, and clinical studies: a consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J*. 2017;38:2459–2472. doi: 10.1093/eurheartj/ehx144
54. Sun L, Clarke R, Bennett D, Guo Y, Walters RG, Hill M, Parish S, Millwood IY, Bian Z, Chen Y, et al; China Kadoorie Biobank Collaborative Group. Causal associations of blood lipids with risk of ischemic stroke and intracerebral hemorrhage in Chinese adults. *Nat Med*. 2019;25:569–574. doi: 10.1038/s41591-019-0366-x
55. Amarenco P, Kim JS, Labreuche J, Charles H, Abtan J, Bejot Y, Cabrejo L, Cha JK, Ducrocq G, Giroud M, et al; Treat Stroke to Target Investigators. A comparison of two LDL cholesterol targets after ischemic stroke. *N Engl J Med*. 2020;382:9. doi: 10.1056/NEJMoa1910355
56. Judge C, Ruttledge S, Costello M, Murphy R, Loughlin E, Alvarez-Iglesias A, Ferguson J, Gorey S, Nolan A, Canavan M, et al. Lipid lowering therapy, low-density lipoprotein level and risk of intracerebral hemorrhage: a meta-analysis. *J Stroke Cerebrovasc Dis*. 2019;28:1703–1709. doi: 10.1016/j.jstrokecerebrovasdis.2019.02.018
57. Masson W, Lobo M, Siniawski D, Masson G, Lavalle-Cobo A, Molinero G. LDL-C levels below 55 mg/dl and risk of hemorrhagic stroke: a meta-analysis. *J Stroke Cerebrovasc Dis*. 2021;30:105655. doi: 10.1016/j.jstrokecerebrovasdis.2021.105655
58. Hindy G, Engstrom G, Larsson SC, Traylor M, Markus HS, Melander O, Orho-Melander M; Stroke Genetics Network (SiGN). Role of blood lipids in the development of ischemic stroke and its subtypes: a mendelian randomization study. *Stroke*. 2018;49:820–827. doi: 10.1161/STROKEAHA.117.019653
59. Qie R, Liu L, Zhang D, Han M, Wang B, Zhao Y, Liu D, Guo C, Li Q, Zhou Q, et al. Dose-response association between high-density lipoprotein cholesterol and stroke: a systematic review and meta-analysis of prospective cohort studies. *Prev Chronic Dis*. 2021;18:E45. doi: 10.5888/pcd18.200278
60. Georgakis MK, Malik R, Anderson CD, Parhofer KG, Hopewell JC, Dichgans M. Genetic determinants of blood lipids and cerebral small vessel disease: role of high-density lipoprotein cholesterol. *Brain*. 2020;143:597–610. doi: 10.1093/brain/awz413
61. Lee H, Park JB, Hwang IC, Yoon YE, Park HE, Choi SY, Kim YJ, Cho GY, Han K, Kim HK. Association of four lipid components with mortality, myocardial infarction, and stroke in statin-naive young adults: a nationwide cohort study. *Eur J Prev Cardiol*. 2020;27:870–881. doi: 10.1177/2047487319898571
62. Rist PM, Buring JE, Ridker PM, Kase CS, Kurth T, Rexrode KM. Lipid levels and the risk of hemorrhagic stroke among women. *Neurology*. 2019;92:e2286–e2294. doi: 10.1212/WNL.0000000000007454
63. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, Doyle RT Jr, Juliano RA, Jiao L, Granowitz C, et al; REDUCE-IT Investigators. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med*. 2019;380:11–22. doi: 10.1056/NEJMoa1812792
64. Chauhan G, Adams HHH, Satizabal CL, Bis JC, Teumer A, Sargurupremraj M, Hofer E, Trompet S, Hilal S, Smith AV, et al; Stroke Genetics Network (SiGN), the International Stroke Genetics Consortium (ISGC), METASTROKE, Alzheimer's Disease Genetics Consortium (ADGC), and the Neurology Working Group of the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium. Genetic and lifestyle risk factors for MRI-defined brain infarcts in a population-based setting. *Neurology*. 2019;92:e486–e503. doi: 10.1212/WNL.0000000000006851
65. Hackshaw A, Morris JK, Boniface S, Tang JL, Milenkovic D. Low cigarette consumption and risk of coronary heart disease and stroke: meta-analysis of 141 cohort studies in 55 study reports. *BMJ*. 2018;360:j5855. doi: 10.1136/bmj.j5855
66. Oono IP, Mackay DF, Pell JP. Meta-analysis of the association between secondhand smoke exposure and stroke. *J Public Health (Oxf)*. 2011;33:496–502. doi: 10.1093/pubmed/fdr025
67. Lin MP, Ovbiagele B, Markovic D, Towfighi A. Association of secondhand smoke with stroke outcomes. *Stroke*. 2016;47:2828–2835. doi: 10.1161/STROKEAHA.116.014099
68. Vidyasagaran AL, Siddiqi K, Kanaan M. Use of smokeless tobacco and risk of cardiovascular disease: a systematic review and meta-analysis. *Eur J Prev Cardiol*. 2016;23:1970–1981. doi: 10.1177/2047487316654026
69. Lindbohm JV, Kaprio J, Jousilahti P, Salomaa V, Korja M. Sex, smoking, and risk for subarachnoid hemorrhage. *Stroke*. 2016;47:1975–1981. doi: 10.1161/STROKEAHA.116.012957
70. Parikh NS, Salehi Omran S, Kamel H, Elkind MSV, Willey JZ. Smoking-cessation pharmacotherapy for patients with stroke and TIA: systematic review. *J Clin Neurosci*. 2020;78:236–241. doi: 10.1016/j.jocn.2020.04.026
71. Wu AD, Lindson N, Hartmann-Boyce J, Wahedi A, Hajizadeh A, Theodoulou A, Thomas ET, Lee C, Aveyard P. Smoking cessation for secondary prevention of cardiovascular disease. *Cochrane Database Syst Rev*. 2022;8:CD014936. doi: 10.1002/14651858.CD014936.pub2
72. Parikh NS, Navi BB, Merkler AE, Kamel H. Electronic cigarette use and cigarette-smoking cessation attempts among stroke survivors in the US. *JAMA Neurol*. 2021;78:759–760. doi: 10.1001/jamaneurol.2021.0636
73. Ghozy S, Zayan AH, El-Qushayri AE, Parker KE, Varney J, Kallmes KM, Morsy S, Abbas AS, Diestro JDB, Dmytriw AA, et al. Physical activity level and stroke risk in US population: a matched case-control study of 102,578 individuals. *Ann Clin Transl Neurol*. 2022;9:264–275. doi: 10.1002/acn3.51511
74. Qi W, Ma J, Guan T, Zhao D, Abu-Hanna A, Schut M, Chao B, Wang L, Liu Y. Risk factors for incident stroke and its subtypes in China: a prospective study. *J Am Heart Assoc*. 2020;9:e016352. doi: 10.1161/JAHA.120.016352
75. Hooker SP, Diaz KM, Blair SN, Colabianchi N, Hutto B, McDonnell MN, Vena JE, Howard VJ. Association of accelerometer-measured sedentary time and physical activity with risk of stroke among US adults. *JAMA Netw Open*. 2022;5:e2215385. doi: 10.1001/jamanetworkopen.2022.15385
76. Hung SH, Ebaid D, Kramer S, Werden E, Baxter H, Campbell BC, Brodtmann A. Pre-stroke physical activity and admission stroke severity: a systematic review. *Int J Stroke*. 2021;16:1009–1018. doi: 10.1177/1747493021995271
77. Susts J, Reinholdsson M, Sunnerhagen KS, Abzhandadze T. Physical inactivity before stroke is associated with dependency in basic activities of daily living 3 months after stroke. *Front Neurol*. 2023;14:1094232. doi: 10.3389/fneur.2023.1094232
78. Sui X, Howard VJ, McDonnell MN, Ernstsen L, Flaherty ML, Hooker SP, Lavie CJ. Racial differences in the association between nonexercise estimated cardiorespiratory fitness and incident stroke. *Mayo Clin Proc*. 2018;93:884–894. doi: 10.1016/j.mayocp.2018.05.002
79. Prestgaard E, Mariampillai J, Engeseth K, Erikssen J, Bodegard J, Liestol K, Gjesdal K, Kjeldsen S, Grundvold I, Berge E. Change in cardiorespiratory fitness and risk of stroke and death: long-term follow-up of healthy middle-aged men. *Stroke*. 2019;50:155–161. doi: 10.1161/STROKEAHA.118.021798
80. Tikkanen E, Gustafsson S, Ingelsson E. Associations of fitness, physical activity, strength, and genetic risk with cardiovascular disease: longitudinal analyses in the UK Biobank study. *Circulation*. 2018;137:2583–2591. doi: 10.1161/CIRCULATIONAHA.117.032432
81. Wang Y, Su X, Chen Y, Wang Y, Zhou J, Liu T, Wang N, Fu C. Unfavorable dietary quality contributes to elevated risk of ischemic stroke among

residents in southwest China: based on the Chinese Diet Balance Index 2016 (DBI-16). *Nutrients*. 2022;14:694. doi: 10.3390/nu14030694
82. Johansson A, Drake I, Engström G, Acosta S. Modifiable and non-modifiable risk factors for atherothrombotic ischemic stroke among subjects in the Malmö Diet and Cancer Study. *Nutrients*. 2021;13:1952–1952. doi: 10.3390/nu13061952
83. Choi Y, Gallaher DD, Svendsen K, Meyer KA, Steffen LM, Schreiner PJ, Shikany JM, Rana JS, Duprez DA, Jacobs DR. Simple nutrient-based rules vs. a nutritionally rich plant-centered diet in prediction of future coronary heart disease and stroke: prospective observational study in the US. *Nutrients*. 2022;14:469. doi: 10.3390/nu14030469
84. Dybvik JS, Svendsen M, Aune D. Vegetarian and vegan diets and the risk of cardiovascular disease, ischemic heart disease and stroke: a systematic review and meta-analysis of prospective cohort studies. *Eur J Nutr*. 2023;62:51–69. doi: 10.1007/s00394-022-02942-8
85. Luo L, Jiang J, Yu C, Zhao M, Wang Y, Li Q, Jin Y. Stroke mortality attributable to low fruit intake in China: a joinpoint and age-period-cohort analysis. *Front Neurosci*. 2020;14:552113. doi: 10.3389/fnins.2020.552113
86. Gao Q, Dong J-Y, Cui R, Muraki I, Yamagishi K, Sawada N, Iso H, Tsugane S; Japan Public Health Center-based Prospective Study Group. Consumption of flavonoid-rich fruits, flavonoids from fruits and stroke risk: a prospective cohort study. *Br J Nutr*. 2021;126:1717–1724. doi: 10.1017/S0007114521000404
87. Ojagbemi A, Okekunle AP, Olowoyo P, Akpa OM, Akinyemi R, Ovbiagele B, Owolabi M. Dietary intakes of green leafy vegetables and incidence of cardiovascular diseases. *Cardiovasc J Afr*. 2021;32:215–223. doi: 10.5830/CVJA-2021-017
88. Stanaway JD, Afshin A, Ashbaugh C, Bisignano C, Brauer M, Ferrara G, Garcia V, Haile D, Hay SI, He J, et al. Health effects associated with vegetable consumption: a burden of proof study. *Nat Med*. 2022;28:2066–2074. doi: 10.1038/s41591-022-01970-5
89. Reynolds A, Mann J, Cummings J, Winter N, Mete E, Te Morenga L. Carbohydrate quality and human health: a series of systematic reviews and meta-analyses. *Lancet*. 2019;393:434–445. doi: 10.1016/S0140-6736(18)31809-9
90. Shao C, Tang H, Wang X, He J. Coffee consumption and stroke risk: evidence from a systematic review and meta-analysis of more than 2.4 million men and women. *J Stroke Cerebrovasc Dis*. 2021;30:105452. doi: 10.1016/j.jstrokecerebrovasdis.2020.105452
91. Simon J, Fung K, Raisi-Estabragh Z, Aung N, Khanji MY, Kolossváry M, Merkely B, Munroe PB, Harvey NC, Piechnik SK, et al. Light to moderate coffee consumption is associated with lower risk of death: a UK Biobank study. *Eur J Prev Cardiol*. 2022;29:982–991. doi: 10.1093/eurjpc/zwac008
92. Wang C, Yatsuya H, Lin Y, Sasakabe T, Kawai S, Kikuchi S, Iso H, Tamakoshi A. Milk Intake and stroke mortality in the Japan Collaborative Cohort Study: a bayesian survival analysis. *Nutrients*. 2020;12:2743. doi: 10.3390/nu12092743
93. Jakobsen MU, Trolle E, Outzen M, Mejborn H, Grønberg MG, Lyndgaard CB, Stockmarr A, Venø SK, Bysted A. Intake of dairy products and associations with major atherosclerotic cardiovascular diseases: a systematic review and meta-analysis of cohort studies. *Sci Rep*. 2021;11:1303. doi: 10.1038/s41598-020-79708-x
94. Pase MP, Himali JJ, Beiser AS, Aparicio HJ, Satizabal CL, Vasan RS, Seshadri S, Jacques PF. Sugar- and artificially sweetened beverages and the risks of incident stroke and dementia: a prospective cohort study. *Stroke*. 2017;48:1139–1146. doi: 10.1161/STROKEAHA.116.016027
95. Yang B, Glenn AJ, Liu Q, Madsen T, Allison MA, Shikany JM, Manson JE, Chan KHK, Wu WC, Li J, et al. Added sugar, sugar-sweetened beverages, and artificially sweetened beverages and risk of cardiovascular disease: findings from the Women's Health Initiative and a network meta-analysis of prospective studies. *Nutrients*. 2022;14:4226. doi: 10.3390/nu14204226
96. Veno SK, Bork CS, Jakobsen MU, Lundbye-Christensen S, McLennan PL, Bach FW, Overvad K, Schmidt EB. Marine n-3 polyunsaturated fatty acids and the risk of ischemic stroke. *Stroke*. 2019;50:274–282. doi: 10.1161/STROKEAHA.118.023384
97. Manson JE, Cook NR, Lee IM, Christen W, Bassuk SS, Mora S, Gibson H, Albert CM, Gordon D, Copeland T, et al; VITAL Research Group. Marine n-3 fatty acids and prevention of cardiovascular disease and cancer. *N Engl J Med*. 2019;380:23–32. doi: 10.1056/NEJMoa1811403
98. Ward RE, Cho K, Nguyen XM, Vassy JL, Ho YL, Quaden RM, Gagnon DR, Wilson PWF, Gaziano JM, Djousse L. Omega-3 supplement use, fish intake, and risk of non-fatal coronary artery disease and ischemic stroke in the Million Veteran Program. *Clin Nutr*. 2019;39:574–579. doi: 10.1016/j.clnu.2019.03.005
99. Shi H, Chen H, Zhang Y, Li J, Fu K, Xue W, Teng W, Tian L. 25-Hydroxyvitamin D level, vitamin D intake, and risk of stroke: a dose–response meta-analysis. *Clin Nutr*. 2020;39:2025–2034. doi: 10.1016/j.clnu.2019.08.029
100. Nudy M, Krakowski G, Ghahramani M, Ruzieh M, Foy AJ. Vitamin D supplementation, cardiac events and stroke: a systematic review and meta-regression analysis. *Int J Cardiol Heart Vasc*. 2020;28:100537. doi: 10.1016/j.ijcha.2020.100537
101. Kang ZQ, Yang Y, Xiao B. Dietary saturated fat intake and risk of stroke: systematic review and dose-response meta-analysis of prospective cohort studies. *Nutr Metab Cardiovasc Dis*. 2020;30:179–189. doi: 10.1016/j.numecd.2019.09.028
102. Kelly DM, Rothwell PM. Proteinuria as an independent predictor of stroke: systematic review and meta-analysis. *Int J Stroke*. 2020;15:29–38. doi: 10.1177/1747493019895206
103. Miwa K, Koga M, Nakai M, Yoshimura S, Sasahara Y, Koge J, Sonoda K, Ishigami A, Iwanaga Y, Miyamoto Y, et al; Japan Stroke Data Bank Investigators. Etiology and outcome of ischemic stroke in patients with renal impairment including chronic kidney disease: Japan Stroke Data Bank. *Neurology*. 2022;98:e1738–e1747. doi: 10.1212/WNL.0000000000200153
104. Huang R, Chen X. Increased spot urine albumin-to-creatinine ratio and stroke incidence: a systematic review and meta-analysis. *J Stroke Cerebrovasc Dis*. 2019;28:104260. doi: 10.1016/j.jstrokecerebrovasdis.2019.06.018
105. El Husseini N, Fonarow GC, Smith EE, Ju C, Schwamm LH, Hernandez AF, Schulte PJ, Xian Y, Goldstein LB. Renal dysfunction is associated with poststroke discharge disposition and in-hospital mortality: findings from Get With The Guidelines–Stroke. *Stroke*. 2017;48:327–334. doi: 10.1161/STROKEAHA.116.014601
106. Arnson Y, Hoshen M, Berliner-Sendrey A, Reges O, Balicer R, Leibowitz M, Avgil Tsadok M, Haim M. Risk of stroke, bleeding, and death in patients with nonvalvular atrial fibrillation and chronic kidney disease. *Cardiology*. 2020;145:178–186. doi: 10.1159/000504877
107. Toth-Manikowski SM, Yang W, Appel L, Chen J, Deo R, Frydrych A, Krousel-Wood M, Rahman M, Rosas SE, Sha D, et al; Chronic Renal Insufficiency Cohort (CRIC) Study Investigators. Sex differences in cardiovascular outcomes in CKD: findings from the CRIC study. *Am J Kidney Dis*. 2021;78:200–209.e1. doi: 10.1053/j.ajkd.2021.01.020
108. Tsuneyoshi S, Matsukuma Y, Kawai Y, Hiyamuta H, Yamada S, Kitamura H, Tanaka S, Taniguchi M, Tsuruya K, Nakano T, et al. Association between geriatric nutritional risk index and stroke risk in hemodialysis patients: 10-years outcome of the Q-Cohort study. *Atherosclerosis*. 2021;323:30–36. doi: 10.1016/j.atherosclerosis.2021.03.006
109. Ruban A, Daya N, Schneider ALC, Gottesman R, Selvin E, Coresh J, Lazo M, Koton S. Liver enzymes and risk of stroke: the Atherosclerosis Risk in Communities (ARIC) study. *J Stroke*. 2020;22:357–368. doi: 10.5853/jos.2020.00290
110. Parikh NS, Koh I, VanWagner LB, Elkind MSV, Zakai NA, Cushman M. Liver fibrosis is associated with ischemic stroke risk in women but not men: the REGARDS study. *J Stroke Cerebrovasc Dis*. 2021;30:105788. doi: 10.1016/j.jstrokecerebrovasdis.2021.105788
111. Carroll JD, Mack MJ, Vemulapalli S, Herrmann HC, Gleason TG, Hanzel G, Deeb GM, Thourani VH, Cohen DJ, Desai N, et al. STS-ACC TVT Registry of transcatheter aortic valve replacement. *J Am Coll Cardiol*. 2020;76:2492–2516. doi: 10.1016/j.jacc.2020.09.595
112. Butala NM, Faridi KF, Tamez H, Strom JB, Song Y, Shen C, Secemsky EA, Mauri L, Kereiakes DJ, Curtis JP, et al. Estimation of DAPT study treatment effects in contemporary clinical practice: findings from the EXTEND-DAPT study. *Circulation*. 2022;145:97–106. doi: 10.1161/CIRCULATIONAHA.121.056878
113. Kapadia SR, Makkar R, Leon M, Abdel-Wahab M, Waggoner T, Massberg S, Rottbauer W, Horr S, Sondergaard L, Karha J, et al; PROTECTED TAVR Investigators. Cerebral embolic protection during transcatheter aortic-valve replacement. *N Engl J Med*. 2022;387:1253–1263. doi: 10.1056/NEJMoa2204961
114. Ghoreishi M, Sundt TM, Cameron DE, Holmes SD, Roselli EE, Pasrija C, Gammie JS, Patel HJ, Bavaria JE, Svensson LG, et al. Factors associated with acute stroke after type A aortic dissection repair: an analysis of the Society of Thoracic Surgeons National Adult Cardiac Surgery Database. *J Thorac Cardiovasc Surg*. 2020;159:2143–2154.e3. doi: 10.1016/j.jtcvs.2019.06.016
115. Hjelholt TJ, Johnsen SP, Brynningsen PK, Pedersen AB. Association of CHA2 DS2 -VASc score with stroke, thromboembolism, and death

in hip fracture patients. *J Am Geriatr Soc*. 2020;68:1698–1705. doi: 10.1111/jgs.16452
116. Park DW, Ahn JM, Park H, Yun SC, Kang DY, Lee PH, Kim YH, Lim DS, Rha SW, Park GM, et al; PRECOMBAT Investigators. Ten-year outcomes after drug-eluting stents versus coronary artery bypass grafting for left main coronary disease: extended follow-up of the PRECOMBAT trial. *Circulation*. 2020;141:1437–1446. doi: 10.1161/CIRCULATIONAHA.120.046039
117. Swartz RH, Cayley ML, Foley N, Ladhani NNN, Leffert L, Bushnell C, McClure JA, Lindsay MP. The incidence of pregnancy-related stroke: a systematic review and meta-analysis. *Int J Stroke*. 2017;12:687–697. doi: 10.1177/1747493017723271
118. Jacobson LT, Hade EM, Collins TC, Margolis KL, Waring ME, Van Horn LV, Silver B, Sattari M, Bird CE, Kimminau K, et al. Breastfeeding history and risk of stroke among parous postmenopausal women in the Women's Health Initiative. *J Am Heart Assoc*. 2018;7:e008739. doi: 10.1161/JAHA.118.008739
119. Poorthuis MH, Algra AM, Algra A, Kappelle LJ, Klijn CJ. Female- and male-specific risk factors for stroke: a systematic review and meta-analysis. *JAMA Neurol*. 2017;74:75–81. doi: 10.1001/jamaneurol.2016.3482
120. Liang C, Chung HF, Dobson AJ, Mishra GD. Infertility, miscarriage, stillbirth, and the risk of stroke among women: a systematic review and meta-analysis. *Stroke*. 2022;53:328–337. doi: 10.1161/STROKEAHA.121.036271
121. de Havenon A, Delic A, Stulberg E, Sheibani N, Stoddard G, Hanson H, Theilen L. Association of preeclampsia with incident stroke in later life among women in the Framingham Heart Study. *JAMA Netw Open*. 2021;4:e215077. doi: 10.1001/jamanetworkopen.2021.5077
122. Kisanuki K, Muraki I, Yamagishi K, Kokubo Y, Saito I, Yatsuya H, Sawada N, Iso H, Tsugane S; JPHC Study Group. Weight change during middle age and risk of stroke and coronary heart disease: the Japan Public Health Center-based Prospective Study. *Atherosclerosis*. 2021;322:67–73. doi: 10.1016/j.atherosclerosis.2021.02.017
123. Okoth K, Wang J, Zemedikun D, Thomas GN, Nirantharakumar K, Adderley NJ. Risk of cardiovascular outcomes among women with endometriosis in the United Kingdom: a retrospective matched cohort study. *BJOG*. 2021;128:1598–1609. doi: 10.1111/1471-0528.16692
124. Lin YW, Wang JY, Lin MH. Stroke risk associated with NSAIDs uses in women with dysmenorrhea: a population-based cohort study. *PLoS One*. 2021;16:e0259047. doi: 10.1371/journal.pone.0259047
125. Chang WC, Wang JH, Ding DC. Conjugated equine estrogen used in postmenopausal women associated with a higher risk of stroke than estradiol. *Sci Rep*. 2021;11:10801. doi: 10.1038/s41598-021-90357-6
126. Chow FC, Wilson MR, Wu K, Ellis RJ, Bosch RJ, Linas BP. Stroke incidence is highest in women and non-Hispanic blacks living with HIV in the AIDS Clinical Trials Group Longitudinal Linked Randomized Trials cohort. *AIDS*. 2018;32:1125–1135. doi: 10.1097/QAD.0000000000001799
127. Chow FC, Regan S, Zanni MV, Looby SE, Bushnell CD, Meigs JB, Grinspoon SK, Feske SK, Triant VA. Elevated ischemic stroke risk among women living with HIV infection. *AIDS*. 2018;32:59–67. doi: 10.1097/QAD.0000000000001650
128. Austin K, Seeho S, Ibiebele I, Ford J, Morris J, Torvaldsen S. Pregnancy outcomes for women with a history of stroke: a population-based record linkage study. *Aust N Z J Obstet Gynaecol*. 2021;61:239–243. doi: 10.1111/ajo.13267
129. Xie C, Zhu R, Tian Y, Wang K. Association of obstructive sleep apnoea with the risk of vascular outcomes and all-cause mortality: a meta-analysis. *BMJ Open*. 2017;7:e013983. doi: 10.1136/bmjopen-2016-013983
130. Xiao Z, Xie M, You Y, Wu H, Zhou G, Li M. Wake-up stroke and sleep-disordered breathing: a meta-analysis of current studies. *J Neurol*. 2018;265:1288–1294. doi: 10.1007/s00415-018-8810-2
131. Lisabeth LD, Sánchez BN, Chervin RD, Morgenstern LB, Zahuranec DB, Tower SD, Brown DL. High prevalence of post-stroke sleep disordered breathing in Mexican Americans. *Sleep Med*. 2017;33:97–102. doi: 10.1016/j.sleep.2016.01.010
132. Wu Z, Chen F, Yu F, Wang Y, Guo Z. A meta-analysis of obstructive sleep apnea in patients with cerebrovascular disease. *Sleep Breath*. 2018;22:729–742. doi: 10.1007/s11325-017-1604-4
133. Seiler A, Camilo M, Korostovtseva L, Haynes AG, Brill AK, Horvath T, Egger M, Bassetti CL. Prevalence of sleep-disordered breathing after stroke and TIA: a meta-analysis. *Neurology*. 2019;92:e648–e654. doi: 10.1212/WNL.0000000000006904
134. Liu X, Lam DC, Chan KPF, Chan HY, Ip MS, Lau KK. Prevalence and determinants of sleep apnea in patients with stroke: a meta-analysis. *J Stroke Cerebrovasc Dis*. 2021;30:106129. doi: 10.1016/j.jstrokecerebrovasdis.2021.106129
135. Jike M, Itani O, Watanabe N, Buysse DJ, Kaneita Y. Long sleep duration and health outcomes: a systematic review, meta-analysis and meta-regression. *Sleep Med Rev*. 2018;39:25–36. doi: 10.1016/j.smrv.2017.06.011
136. Li W, Kondracki A, Gautam P, Rahman A, Kiplagat S, Liu H, Sun W. The association between sleep duration, napping, and stroke stratified by self-health status among Chinese people over 65 years old from the China Health and Retirement Longitudinal Study. *Sleep Breath*. 2021;25:1239–1246. doi: 10.1007/s11325-020-02214-x
137. Lu H, Wu PF, Li RZ, Zhang W, Huang GX. Sleep duration and stroke: a mendelian randomization study. *Front Neurol*. 2020;11:976. doi: 10.3389/fneur.2020.00976
138. Ma Y, Wang M, Chen X, Ruan W, Yao J, Lian X. Daytime sleepiness and risk of stroke: a mendelian randomization analysis. *Clin Neurol Neurosurg*. 2021;208:106857. doi: 10.1016/j.clineuro.2021.106857
139. O'Donnell MJ, Chin SL, Rangarajan S, Xavier D, Liu L, Zhang H, Rao-Melacini P, Zhang X, Pais P, Agapay S, et al; INTERSTROKE Investigators. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. *Lancet*. 2016;388:761–775. doi: 10.1016/S0140-6736(16)30506-2
140. Murphy RP, Reddin C, Rosengren A, Judge C, Hankey GJ, Ferguson J, Alvarez-Iglesias A, Oveisgharan S, Wasay M, McDermott C, et al; INTERSTROKE Investigators. Depressive symptoms and risk of acute stroke: INTERSTROKE case-control study. *Neurology*. 2023;100:e1787–e1798. doi: 10.1212/wnl.0000000000207093
141. Cummings DM, Lutes LD, Wilson JL, Carraway M, Safford MM, Cherrington A, Long DL, Carson AP, Yuan Y, Howard VJ, et al. Persistence of depressive symptoms and risk of incident cardiovascular disease with and without diabetes: results from the REGARDS study. *J Gen Intern Med*. 2022;37:4080–4087. doi: 10.1007/s11606-022-07449-w
142. Jackson CA, Sudlow CLM, Mishra GD. Psychological distress and risk of myocardial infarction and stroke in the 45 and Up Study. *Circ Cardiovasc Qual Outcomes*. 2018;11:e004500. doi: 10.1161/CIRCOUTCOMES.117.004500
143. Li H, He P, Zhang Y, Lin T, Liu C, Xie D, Liang M, Wang G, Nie J, Song Y, et al. Self-perceived psychological stress and risk of first stroke in treated hypertensive patients. *Psychosom Med*. 2022;84:237–243. doi: 10.1097/PSY.0000000000001030
144. Ford CD, Gray MS, Crowther MR, Wadley VG, Austin AL, Crowe MG, Pulley L, Unverzagt F, Kleindorfer DO, Kissela BM, et al. Depressive symptoms and risk of stroke in a national cohort of blacks and whites from REGARDS. *Neurol Clin Pract*. 2020;11:e454–e461. doi: 10.1212/cpj.0000000000000983
145. Wassertheil-Smoller S, Qi Q, Dave T, Mitchell BD, Jackson RD, Liu S, Park K, Salinas J, Dunn EC, Leira EC, et al. Polygenic risk for depression increases risk of ischemic stroke: from the Stroke Genetics Network Study. *Stroke*. 2018;49:543–548. doi: 10.1161/STROKEAHA.117.018857
146. On BI, Vidal X, Berger U, Sabate M, Ballarin E, Maisterra O, San-Jose A, Ibanez L. Antidepressant use and stroke or mortality risk in the elderly. *Eur J Neurol*. 2022;29:469–477. doi: 10.1111/ene.15137
147. Hakulinen C, Pulkki-Råback L, Virtanen M, Jokela M, Kivimäki M, Elovainio M. Social isolation and loneliness as risk factors for myocardial infarction, stroke and mortality: UK Biobank cohort study of 479 054 men and women. *Heart*. 2018;104:1536–1542. doi: 10.1136/heartjnl-2017-312663
148. Hu J, Zheng X, Shi G, Guo L. Associations of multiple chronic disease and depressive symptoms with incident stroke among Chinese middle-aged and elderly adults: a nationwide population-based cohort study. *BMC Geriatr*. 2022;22:660. doi: 10.1186/s12877-022-03329-4
149. Heron M. Deaths: leading causes for 2019. *Natl Vital Stat Rep*. 2021;70:1–114.
150. Seshadri S, Beiser A, Kelly-Hayes M, Kase CS, Au R, Kannel WB, Wolf PA. The lifetime risk of stroke: estimates from the Framingham study. *Stroke*. 2006;37:345–350. doi: 10.1161/01.STR.0000199613.38911.b2
151. Madsen TE, Khoury JC, Leppert M, Alwell K, Moomaw CJ, Sucharew H, Woo D, Ferioli S, Martini S, Adeoye O, et al. Temporal trends in stroke incidence over time by sex and age in the GCNKSS. *Stroke*. 2020;51:1070–1076. doi: 10.1161/STROKEAHA.120.028910
152. Park B, Budzynska K, Almasri N, Islam S, Alyas F, Carolan RL, Abraham BE, Castro-Camero PA, Shreve ME, Rees DA, et al. Tight versus standard blood pressure control on the incidence of myocardial infarction and stroke: an observational retrospective cohort study in the general ambulatory setting. *BMC Fam Pract*. 2020;21:91. doi: 10.1186/s12875-020-01163-4
153. Leppert MH, Burke JF, Lisabeth LD, Madsen TE, Kleindorfer DO, Sillau S, Schwamm LH, Daugherty SL, Bradley CJ, Ho PM, et al. Systematic review of sex differences in ischemic strokes among young adults: are

young women disproportionately at risk? *Stroke*. 2022;53:319–327. doi: 10.1161/STROKEAHA.121.037117
154. Gardener H, Sacco RL, Rundek T, Battistella V, Cheung YK, Elkind MSV. Race and ethnic disparities in stroke incidence in the Northern Manhattan Study. *Stroke*. 2020;51:1064–1069. doi: 10.1161/STROKEAHA.119.028806
155. Herman AL, Sheth KN, Williams OA, Johnston KC, Prabhakaran S, de Havenon A. Self-reported race as a social determinant of stroke risk in observational versus clinical trial datasets. *J Stroke Cerebrovasc Dis*. 2022;31:106219. doi: 10.1016/j.jstrokecerebrovasdis.2021.106219
156. Hong C, Pencina MJ, Wojdyla DM, Hall JL, Judd SE, Cary M, Engelhard MM, Berchuck S, Xian Y, D'Agostino R Sr, et al. Predictive accuracy of stroke risk prediction models across Black and White race, sex, and age groups. *JAMA*. 2023;329:306–317. doi: 10.1001/jama.2022.24683
157. Jimenez MC, Manson JE, Cook NR, Kawachi I, Wassertheil-Smoller S, Haring B, Nassir R, Rhee JJ, Sealy-Jefferson S, Rexrode KM. Racial variation in stroke risk among women by stroke risk factors. *Stroke*. 2019;50:797–804. doi: 10.1161/STROKEAHA.117.017759
158. Muller CJ, Alonso A, Forster J, Vock DM, Zhang Y, Gottesman RF, Rosamond W, Longstreth WT Jr, MacLehose RF. Stroke incidence and survival in American Indians, Blacks, and Whites: the Strong Heart Study and Atherosclerosis Risk in Communities Study. *J Am Heart Assoc*. 2019;8:e010229. doi: 10.1161/JAHA.118.010229
159. Clark DG, Boan AD, Sims-Robinson C, Adams RJ, Amella EJ, Benitez A, Lackland DT, Ovbiagele B. Differential impact of index stroke on dementia risk in African-Americans compared to Whites. *J Stroke Cerebrovasc Dis*. 2018;27:2725–2730. doi: 10.1016/j.jstrokecerebrovasdis.2018.05.048
160. Wallace AN, Gibson DP, Asif KS, Sahlein DH, Warach SJ, Malisch T, Lamonte MP. Racial disparity in mechanical thrombectomy utilization: multicenter registry results from 2016 to 2020. *J Am Heart Assoc*. 2022;11:e021865. doi: 10.1161/JAHA.121.021865
161. Burns SP, Mueller M, Magwood G, White BM, Lackland D, Ellis C. Racial and ethnic differences in post-stroke subjective cognitive decline exist. *Disabil Health J*. 2019;12:87–92. doi: 10.1016/j.dhjo.2018.08.005
162. Najib N, Magin P, Lasserson D, Quain D, Attia J, Oldmeadow C, Garcia-Esperon C, Levi C. Contemporary prognosis of transient ischemic attack patients: a systematic review and meta-analysis. *Int J Stroke*. 2019;14:460–467. doi: 10.1177/1747493018823568
163. Hurford R, Li L, Lovett N, Kubiak M, Kuker W, Rothwell PM; Oxford Vascular Study. Prognostic value of "tissue-based" definitions of TIA and minor stroke: population-based study. *Neurology*. 2019;92:e2455–e2461. doi: 10.1212/WNL.0000000000007531
164. Joundi RA, Yu AYX, Smith EE, Zerna C, Penn AM, Balshaw RF, Votova K, Bibok MB, Penn M, Saly V, et al; SpecTRA Study Group. Association between duration of transient neurological events and diffusion-weighted brain lesions. *J Am Heart Assoc*. 2023;12:e027861. doi: 10.1161/JAHA.122.027861
165. Shahjouei S, Sadighi A, Chaudhary D, Li J, Abedi V, Holland N, Phipps M, Zand R. A 5-decade analysis of incidence trends of ischemic stroke after transient ischemic attack: a systematic review and meta-analysis. *JAMA Neurol*. 2021;78:77–87. doi: 10.1001/jamaneurol.2020.3627
166. Cucchiara B, Elm J, Easton JD, Coutts SB, Willey JZ, Biros MH, Ross MA, Johnston SC. Disability after minor stroke and transient ischemic attack in the POINT trial. *Stroke*. 2020;51:792–799. doi: 10.1161/STROKEAHA.119.027465
167. Zhang F, Liu L, Zhang C, Ji S, Mei Z, Li T. Association of metabolic syndrome and its components with risk of stroke recurrence and mortality: a meta-analysis. *Neurology*. 2021;97:e695–e705. doi: 10.1212/WNL.0000000000012415
168. Goeggel Simonetti B, Rafay MF, Chung M, Lo WD, Beslow LA, Billinghurst LL, Fox CK, Pagnamenta A, Steinlin M, Mackay MT; IPSS Study Group. Comparative study of posterior and anterior circulation stroke in childhood: results from the International Pediatric Stroke Study. *Neurology*. 2020;94:e337–e344. doi: 10.1212/WNL.0000000000008837
169. Del Brutto VJ, Diener HC, Easton JD, Granger CB, Cronin L, Kleine E, Grauer C, Brueckmann M, Toyoda K, Schellinger PD, et al. Predictors of recurrent stroke after embolic stroke of undetermined source in the RE-SPECT ESUS trial. *J Am Heart Assoc*. 2022;11:e023545. doi: 10.1161/JAHA.121.023545
170. Xu J, Zhang X, Jin A, Pan Y, Li Z, Meng X, Wang Y. Trends and risk factors associated with stroke recurrence in China, 2007-2018. *JAMA Netw Open*. 2022;5:e2216341. doi: 10.1001/jamanetworkopen.2022.16341
171. Albright KC, Huang L, Blackburn J, Howard G, Mullen M, Bittner V, Muntner P, Howard V. Racial differences in recurrent ischemic stroke risk and recurrent stroke case fatality. *Neurology*. 2018;91:e1741–e1750. doi: 10.1212/WNL.0000000000006467
172. Kauw F, Takx RAP, De Jong HWAM, Velthuis BK, Kappelle LJ, Dankbaar JW. Clinical and imaging predictors of recurrent ischemic stroke: a systematic review and meta-analysis. *Cerebrovasc Dis*. 2018;45:279–287. doi: 10.1159/000490422
173. Georgakis MK, Duering M, Wardlaw JM, Dichgans M. WMH and long-term outcomes in ischemic stroke: a systematic review and meta-analysis. *Neurology*. 2019;92:e1298–e1308. doi: 10.1212/WNL.0000000000007142
174. Ryu WS, Schellingerhout D, Hong KS, Jeong SW, Jang MU, Park MS, Choi KH, Kim JT, Kim BJ, Lee J, et al. White matter hyperintensity load on stroke recurrence and mortality at 1 year after ischemic stroke. *Neurology*. 2019;93:e578–e589. doi: 10.1212/WNL.0000000000007896
175. Yafasova A, Fosbol EL, Johnsen SP, Kruuse C, Petersen JK, Alhakak A, Vinding NE, Torp-Pedersen C, Gislason GH, Kober L, et al. Time to thrombolysis and long-term outcomes in patients with acute ischemic stroke: a nationwide study. *Stroke*. 2021;52:1724–1732. doi: 10.1161/strokeaha.120.032837
176. Pan Y, Li Z, Li J, Jin A, Lin J, Jing J, Li H, Meng X, Wang Y, Wang Y. Residual risk and its risk factors for ischemic stroke with adherence to guideline-based secondary stroke prevention. *J Stroke*. 2021;23:51–60. doi: 10.5853/jos.2020.03391
177. Liu T, Jiang Y, Hu J, Li Z, Guo Y, Li X, Xiao J, Yuan L, He G, Zeng W, et al. Association of ambient PM1 with hospital admission and recurrence of stroke in China. *Sci Total Environ*. 2022;828:154131. doi: 10.1016/j.scitotenv.2022.154131
178. Andersen KK, Olsen TS. Social inequality by income in short- and long-term cause-specific mortality after stroke. *J Stroke Cerebrovasc Dis*. 2019;28:1529–1536. doi: 10.1016/j.jstrokecerebrovasdis.2019.03.013
179. Sato T, Sakai K, Nakada R, Shiraishi T, Tanabe M, Komatsu T, Sakuta K, Terasawa Y, Umehara T, Omoto S, et al. Employment status prior to ischemic stroke and weekly variation of stroke onset. *J Stroke Cerebrovasc Dis*. 2021;30:105873. doi: 10.1016/j.jstrokecerebrovasdis.2021.105873
180. Gafarova AV, Gromova EA, Panov DO, Gagulin IV, Krymov EA, Gafarov VV. Social support and stroke risk: an epidemiological study of a population aged 25–64 years in Russia/Siberia (the WHO MONICA-psychosocial program). *Neurol Neuropsychiatry Psychosom*. 2019;11:12–20. doi: 10.14412/2074-2711-2019-1-12-20
181. Bevan S, Traylor M, Adib-Samii P, Malik R, Paul NL, Jackson C, Farrall M, Rothwell PM, Sudlow C, Dichgans M, et al. Genetic heritability of ischemic stroke and the contribution of previously reported candidate gene and genomewide associations. *Stroke*. 2012;43:3161–3167. doi: 10.1161/STROKEAHA.112.665760
182. Markus HS, Bevan S. Mechanisms and treatment of ischaemic stroke: insights from genetic associations. *Nat Rev Neurol*. 2014;10:723–730. doi: 10.1038/nrneurol.2014.196
183. Malik R, Chauhan G, Traylor M, Sargurupremraj M, Okada Y, Mishra A, Rutten-Jacobs L, Giese AK, van der Laan SW, Gretarsdottir S, et al; AFGen Consortium. Multiancestry genome-wide association study of 520,000 subjects identifies 32 loci associated with stroke and stroke subtypes. *Nat Genet*. 2018;50:524–537. doi: 10.1038/s41588-018-0058-3
184. Mishra A, Malik R, Hachiya T, Jurgenson T, Namba S, Posner DC, Kamanu FK, Koido M, Le Grand Q, Shi M, et al; COMPASS Consortium. Stroke genetics informs drug discovery and risk prediction across ancestries. *Nature*. 2022;611:115–123. doi: 10.1038/s41586-022-05165-3
185. Devan WJ, Falcone GJ, Anderson CD, Jagiella JM, Schmidt H, Hansen BM, Jimenez-Conde J, Giralt-Steinhauer E, Cuadrado-Godia E, Soriano C, et al; International Stroke Genetics Consortium. Heritability estimates identify a substantial genetic contribution to risk and outcome of intracerebral hemorrhage. *Stroke*. 2013;44:1578–1583. doi: 10.1161/STROKEAHA.111.000089
186. Carpenter AM, Singh IP, Gandhi CD, Prestigiacomo CJ. Genetic risk factors for spontaneous intracerebral haemorrhage. *Nat Rev Neurol*. 2016;12:40–49. doi: 10.1038/nrneurol.2015.226
187. Woo D, Falcone GJ, Devan WJ, Brown WM, Biffi A, Howard TD, Anderson CD, Brouwers HB, Valant V, Battey TW, et al; International Stroke Genetics Consortium. Meta-analysis of genome-wide association studies identifies 1q22 as a susceptibility locus for intracerebral hemorrhage. *Am J Hum Genet*. 2014;94:511–521. doi: 10.1016/j.ajhg.2014.02.012
188. Bakker MK, van der Spek RAA, van Rheenen W, Morel S, Bourcier R, Hostettler IC, Alg VS, van Eijk KR, Koido M, Akiyama M, et al; HUNT All-In Stroke. Genome-wide association study of intracranial aneurysms identifies 17 risk loci and genetic overlap with clinical risk factors. *Nat Genet*. 2020;52:1303–1313. doi: 10.1038/s41588-020-00725-7
189. Traylor M, Malik R, Nalls MA, Cotlarciuc I, Radmanesh F, Thorleifsson G, Hanscombe KB, Langefeld C, Saleheen D, Rost NS, et al; METASTROKE,

UK Young Lacunar DNA Study, NINDS Stroke Genetics Network, Neurology Working Group of the CHARGE Consortium. Genetic variation at 16q24.2 is associated with small vessel stroke. *Ann Neurol*. 2017;81:383–394. doi: 10.1002/ana.24840
190. Traylor M, Persyn E, Tomppo L, Klasson S, Abedi V, Bakker MK, Torres N, Li L, Bell S, Rutten-Jacobs L, et al; Helsinki Stroke, Study Dutch Parelsnoer Institute-Cerebrovascular Accident (CVA) Study Group. Genetic basis of lacunar stroke: a pooled analysis of individual patient data and genome-wide association studies. *Lancet Neurol*. 2021;20:351–361. doi: 10.1016/S1474-4422(21)00031-4
191. Jaworek T, Xu H, Gaynor BJ, Cole JW, Rannikmae K, Stanne TM, Tomppo L, Abedi V, Amouyel P, Armstrong ND, et al; Cervical Artery Dissections and Ischemic Stroke Patients (CADSIP) ConsortiumINVENT ConsortiumEarly Onset Stroke Genetics Consortium of the International Stroke Genetics C. Contribution of common genetic variants to risk of early onset ischemic stroke. *Neurology*. 2022;99:e1738–e1754. doi: 10.1212/WNL.0000000000201006
192. Malik R, Traylor M, Pulit SL, Bevan S, Hopewell JC, Holliday EG, Zhao W, Abrantes P, Amouyel P, Attia JR, et al; ISGC Analysis Group. Low-frequency and common genetic variation in ischemic stroke: the METASTROKE collaboration. *Neurology*. 2016;86:1217–1226. doi: 10.1212/WNL.0000000000002528
193. Xu H, Nguyen K, Gaynor BJ, Ling H, Zhao W, McArdle PF, O'Connor TD, Stine OC, Ryan KA, Lynch M, et al; Trans-Omics For Precision Medicine TOPMed Stroke Working Group, SiGN Consortium. Exome array analysis of 9721 ischemic stroke cases from the SiGN Consortium. *Genes (Basel)*. 2022;14:6. doi: 10.3390/genes14010061
194. Georgakis MK, Gill D, Rannikmae K, Traylor M, Anderson CD, Lee JM, Kamatani Y, Hopewell JC, Worrall BB, Bernhagen J, et al. Genetically determined levels of circulating cytokines and risk of stroke. *Circulation*. 2019;139:256–268. doi: 10.1161/CIRCULATIONAHA.118.035905
195. Gill D, Georgakis MK, Laffan M, Sabater-Lleal M, Malik R, Tzoulaki I, Veltkamp R, Dehghan A. Genetically determined FXI (factor XI) levels and risk of stroke. *Stroke*. 2018;49:2761–2763. doi: 10.1161/STROKEAHA.118.022792
196. de Vries PS, Sabater-Lleal M, Huffman JE, Marten J, Song C, Pankratz N, Bartz TM, de Haan HG, Delgado GE, Eicher JD, et al; INVENT Consortium. A genome-wide association study identifies new loci for factor VII and implicates factor VII in ischemic stroke etiology. *Blood*. 2019;133:967–977. doi: 10.1182/blood-2018-05-849240
197. Cai H, Cai B, Liu Z, Wu W, Chen D, Fang L, Chen L, Sun W, Liang J, Zhang H. Genetic correlations and causal inferences in ischemic stroke. *J Neurol*. 2020;267:1980–1990. doi: 10.1007/s00415-020-09786-4
198. Patel A, Fang J, Gillespie C, Odom E, King SC, Luncheon C, Ayala C. Awareness of stroke signs and symptoms and calling 9-1-1 among US adults: National Health Interview Survey, 2009 and 2014. *Prev Chronic Dis*. 2019;16:E78. doi: 10.5888/pcd16.180564
199. Visaria A, Dharamdasani T, Gaur S, Ghoshal B, Singh V, Mathur S, Varghese C, Demissie K. Effectiveness of a cultural stroke prevention program in the United States-South Asian Health Awareness About Stroke (SAHAS). *J Immigr Minor Health*. 2021;23:747–754. doi: 10.1007/s10903-020-01071-w
200. Menkin JA, McCreath HE, Song SY, Carrillo CA, Reyes CE, Trejo L, Choi SE, Willis P, Jimenez E, Ma S, et al. "Worth the walk": culturally tailored stroke risk factor reduction intervention in community senior centers. *J Am Heart Assoc*. 2019;8:e011088. doi: 10.1161/JAHA.118.011088
201. Simmons C, Noble JM, Leighton-Herrmann E, Hecht MF, Williams O. Community-level measures of stroke knowledge among children: findings from Hip Hop Stroke. *J Stroke Cerebrovasc Dis*. 2017;26:139–142. doi: 10.1016/j.jstrokecerebrovasdis.2016.08.045
202. Centers for Disease Control and Prevention and National Center for Health Statistics. Multiple cause of death, CDC WONDER online database. Accessed April 1, 2023. https://wonder.cdc.gov/mcd-icd10.html
203. Centers for Disease Control and Prevention and National Center for Health Statistics. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death micro-data files. Accessed April 8, 2023. https://cdc.gov/nchs/nvss/mortality_public_use_data.htm
204. Howard G, Evans GW, Pearce K, Howard VJ, Bell RA, Mayer EJ, Burke GL. Is the Stroke Belt disappearing? An analysis of racial, temporal, and age effects. *Stroke*. 1995;26:1153–1158. doi: 10.1161/01.str.26.7.1153
205. Schieb LJ, Ayala C, Valderrama AL, Veazie MA. Trends and disparities in stroke mortality by region for American Indians and Alaska Natives. *Am J Public Health*. 2014;104:S368–S376. doi: 10.2105/AJPH.2013.301698
206. Pearson-Stuttard J, Guzman-Castillo M, Penalvo JL, Rehm CD, Afshin A, Danaei G, Kypridemos C, Gaziano T, Mozaffarian D, Capewell S, et al. Modeling future cardiovascular disease mortality in the United States: national trends and racial and ethnic disparities. *Circulation*. 2016;133:967–978. doi: 10.1161/CIRCULATIONAHA.115.019904
207. Hay CC, Graham JE, Pappadis MR, Sander AM, Hong I, Reistetter TA. The impact of one's sex and social living situation on rehabilitation outcomes after a stroke. *Am J Phys Med Rehabil*. 2020;99:48–55. doi: 10.1097/PHM.0000000000001276
208. Sennfalt S, Pihlsgard M, Petersson J, Norrving B, Ullberg T. Long-term outcome after ischemic stroke in relation to comorbidity: an observational study from the Swedish Stroke Register (Riksstroke). *Eur Stroke J*. 2020;5:36–46. doi: 10.1177/2396987319883154
209. Dai S, Lemaire C, Piscicelli C, Pérennou D. Lateropulsion prevalence after stroke: a systematic review and meta-analysis. *Neurology*. 2022;98:e1574–e1584. doi: 10.1212/WNL.0000000000200010
210. Duong P, Sauve-Schenk K, Egan MY, Meyer MJ, Morrison T. Operational definitions and estimates of return to work poststroke: a systematic review and meta-analysis. *Arch Phys Med Rehabil*. 2019;100:1140–1152. doi: 10.1016/j.apmr.2018.09.121
211. Badve MS, Zhou Z, van de Beek D, Anderson CS, Hackett ML. Frequency of post-stroke pneumonia: systematic review and meta-analysis of observational studies. *Int J Stroke*. 2019;14:125–136. doi: 10.1177/1747493018806196
212. Chan L, Hu CJ, Fan YC, Li FY, Hu HH, Hong CT, Bai CH. Incidence of poststroke seizures: a meta-analysis. *J Clin Neurosci*. 2018;47:347–351. doi: 10.1016/j.jocn.2017.10.088
213. Holmes RJ, McManus KJ, Koulouglioti C, Hale B. Risk factors for poststroke shoulder pain: a systematic review and meta-analysis. *J Stroke Cerebrovasc Dis*. 2020;29:104787. doi: 10.1016/j.jstrokecerebrovasdis.2020.104787
214. Banda KJ, Chu H, Kang XL, Liu D, Pien LC, Jen HJ, Hsiao SS, Chou KR. Prevalence of dysphagia and risk of pneumonia and mortality in acute stroke patients: a meta-analysis. *BMC Geriatr*. 2022;22:420. doi: 10.1186/s12877-022-02960-5
215. Winovich DT, Longstreth WT Jr, Arnold AM, Varadhan R, Zeki Hazzouri A, Cushman M, Newman AB, Odden MC. Factors associated with ischemic stroke survival and recovery in older adults. *Stroke*. 2017;48:1818–1826. doi: 10.1161/STROKEAHA.117.016726
216. Faura J, Bustamante A, Reverte S, Garcia-Berrocoso T, Millan M, Castellanos M, Lara-Rodriguez B, Zaragoza J, Ventura O, Hernandez-Perez M, et al. Blood biomarker panels for the early prediction of stroke-associated complications. *J Am Heart Assoc*. 2021;10:e018946. doi: 10.1161/JAHA.120.018946
217. Mayman NA, Tuhrim S, Jette N, Dhamoon MS, Stein LK. Sex differences in post-stroke depression in the elderly. *J Stroke Cerebrovasc Dis*. 2021;30:105948. doi: 10.1016/j.jstrokecerebrovasdis.2021.105948
218. Avadhani R, Thompson RE, Carhuapoma L, Yenokyan G, McBee N, Lane K, Ostapkovich N, Stadnik A, Awad IA, Hanley DF, et al. Post-stroke depression in patients with large spontaneous intracerebral hemorrhage. *J Stroke Cerebrovasc Dis*. 2021;30:106082. doi: 10.1016/j.jstrokecerebrovasdis.2021.106082
219. Cai W, Mueller C, Li YJ, Shen WD, Stewart R. Post stroke depression and risk of stroke recurrence and mortality: a systematic review and meta-analysis. *Ageing Res Rev*. 2019;50:102–109. doi: 10.1016/j.arr.2019.01.013
220. Almeida OP, Hankey GJ, Ford AH, Etherton-Beer C, Flicker L, Hackett ML; AFFINITY Trial Investigators. Measures associated with early, late, and persistent clinically significant symptoms of depression 1 year after stroke in the AFFINITY trial. *Neurology*. 2022;98:e1021–e1030. doi: 10.1212/WNL.0000000000200058
221. Dhamoon MS, Longstreth WT Jr, Bartz TM, Kaplan RC, Elkind MSV. Disability trajectories before and after stroke and myocardial infarction: the Cardiovascular Health Study. *JAMA Neurol*. 2017;74:1439–1445. doi: 10.1001/jamaneurol.2017.2802
222. Chye A, Hackett ML, Hankey GJ, Lundström E, Almeida OP, Gommans J, Dennis M, Jan S, Mead GE, Ford AH, et al. Repeated measures of modified Rankin Scale scores to assess functional recovery from stroke: AFFINITY study findings. *J Am Heart Assoc*. 2022;11:e025425. doi: 10.1161/JAHA.121.025425
223. Dong Y, Ding M, Cui M, Fang M, Gong L, Xu Z, Zhang Y, Wang X, Xu X, Liu X, et al. Development and validation of a clinical model (DREAM-LDL) for post-stroke cognitive impairment at 6 months. *Aging (Albany NY)*. 2021;13:21628–21641. doi: 10.18632/aging.203507
224. Khan M, Heiser H, Bernicchi N, Packard L, Parker JL, Edwardson MA, Silver B, Elisevich KV, Henninger N. Leukoaraiosis predicts

short-term cognitive but not motor recovery in ischemic stroke patients during rehabilitation. *J Stroke Cerebrovasc Dis*. 2019;28:1597–1603. doi: 10.1016/j.jstrokecerebrovasdis.2019.02.037
225. Ohlmeier L, Nannoni S, Pallucca C, Brown RB, Loubiere L, Markus HS; DNA Lacunar 2 Investigators. Prevalence of, and risk factors for, cognitive impairment in lacunar stroke. *Int J Stroke*. 2023;18:62–69. doi: 10.1177/17474930211064965
226. Ferriero DM, Fullerton HJ, Bernard TJ, Billinghurst L, Daniels SR, DeBaun MR, deVeber G, Ichord RN, Jordan LC, Massicotte P, et al; on behalf of the American Heart Association Stroke Council and Council on Cardiovascular and Stroke Nursing. Management of stroke in neonates and children: a scientific statement from the American Heart Association/American Stroke Association. *Stroke*. 2019;50:e51–e96. doi: 10.1161/STR.0000000000000183
227. Xia Q, Yang Z, Xie Y, Zhu Y, Yang Z, Hei M, Ding Y, Kong W, Kang L, Yang S, et al. The incidence and characteristics of perinatal stroke in Beijing: a multicenter study. *Front Public Health*. 2022;10:783153. doi: 10.3389/fpubh.2022.783153
228. Munoz D, Hidalgo MJ, Balut F, Troncoso M, Lara S, Barrios A, Parra P. Risk factors for perinatal arterial ischemic stroke: a case-control study. *Cell Med*. 2018;10:2155179018785341. doi: 10.1177/2155179018785341
229. Mastrangelo M, Giordo L, Ricciardi G, De Michele M, Toni D, Leuzzi V. Acute ischemic stroke in childhood: a comprehensive review. *Eur J Pediatr*. 2022;181:45–58. doi: 10.1007/s00431-021-04212-x
230. Cornet MC, Grose C, Vexler Z, Wu YW, Fullerton HJ. The role of infection and inflammation in the pathogenesis of pediatric arterial ischemic stroke. *Semin Pediatr Neurol*. 2022;44:100995. doi: 10.1016/j.spen.2022.100995
231. Rafay MF, Shapiro KA, Surmava AM, deVeber GA, Kirton A, Fullerton HJ, Amlie-Lefond C, Weschke B, Dlamini N, Carpenter JL, et al; International Pediatric Stroke Study (IPSS) Group. Spectrum of cerebral arteriopathies in children with arterial ischemic stroke. *Neurology*. 2020;94:e2479–e2490. doi: 10.1212/WNL.0000000000009557
232. Brosius SN, Vossough A, Fisher MJ, Lang SS, Beslow LA, George BJ, Ichord R. Characteristics of moyamoya syndrome in pediatric patients with neurofibromatosis type 1. *Pediatr Neurol*. 2022;134:85–92. doi: 10.1016/j.pediatrneurol.2022.05.013
233. Çaksen H, Köseoğlu FT, Güven AS, Altunhan H, Iyisoy MS, Açikgözoğlu S. Risk and prognostic factors in perinatal hemorrhagic stroke. *Ann Indian Acad Neurol*. 2021;24:227–233. doi: 10.4103/aian.AIAN_580_20
234. Curtis C, Mineyko A, Massicotte P, Leaker M, Jiang XY, Floer A, Kirton A. Thrombophilia risk is not increased in children after perinatal stroke. *Blood*. 2017;129:2793–2800. doi: 10.1182/blood-2016-11-750893
235. Fullerton HJ, Wintermark M, Hills NK, Dowling MM, Tan M, Rafay MF, Elkind MS, Barkovich AJ, deVeber GA; VIPS Investigators. Risk of recurrent arterial ischemic stroke in childhood: a prospective international study. *Stroke*. 2016;47:53–59. doi: 10.1161/STROKEAHA.115.011173
236. Srivastava R, Shaw OEF, Armstrong E, Morneau-Jacob FD, Yager JY. Patterns of brain injury in perinatal arterial ischemic stroke and the development of infantile spasms. *J Child Neurol*. 2021;36:583–588. doi: 10.1177/0883073820986056
237. Pangprasertkul S, Borisoot W, Buawangpong N, Sirikul W, Wiwattanadittakul N, Katanyuwong K, Sanguansermsri C. Comparison of arterial ischemic and hemorrhagic pediatric stroke in etiology, risk factors, clinical manifestations, and prognosis. *Pediatr Emerg Care*. 2022;38:e1569–e1573. doi: 10.1097/PEC.0000000000002614
238. Hamilton W, Huang H, Seiber E, Lo W. Cost and outcome in pediatric ischemic stroke. *J Child Neurol*. 2015;30:1483–1488. doi: 10.1177/0883073815570673
239. Plumb P, Seiber E, Dowling MM, Lee J, Bernard TJ, deVeber G, Ichord RN, Bastian R, Lo WD. Out-of-pocket costs for childhood stroke: the impact of chronic illness on parents' pocketbooks. *Pediatr Neurol*. 2015;52:73–76.e2. doi: 10.1016/j.pediatrneurol.2014.09.010
240. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Delling FN, et al; on behalf of the American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics–2020 update: a report from the American Heart Association. *Circulation*. 2020;141:e139–e596. doi: 10.1161/CIR.0000000000000757
241. George MG, Tong X, Bowman BA. Prevalence of cardiovascular risk factors and strokes in younger adults. *JAMA Neurol*. 2017;74:695–703. doi: 10.1001/jamaneurol.2017.0020
242. Howard VJ, Madsen TE, Kleindorfer DO, Judd SE, Rhodes JD, Soliman EZ, Kissela BM, Safford MM, Moy CS, McClure LA, et al. Sex and race differences in the association of incident ischemic stroke with risk factors. *JAMA Neurol*. 2019;76:179–186. doi: 10.1001/jamaneurol.2018.3862
243. Jacob MA, Ekker MS, Allach Y, Cai M, Aarnio K, Arauz A, Arnold M, Bae HJ, Bandeo L, Barboza MA, et al. Global differences in risk factors, etiology, and outcome of ischemic stroke in young adults-a worldwide meta-analysis: the GOAL Initiative. *Neurology*. 2022;98:e573–e588. doi: 10.1212/WNL.0000000000013195
244. Ekker MS, Verhoeven JI, Schellekens MMI, Boot EM, van Alebeek ME, Brouwers P, Arntz RM, van Dijk GW, Gons RAR, van Uden IWM, et al. Risk factors and causes of ischemic stroke in 1322 young adults. *Stroke*. 2023;54:439–447. doi: 10.1161/STROKEAHA.122.040524
245. Bonardo P, León Cejas L, Mazziotti J, Zinnerman A, Fernández Pardal M, Martínez A, Riccio P, Ameriso S, Bendersky E, Nofal P, et al. AISYF: first national, prospective, multicenter study of young patients with stroke in Argentina. *Medicina (B Aires)*. 2021;81:588–596.
246. Hall EW, Vaughan AS, Ritchey MD, Schieb L, Casper M. Stagnating national declines in stroke mortality mask widespread county-level increases, 2010-2016. *Stroke*. 2019;50:3355–3359. doi: 10.1161/STROKEAHA.119.026695
247. Perera KS, de Sa Boasquevisque D, Rao-Melacini P, Taylor A, Cheng A, Hankey GJ, Lee S, Fabregas JM, Ameriso SF, Field TS, et al; Young ESUS Investigators. Evaluating rates of recurrent ischemic stroke among young adults with embolic stroke of undetermined source: the Young ESUS Longitudinal Cohort Study. *JAMA Neurol*. 2022;79:450–458. doi: 10.1001/jamaneurol.2022.0048
248. Pérez de la Ossa N, Abilleira S, Jovin TG, García-Tornel A, Jimenez X, Urra X, Cardona P, Cocho D, Purroy F, Serena J, et al. Effect of direct transportation to thrombectomy-capable center vs local stroke center on neurological outcomes in patients with suspected large-vessel occlusion stroke in nonurban areas: the RACECAT randomized clinical trial. *JAMA*. 2022;327:1782–1794. doi: 10.1001/jama.2022.4404
249. Regenhardt RW, Mecca AP, Flavin SA, Boulouis G, Lauer A, Zachrison KS, Boomhower J, Patel AB, Hirsch JA, Schwamm LH, et al. Delays in the air or ground transfer of patients for endovascular thrombectomy. *Stroke*. 2018;49:1419–1425. doi: 10.1161/STROKEAHA.118.020618
250. Ospel JM, Almekhlafi MA, Menon BK, Kashani N, Chapot R, Fiehler J, Hassan AE, Yavagal D, Majoie C, Jayaraman MV, et al. Workflow patterns and potential for optimization in endovascular stroke treatment across the world: results from a multinational survey. *J Neurointerv Surg*. 2020;12:1194–1198. doi: 10.1136/neurintsurg-2020-015902
251. Flores A, Seró L, Gomez-Choco M, Ustrell X, Pellisé A, Viñas J, Rodriguez P, Monterde A, Castilho G, Rubiera M, et al; Catalan Stroke Code and Reperfusion Consortium. The role of vascular imaging at referral centers in the drip and ship paradigm. *J Stroke Cerebrovasc Dis*. 2022;31:106209. doi: 10.1016/j.jstrokecerebrovasdis.2021.106209
252. Zheng S, Zhang T, Gu HQ, Zhang ZQ, Yang X, Wang C, Li H, Jiang Y, Shen H, Li Z, et al. Adherence to stroke care performance measures in different regions in China, 2015-2019: evidence from the Chinese Stroke Center Alliance. *Neurology*. 2022;99:e1767–e1778. doi: 10.1212/WNL.0000000000201024
253. Man S, Zhao X, Uchino K, Hussain MS, Smith EE, Bhatt DL, Xian Y, Schwamm LH, Shah S, Khan Y, et al. Comparison of acute ischemic stroke care and outcomes between comprehensive stroke centers and primary stroke centers in the United States. *Circ Cardiovasc Qual Outcomes*. 2018;11:e004512. doi: 10.1161/CIRCOUTCOMES.117.004512
254. Dong C, Gardener H, Rundek T, Marulanda E, Gutierrez CM, Campo-Bustillo I, Gordon Perue G, Johnson KH, Sacco RL, Romano JG; Transitions of Care Stroke Disparities Study (TCSD-S) Investigators. Factors and behaviors related to successful transition of care after hospitalization for ischemic stroke. *Stroke*. 2023;54:468–475. doi: 10.1161/STROKEAHA.122.040891
255. Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project (HCUP). Accessed April 1, 2023. http://hcupnet.ahrq.gov/
256. Centers for Disease Control and Prevention and National Center for Health Statistics. National Ambulatory Medical Care Survey (NAMCS) public use data files. Accessed April 1, 2023. https://cdc.gov/nchs/ahcd/datasets_documentation_related.htm#data
257. Ramirez L, Kim-Tenser MA, Sanossian N, Cen S, Wen G, He S, Mack WJ, Towfighi A. Trends in acute ischemic stroke hospitalizations in the United States. *J Am Heart Assoc*. 2016;5:e003233. doi: 10.1161/JAHA.116.003233
258. Kumar N, Khera R, Pandey A, Garg N. Racial differences in outcomes after acute ischemic stroke hospitalization in the United

States. *J Stroke Cerebrovasc Dis*. 2016;25:1970–1977. doi: 10.1016/j.jstrokecerebrovasdis.2016.03.049
259. Stein L, Tuhrim S, Fifi J, Mocco J, Dhamoon M. National trends in endovascular therapy for acute ischemic stroke: utilization and outcomes. *J Neurointerv Surg*. 2020;12:356–362. doi: 10.1136/neurintsurg-2019-015019
260. Mehta A, Fifi JT, Shoirah H, Singh IP, Shigematsu T, Kellner CP, De Leacy R, Mocco J, Majidi S. National trends in utilization and outcome of endovascular thrombectomy for acute ischemic stroke in elderly. *J Stroke Cerebrovasc Dis*. 2021;30:105505. doi: 10.1016/j.jstrokecerebrovasdis.2020.105505
261. Katsanos AH, Malhotra K, Ahmed N, Seitidis G, Mistry EA, Mavridis D, Kim JT, Veroniki AA, Maier I, Matusevicius M, et al. Blood pressure after endovascular thrombectomy and outcomes in patients with acute ischemic stroke: an individual patient data meta-analysis. *Neurology*. 2022;98:e291–e301. doi: 10.1212/WNL.0000000000013049
262. Yang P, Song L, Zhang Y, Zhang X, Chen X, Li Y, Sun L, Wan Y, Billot L, Li Q, et al; ENCHANTED2/MT Investigators. Intensive blood pressure control after endovascular thrombectomy for acute ischaemic stroke (ENCHANTED2/MT): a multicentre, open-label, blinded-endpoint, randomised controlled trial. *Lancet*. 2022;400:1585–1596. doi: 10.1016/S0140-6736(22)01882-7
263. Malhotra A, Wu X, Payabvash S, Matouk CC, Forman HP, Gandhi D, Sanelli P, Schindler J. Comparative effectiveness of endovascular thrombectomy in elderly stroke patients. *Stroke*. 2019;50:963–969. doi: 10.1161/STROKEAHA.119.025031
264. Wang J, Bai X, Wang T, Dmytriw AA, Patel AB, Jiao L. Carotid stenting versus endarterectomy for asymptomatic carotid artery stenosis: a systematic review and meta-analysis. *Stroke*. 2022;53:3047–3054. doi: 10.1161/STROKEAHA.122.038994
265. Krawisz AK, Rosenfield K, White CJ, Jaff MR, Campbell J, Kennedy K, Tsai T, Hawkins B, Jones S, Secemsky EA. Clinical impact of contralateral carotid occlusion in patients undergoing carotid artery revascularization. *J Am Coll Cardiol*. 2021;77:835–844. doi: 10.1016/j.jacc.2020.12.032
266. Yee EJ, Wang SK, Timsina LR, Ruiz-Herrera S, Liao JL, Donde NN, Fajardo AC, Motaganahalli RL. Propensity-matched outcomes of transcarotid artery revascularization versus carotid endarterectomy. *J Surg Res*. 2020;252:22–29. doi: 10.1016/j.jss.2019.12.003
267. Agency for Healthcare Research and Quality. Medical Expenditure Panel Survey (MEPS): household component summary tables: medical conditions, United States. Accessed April 2, 2023. https://meps.ahrq.gov/mepsweb/
268. Kaufman BG, Shah S, Hellkamp AS, Lytle BL, Fonarow GC, Schwamm LH, Lesen E, Hedberg J, Tank A, Fita E, et al. Disease burden following non-cardioembolic minor ischemic stroke or high-risk tia: a GWTG-Stroke study. *J Stroke Cerebrovasc Dis*. 2020;29:105399. doi: 10.1016/j.jstrokecerebrovasdis.2020.105399
269. Pines AR, Hagline JMD,B. Changes in Medicare physician reimbursement for stroke procedures from 2000 to 2019. *Neurosurg Open*. 2021;2:okab003. doi: 10.1093/neuopn/okab003
270. RTI International. Projections of cardiovascular disease prevalence and costs: 2015–2035: technical report [report prepared for the American Heart Association]. RTI International; 2016. RTI project No. 021480.003.001.001.
271. Global Burden of Disease Study and Institute for Health Metrics and Evaluation. University of Washington. Accessed August 2, 2023. http://ghdx.healthdata.org/
272. Markus HS, Martins S. COVID-19 and stroke: understanding the relationship and adapting services: a global World Stroke Organisation perspective. *Int J Stroke*. 2021;16:241–247. doi: 10.1177/17474930211005373
273. De Michele M, Kahan J, Berto I, Schiavo OG, Iacobucci M, Toni D, Merkler AE. Cerebrovascular complications of COVID-19 and COVID-19 vaccination. *Circ Res*. 2022;130:1187–1203. doi: 10.1161/CIRCRESAHA.122.319954
274. Paolucci M, Biguzzi S, Cordici F, Lotti EM, Morresi S, Romoli M, Strumia S, Terlizzi R, Vidale S, Menarini M, et al. Impact of COVID-19 pandemic on acute stroke care: facing an epidemiological paradox with a paradigm shift. *Neurol Sci*. 2021;42:399–406. doi: 10.1007/s10072-020-04914-4
275. Yoshimoto T, Yamagami H, Sakai N, Toyoda K, Hashimoto Y, Hirano T, Iwama T, Goto R, Kimura K, Kuroda S, et al. Impact of COVID-19 on the volume of acute stroke admissions: a nationwide survey in Japan. *Neurol Med Chir (Tokyo)*. 2022;62:369–376. doi: 10.2176/jns-nmc.2022-0099
276. White TG, Martinez G, Wang J, Gribko M, Boltyenkov A, Arora R, Katz JM, Woo HH, Sanelli PC. Impact of the COVID-19 pandemic on acute ischemic stroke presentation, treatment, and outcomes. *Stroke Res Treat*. 2021;2021:8653396. doi: 10.1155/2021/8653396
277. Risser C, Tran Ba Loc P, Binder-Foucard F, Fabacher T, Lefèvre H, Sauvage C, Sauleau EA, Wolff V. COVID-19 impact on stroke admissions during France's first epidemic peak: an exhaustive, nationwide, observational study. *Cerebrovasc Dis*. 2022;51:663–669. doi: 10.1159/000523685
278. Peng TJ, Jasne AS, Simonov M, Abdelhakim S, Kone G, Cheng YK, Rethana M, Tarasaria K, Herman AL, Baker AD, et al. Prior stroke and age predict acute ischemic stroke among hospitalized COVID-19 patients: a derivation and validation study. *Front Neurol*. 2021;12:741044. doi: 10.3389/fneur.2021.741044
279. Vidale S. Risk factors, and clinical and etiological characteristics of ischemic strokes in COVID-19-infected patients: a systematic review of literature. *Cerebrovasc Dis*. 2021;50:371–374. doi: 10.1159/000514267
280. Stierman B, Afful J, Carroll M, Chen T, Davy O, Fink S, Fryar C, Gu Q, Hales C, Hughes J, et al. National Health and Nutrition Examination Survey 2017-March 2020 prepandemic data files: development of files and prevalence estimates for selected health outcomes. *Natl Health Stat Rep*. 2021. Accessed November 20, 2023. https://www.cdc.gov/nchs/data/nhsr/nhsr158-508.pdf
281. Centers for Disease Control and Prevention and National Center for Health Statistics. National Health and Nutrition Examination Survey (NHANES) public use data files. Accessed April 1, 2023. https://gov/nchs/nhanes/
282. Kissela BM, Khoury J, Kleindorfer D, Woo D, Schneider A, Alwell K, Miller R, Ewing I, Moomaw CJ, Szaflarski JP, et al. Epidemiology of ischemic stroke in patients with diabetes: the greater Cincinnati/Northern Kentucky Stroke Study. *Diabetes Care*. 2005;28:355–359. doi: 10.2337/diacare.28.2.355
283. National Center for Health Statistics and National Vital Statistics System. Stroke death rates. Accessed November 20, 2023. https://www.cdc.gov/dhdsp/maps

# 16. BRAIN HEALTH

***ICD-9 290, 291.2, 291.8, 294, 331; ICD-10 F00–F03, G30–G31. See Tables 16-1 through 16-3 and Charts 16-1 through 16-4***

Click here to return to the Table of Contents

Click here to return to the Abbreviations

## Definition

Like CVH, brain health can be defined in terms of the absence of disease or the presence of a healthy state. Optimal brain health has been defined as "an optimal capacity to function adaptively in the environment."[1] This definition includes the capacity to perform all the diverse tasks for which the brain is responsible, including movement, perception, learning and memory, communication, problem solving, judgment, decision-making, and emotion. Stroke and cerebrovascular disease more broadly are now recognized to be important precursors and risk factors for cognitive decline and dementia; their presence indicates an absence of brain health. Conversely, evidence of systemic and cerebral vascular health has been associated with healthy aging and retained cognitive function.

Although this chapter provides prevalence and incidence estimates for dementia overall or unspecified, AD, and vascular dementia separately based on the published literature, the chapter authors acknowledge that most dementia pathology is mixed, with contributions of both AD and vascular dementia. Postmortem neuropathology studies suggest that ≈1 in 4 people who receive a clinical diagnosis of AD has non-AD pathology as a primary explanation for their dementia.[2] Notably, neither cognitive performance nor demographic variables appear to have any bearing on which patients diagnosed with MCI will develop postmortem pathology consistent with AD. In addition, vascular dementia prevalence and incidence are likely underestimated because (1) most dementia cases have multiple pathologies at autopsy, including signs of ischemia, and (2) vascular disease is common.[3,4] The list of *ICD* codes at the beginning of this chapter matches the list of codes for dementia used in the GBD Study, which encompasses all common types of dementia.[5] ADRD refers to AD and related dementias, including vascular contributions to cognitive impairment and dementia, frontotemporal degeneration, Lewy body dementia, and dementias of multiple causes.[6]

## Prevalence

### *Dementia*

- The estimated prevalence of dementia in US adults ≥65 years of age was 10.5% (SE, 0.49%) in 2012 according to data from the nationally representative HRS and its dementia substudy, ADAMS.[7] Dementia prevalence was 7.3% (SE, 0.47%) in males and 12.9% (SE, 0.64%) in females.
- A systematic analysis of data from the GBD Study showed that AD/ADRD was the fourth most prevalent neurological disorder in the United States in 2017, affecting 2.9 (95% UI, 2.6–3.2) million people.[8] Among neurological disorders, AD/ADRD was the leading cause of mortality in the United States (38 deaths per 100 000 population per year [95% UI, 38–39]), ahead of stroke.
- According to administrative claims data of US Medicare fee-for-service beneficiaries ≥65 years of age in 2014, AD/ADRD prevalence was 11.5% with a higher prevalence in females (12.2%) compared with males (8.6%).[9] AD/ADRD prevalence increased with age (65–74 years of age, 3.6%; 75–84 years of age, 13.6%; and ≥85 years of age, 34.6%). The prevalence of AD/ADRD was 13.8% in Black individuals, 12.2% in Hispanic individuals, 10.3% in NH White individuals, 9.1% in American Indian and Alaska Native individuals, and 8.4% in Asian and Pacific Islander individuals.
- Among the UDS cohort of the NACC (2005–2020), 26.8% of Black participants and 36.1% of White participants were diagnosed with dementia.[10] The most common dementia causes for White participants were AD (70.4%), frontotemporal degeneration (14.3%), and Lewy body dementia (6.7%). Black participants also had AD as the primary cause (70.4%) but had vascular dementia (5.0%) and then Lewy body dementia (4.0%) as the second and third most common clinical diagnoses, respectively.
- Of the 46.8 million people estimated to be living with dementia globally in 2015, 58% of them were living in low- or middle-income countries.[11] However, the predicted annual total cost of dementia per patient in 2015 was highest in higher-income countries: $10 467 for upper-middle–income countries compared with $3865 for low-middle–income countries and $939 for low-income countries.[12] However, a systematic review estimated that low-income countries had the highest total cost as a percentage of their gross domestic product (0.46%), followed by

The 2024 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2024. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

upper-middle–income countries (0.43%) and then low-middle–income countries (0.35%), dedicated to dementia care.[13]

### Alzheimer Disease

- Results of a multistate model using biomarker data and US population predictions show that ≈3.7 million Americans ≥30 years of age had clinical AD in 2017, and this number is projected to increase to 9.3 million by 2060.[14]
- In 2021, ≈6.2 million adults ≥65 years of age were living with AD. In other words, 11.3% of the US population, or ≈1 in 9 people, were living with AD.[15]

### Vascular Dementia

- Vascular dementia accounts for ≈5% to 10% of patients with dementia when both clinical and neuropathological criteria are used.[15] The prevalence is estimated to be between 15% and 20% in Europe and North America and as high as 30% in some Asian countries.[16]

## Incidence

### Dementia

- In 2017, AD/ADRD had the fifth leading incidence rate of neurological disorders in the United States, after tension-type headache, migraine, traumatic brain injury, and stroke, according to GBD Study data.[8] The US age-standardized incidence rate of AD/ADRD was 85 cases per 100 000 people (95% UI, 78–93).
- In a retrospective analysis of the HRS (N=3435), for up to 3 years after dementia onset, using the TICS to define dementia onset, Black individuals were less likely to receive a diagnosis of ADRD (unadjusted HR 0.73 [95% CI, 0.61–0.88]) compared with White respondents, with the effect estimate attenuated but remaining significant when adjusted for demographics, income, and level of education (HR, 0.79 [95% CI, 0.66–0.96]).[17]
- Among 1 869 090 veterans ≥55 years of age followed up for 10 years, there were differences in dementia incidence by ethnicity and race. Compared with White participants, Hispanic participants had the highest reported risk with an aHR of 1.92 (95% CI, 1.82–2.02), then Black participants with 1.54 (95% CI, 1.51–1.57), Asian participants with 1.20 (95% CI, 1.13–1.28), and American Indian/Alaska Native participants with 1.05 (95% CI, 0.98–1.13).[18]
- In a US cohort of >240 000 females diagnosed with breast cancer at ≥65 years of age with 26 years of follow-up, the incidence rate of dementia compared with White females (51.14 cases per 1000 person-years) was higher in Black females (64.94 cases per 1000 person-years; aHR versus White females, 1.16 [95% CI, 1.13–1.19]) and lower in Asian/Pacific Islander females (41.87 cases per 1000 person-years; aHR versus White females, 0.83 [95% CI, 0.79–0.86]).[19]

### Alzheimer Disease

- Among 2794 individuals from CHAP, the annual incidence of clinically diagnosed AD was 3.6% (95% CI, 3.3%–3.9%).[20] Black individuals had a higher annual incidence of clinically diagnosed AD (4.1% [95% CI, 3.7%–4.6%]) than White individuals (2.6% [95% CI, 2.3%–3.0%]). The annual incidence of clinically diagnosed AD increased with age in both Black and White individuals.
- In a US cohort of >240 000 females diagnosed with breast cancer at ≥65 years of age with 26 years of follow-up, incidence rate of AD compared with White females (18.74 cases per 1000 person-years) was higher in Black females (24.2 cases per 1000 person-years; aHR versus White females, 1.21 [95% CI, 1.16–1.27]) and lower in Asian/Pacific Islander females (13.35 cases per 1000 person-years; aHR versus White females, 0.77 [95% CI, 0.71–0.83]).[19]

### Vascular Dementia

- In a US cohort of >240 000 females diagnosed with breast cancer at ≥65 years of age with 26 years of follow-up, the incidence rate of vascular dementia compared with White females (7.2 cases per 1000 person-years) was higher in Black females (11.3 cases per 1000 person-years; aHR versus White females, 1.51 [95% CI, 1.39–1.64]) and lower in Asian/Pacific Islander females (5.58 cases per 1000 person-years; aHR versus White females, 0.67 [95% CI, 0.57–0.79]).[19]
- Data from the nationally representative MHAS 2012 and 2015 waves found that the age- and sex-standardized incidence of vascular dementia among individuals ≥50 years of age in Mexico was 2.0 (95% CI, 1.3–2.7) per 1000 person-years.[21]

## Lifetime Risk and Cumulative Incidence

### Dementia

- In a population-based Japanese cohort of individuals ≥60 years of age, the lifetime risk of dementia was 54.8% (95% CI, 49.4%–60.1%); elderly females had a greater lifetime risk (64.8% [95% CI, 57.4%–72.1%]) than elderly males (40.8% [95% CI, 33.0%–48.5%]).[22]
- Among participants in the Monzino 80-Plus population-based cohort study from Italy, the lifetime risk of dementia at 80 years of age was 55.9% (95% CI, 51.6%–59.8%) and was higher for females (63.0% [95% CI, 58.4%–67.3%]) than for males (42.9% [95% CI, 34.6%–51.0%]).[23]
- According to nationwide individually linked cause-of-death and health register data in the Netherlands,

the lifetime risk of dementia (estimated by the proportion of deaths in the presence of dementia) was ≈24.0%, higher for females (29.4%) than males (18.3%).[24]

### Alzheimer Disease

- In the FHS, the lifetime risk of AD at 45 years of age was 19.5% (95% CI, 17.8%–21.2%) for females and 10.3% (95% CI, 8.9%–11.8%) for males.[25]
- In a population-based Japanese cohort of individuals ≥60 years of age, the lifetime risk of AD was ≈2-fold higher for females (42.4% [95% CI, 35.1%–49.7%]) than for males (20.4% [95% CI, 6.6%–34.2%]).[22]

### Vascular Dementia

- In a population-based Japanese cohort of individuals ≥60 years of age, the estimated lifetime risk of vascular dementia was similar among females (16.3% [95% CI, 11.5%–21.1%]) and males (17.8% [95% CI, 12.9%–22.7%]).[22]

## Secular Trends

### Dementia

- According to an analysis of GBD Study data from 1990 to 2017, age-standardized incidence rates of AD/ADRD in the United States decreased from 97.2 per 100 000 to 85.2 per 100 000 (12.4% decrease [95% UI, 5.2%–19.2%]), age-standardized prevalence decreased from 542.7 per 100 000 to 470.0 per 100 000 (13.4% decrease [95% UI, 5.1%–20.6%]), but mortality rates increased from 35.0 per 100 000 to 38.5 per 100 000 (9.8% increase [95% UI, 7.3%–12.2%]) and DALY rates increased from 413.6 per 100 000 to 418.8 per 100 000 (1.2% increase [95% UI, 1.9% decrease–4.2% increase]).[8]
- Between 1990 and 2019, the GBD Study estimated a significant increase in age-standardized mortality rates from dementia for males of 5.1% (95% CI, 0.4%–12.0%) and a nonsignificant increase for females of 3.0% (95% CI, −2.6% to 11.0%).[26] The all-age mortality rate from dementia increased 100.1% (95% CI, 89.1%–117.5%).
- The GBD Study estimated secular trends from 1990 to 2017 in dementia prevalence, incidence, DALYs, and mortality, globally and for high-income countries.[27] Globally, prevalent cases increased by 119% (95% UI, 115%–123%); annual incident cases increased by 113% (95% UI, 109%–118%); DALYs increased by 115% (95% UI, 109%–120%); and annual deaths increased by 146% (95% UI, 140%–151%). However, global age-standardized prevalence decreased by 4% (95% UI, 4%–5%); age-standardized annual incidence decreased by 5% (95% UI, 5%–6%); age-standardized DALYs decreased by 6% (95% UI, 4%–8%); and age-standardized annual mortality decreased by 4% (95% UI, 2%–6%). For high-income countries, percent increases in absolute burden measures were smaller than globally: Prevalent cases increased by 93% (95% UI, 87%–99%); annual incident cases increased by 87% (95% UI, 81%–94%); DALYs increased by 90% (95% UI, 86%–94%); and annual deaths increased by 126% (95% UI, 122%–130%). The age-standardized prevalence in high-income countries decreased by 5% (95% UI, 4%–7%); age-standardized annual incidence rate decreased by 6% (95% UI, 4%–7%); age-standardized DALYs decreased by 7% (95% UI, 6%–9%); and age-standardized annual mortality rate decreased by 4% (95% UI, 3%–6%).
- A forecasting analysis based on the GBD Study 2019 projected stable age-standardized prevalence (global percentage change of 0.1% [−7.5% to 10.8%]) but an increase in the number of people living with dementia from 2019 to 2050, attributed largely to population growth and aging (57.4 [95% UI, 50.4–65.1] million cases in 2019 to 152.8 [95% UI, 130.8–175.9]) million cases in 2050.[28] More females were estimated to be living with dementia in 2019 (RR, 1.69 [95% CI, 1.64–1.73]) and 2050 (RR, 1.67 [95% CI, 1.52–1.85]) compared with males.
- Data from the nationally representative HRS provide evidence that the prevalence of dementia among individuals ≥65 years of age declined significantly in the United States from 12.2% (95% CI, 11.7%–12.7%) in 2000 to 8.5% (95% CI, 7.9%–9.1%) in 2016.[29]
- An analysis of Medicare data estimates that the AD/ADRD prevalence in the US population will increase to 3.3% and affect 13.9 million Americans by 2060.[9]
- In an analysis of 2 population-based cohort studies from Sweden, the incidence rate of dementia declined ≈30% (HR, 0.70 [95% CI, 0.61–0.80]) from the late 1980s to the early 2010s in adults ≥75 years of age.[30] The decline in dementia incidence was present even after adjustment for education, psychosocial working conditions, lifestyle factors, and vascular disease (HR, 0.77 [95% CI, 0.65–0.90]).
- In a cohort study of Danish older adults ≥65 years of age, from 2005 to 2018, the incidence of dementia declined by 22.5% in males and 34.2% in females.[31] After accounting for changes in age, the overall incidence of dementia decreased by 18.1% in males and 23.5% in females. Individuals with high educational attainment (10% males, 14.7% females), high household wealth (12.1% males, 21.4% females), no history of stroke (7.0% males, 15.6% females),

and low medication use (21% males, 19.7% females) had a lower incidence of dementia than the general population but with a similar pattern of decline over time.
- An analysis of 7 population-based cohort studies in the United States and Europe demonstrated that for individuals >65 years of age, the incidence of all-cause dementia declined by 13% (95% CI, 7%–19%) per calendar decade from 1998 through 2015 with a more pronounced reduction in males (24% [95% CI, 14%–32%]) than in females (8% [95% CI, 0%–15%]).[32]
- A meta-analysis of 53 cohorts demonstrated a decrease in dementia incidence across 3 older age groups (65–74, 75–84, and ≥85 years of age).[33] Each 10-year increase in birth year was associated with a reduction in the odds of incident dementia for individuals reaching each of the older age groups (OR, 0.20 [95% CI, 0.18–0.22] for individuals reaching 65 to 74 years of age; OR, 0.20 [95% CI, 0.19–0.21] for those 75 to 84 years of age; and OR, 0.72 [95% CI, 0.58–0.90] for individuals ≥85 years of age).
- In the HRS, a nationally representative study of adults ≥50 years of age in the United States, dementia prevalence estimates obtained every 2 years from 2000 to 2016 ranged between 1.5 and 1.9 times as high in NH Black individuals as in NH White individuals, standardized for age and sex.[34] Dementia incidence estimates obtained every 2 years from 2000 to 2016 ranged between 1.4 and 1.8 times as high in NH Black individuals as in NH White individuals, standardized for age and sex. There was no evidence of a significant decrease in the racial difference over time (*P* ranging from 0.55–0.98 for tests of trend over time).
- In contrast to declining trends of dementia typically reported in high-income countries, Africa represents an understudied continent with a paucity of data available. Over a 9-year interval from 2009 to 2010 to 2018 to 2019, there was an increase in dementia prevalence from 6.4% to 8.9% among those >70 years of age in Tanzania.[35] It is estimated that 212 million individuals ≥60 years of age will be living in Africa by the year 2050, suggesting a rapidly aging population.[36]

### *Alzheimer Disease*

- In an analysis of 7 population-based cohorts in the United States and Europe from the Alzheimer Cohort Consortium, among individuals >65 years of age, the incidence of clinical AD declined by 16% (95% CI, 8%–24%) per calendar decade from 1998 through 2015.[32]
- A meta-analysis of 35 cohorts demonstrated no significant decrease in the AD incidence rates across 3 older age groups (65–74 years, *P*=0.26; 75–84 years, *P*=0.90; and ≥85 years of age, *P*=0.54).[33] Although AD incidence rates were stable in Western countries, studies from non-Western countries demonstrated a significant increase in incidence rates for the age group of 65 to 74 years (OR, 2.78 [95% CI, 1.33–5.79]; *P*=0.04). No significant sex differences in AD incidence were found.
- A population-based cross-sectional study of US data from the WHO Mortality Database showed that age-adjusted mortality for AD increased 1.2-fold from 2007 to 2016 (from 244.3 per 1 000 000 individuals in 2007 to 301.1 per 1 000 000 individuals in 2016).[37] In contrast, age-adjusted stroke mortality decreased by 21.6% during the same time period (from 358.4 per 1 000 000 in 2007 to 281.2 per 1 000 000 in 2016).

### *Vascular Dementia*

- For FHS participants ≥60 years of age, the 5-year age- and sex-adjusted hazard rate of vascular dementia declined over 4 epochs of time from 0.8 per 100 individuals (95% CI, 0.6–1.3) in the late 1970s and early 1980s to 0.4 per 100 individuals (95% CI, 0.2–0.7) in the late 2000s and early 2010s ($P_{trend}$=0.004).[38]
- Based on a population-based cross-sectional study of US data from the WHO Mortality Database, age-adjusted mortality for vascular dementia increased by 2-fold from 2007 to 2016 (from 19.2 per 1 000 000 individuals in 2007 to 38.5 per 1 000 000 individuals in 2016).[37]

## Risk Factors

Vascular risk factors are increasingly recognized as the most important cluster of risk factors for brain health, particularly because of their high prevalence and potential for modification.

### *Blood Pressure*

- There is consistent and substantial evidence for the role of BP, including hypertension, as a risk factor for cognitive decline and dementia. In a meta-analysis, midlife hypertension was associated with impairment in global cognition (RR, 1.55 [95% CI, 1.19–2.03]; 4 studies) and executive function (RR, 1.22 [95% CI, 1.06–1.41]; 2 studies), in addition to dementia (RR, 1.20 [95% CI, 1.06–1.35]; 9 studies) and AD (RR, 1.19 [95% CI, 1.08–1.32]; 4 studies).[39]
- In the Whitehall II cohort study (N=8639; 33% females), elevated BP, defined as SBP ≥130 mm Hg at 50 years of age, was associated with increased risk of dementia (HR, 1.38 [95% CI, 1.11–1.70]). Although elevated BP in late life was not associated with greater risk of dementia, longer duration

of elevated BP (exposure between 45 and 61 years of age [mean]) was also associated with risk of dementia (HR, 1.29 [95% CI, 1.00–1.66]).[40]

- Among 2718 adults in CARDIA, longer duration of hypertension from early to middle adulthood was associated with significantly lower midlife scores on a measure of verbal memory (Rey Auditory Verbal Learning Test; 0.18 points lower [95% CI, 0.07–0.29 points lower]; *P*=0.002 per 5 additional years' duration) and with lower midlife scores, but not reaching statistical significance, on a measure of processing speed (digit symbol substitution test; 0.43 points lower [95% CI, 0.10 points higher–0.95 points lower]; *P*=0.112 per 5 additional years' duration) but not with a measure of executive function (Stroop test; 0.01 points lower [95% CI, 0.37 points higher–0.39 points lower]; *P*=0.975 per 5 additional years' duration).[41] Lower scores on verbal memory with longer hypertension duration were observed whether hypertension was controlled or uncontrolled.
- BP in early adulthood may also be associated with worse cognitive health. In a study that pooled data from 4 observational cohorts of adults between 18 and 95 years of age at enrollment (N=15 001; 34% Black participants; 55% females), early adult vascular risk factors were associated with late-life cognitive decline.[42] Vascular risk factors were imputed across the life course in early adulthood, midlife, and late life for older adults. Early-adult elevated SBP was associated with an approximate doubling of mean 10-year decline in late life, even after adjustment for SBP exposure at midlife and late life.
- In a meta-analysis of 3 studies including >2.3 million females, HDP was not significantly associated with higher risk for dementia (fixed-effects pooled HR, 1.08 [95% CI, 0.93–1.25]).[43]
- Elevated and increasing BP from early adulthood to midlife (36–53 years of age) was associated with greater WMH volume (but not amyloid deposition) in late life in the Insight 46 cohort (N=499; 49% females).[44]
- In a meta-analysis of 8 studies including between 1000 and 8000 participants, depending on cognitive domain, arterial hypertension was cross-sectionally associated with poorer performance on measures of processing speed (standardized mean difference, 0.40 [95% CI, 0.25–0.54]), working memory (0.28 [95% CI, 0.15–0.41]), short-term memory and learning (–0.27 [95% CI, –0.37 to –0.17]), and delayed recall (–0.20 [95% CI, –0.35 to –0.05]).[45]
- In studies of late-life hypertension, there is often no association or a protective association between hypertension and cognitive outcomes, particularly among the oldest old.[42,46,47] Among 17 286 older adults (mean age, 74.5 years) in 7 pooled cohorts in Europe and the United States with 2799 incident dementia cases over a median of 7.3 years of follow-up, SBP at baseline had a U-shaped association with dementia risk, and the lowest dementia risk was observed at SBP of 185 mm Hg (95% CI, 161–230).[48] The U-shaped relationship was more prominent in the oldest age groups, with lowest-risk SBP of 170 mm Hg (95% CI, 160–260) at 75 to 85 years of age and lowest-risk SBP of 162 mm Hg (95% CI, 153–240) at 85 to 95 years of age.
- Older adults randomized to intensive BP control in SPRINT (a subset with MRI at baseline and follow-up; N=454) had greater declines in hippocampal volume over 4 years compared with those on standard treatment (β=–0.033 $cm^3$ [95% CI, –0.062 to –0.003]; *P*=0.03).[49]
- Among 3319 older adults in the S.AGES cohort in France (mean age, 78 years; 57% females), BP variability may also be a marker of risk for poor brain health outcomes. Greater visit-to-visit SBP, DBP, and mean arterial BP variability, measured every 6 months over 3 years, was associated with worse global cognition (for each 1-SD increase of coefficient of variation: β=–0.12 [SE, 0.06], –0.20 [SE, 0.06], and –0.20 [SE, 0.06], respectively; *P*<0.05 for all) and risk of dementia (for each 1-SD increase of coefficient of variation: HR, 1.23 [95% CI, 1.01–1.50], 1.28 [95% CI, 1.05–1.56], and 1.35 [95% CI, 1.12–1.63], respectively).[50] Among 12 298 adults in HRS and ELSA who were free of dementia at baseline, each 10% increment in coefficient of variation of visit-to-visit SBP variability was associated with 0.026–SD/y faster (95% CI, 0.016–0.036) global cognitive decline and each 10% increment in DBP variability with 0.022–SD/y faster (95% CI, 0.017–0.027) global cognitive decline.[51] Among 19 114 participants in the ASPREE trial, males in the highest SBP variability tertile compared with the lowest had higher incidence of dementia (HR, 1.68 [95% CI, 1.19–2.39]), but females in the highest tertile did not (HR, 1.01 [95% CI, 0.98–1.32]).[52] Among 13 284 adults ≥50 years of age in the NACC study who were dementia free at baseline, those in the highest quintile of visit-to-visit SBP variability had 2.64 times the odds (95% CI, 2.29–3.04) of conversion from normal cognition to cognitive impairment or dementia.[53]
- Among 8493 older adults (mean age, 80.6 years) in the Chinese Longitudinal Healthy Longevity Survey, those whose SBP increased from 130 to 150 mm Hg at baseline to >150 mm Hg at follow-up had 48% higher odds (95% CI, 13%–93%) of incident cognitive impairment and those whose SBP decreased from 130 to 150 mm Hg at baseline to <130 mm Hg at follow-up had 28% higher odds

(95% CI, 2%–61%) of incident cognitive impairment compared with those who maintained stable SBP from 130 to 150 mm Hg.[54]

- In ARIC (N=4761; 21% Black participants; 59% females), hypertension (both mid and late life) was associated with increased risk of dementia compared with normal BP at both time periods (HR, 1.49 [95% CI, 1.06–2.08]).[55] A pattern of hypertension in midlife with hypotension in late life was also associated with increased risk of dementia (HR, 1.62 [95% CI, 1.11–2.37]).
- Orthostatic hypotension (a decrease of ≥15 mm Hg in SBP or ≥7 mm Hg in DBP after 2 minutes standing from a sitting position) in the HYVET cohort was associated with greater cognitive decline (HR, 1.39 [95% CI, 1.1–1.62]) and dementia (HR, 1.34 [95% CI, 1.05–1.73]) over 2 years. In a meta-analysis, HYVET results were pooled with results from 4 other studies of orthostatic hypotension, with a pooled risk ratio of dementia of 1.21 (95% CI, 1.09–1.35).[56]
- Aortic stiffness, measured by carotid-femoral PWV, was also associated with increased risk of dementia (HR, 1.60 [95% CI, 1.02–2.51]) over 15 years in the CHS Cognition Study (N=356; mean age, 78 years; 22% Black participants; 59% females).[57]
- In a cross-sectional study (ARIC-PET; N=321; mean age, 76 years; 45% Black participants; 43% females), central arterial stiffness was associated with greater amyloid burden (OR, 1.31 [95% CI, 1.01–1.71]) and WMH burden (OR, 1.6 [95% CI, 1.2–2.1]), as well as lower brain volume in regions vulnerable to AD (in cubic millimeters; β=−1.5 [SD, 0.7]; *P*=0.03), including the precuneus.[58]
- An individual patient meta-analysis of 19 378 participants from 5 cohort studies found that differences between Black and White individuals in global cognition decline were no longer statistically significant after adjustment for cumulative mean SBP, suggesting that Black individuals' higher cumulative BP levels might contribute to racial disparities in cognitive decline.[59]

## Cardiac Dysfunction

### Heart Failure

- A diagnosis of HF is associated with cognitive decline. Among 4864 males and females in CHS initially free of HF and stroke, 496 participants who developed incident HF had greater adjusted declines over 5 years on the modified MMSE than those without HF (10.2 points [95% CI, 8.6–11.8] versus 5.8 points [95% CI, 5.3–6.2]).[60] The effect did not vary significantly by HFrEF versus HFpEF.
- In a meta-analysis of 4 longitudinal studies, the pooled risk ratio for dementia associated with HF was 1.80 (95% CI, 1.41–2.31).[61]
- Among 6336 patients, the 1-year and 3-year cumulative incidences of ADRD after incident HF diagnosis were 7.6% (95% CI, 6.9%–8.3%) and 17.1% (95% CI, 16.2%–18.0%), respectively.[62] Patients with ADRD diagnosed after HF had a 3.7 times increased risk of death (95% CI, 3.34–4.10) compared with those who did not develop ADRD, even after adjustment for vascular risk factors, marital status, and education.

### Atrial Fibrillation

- AF is a potential risk factor associated with both cognitive decline and dementia. In ARIC-NCS (N=12 515; mean age, 57 years; 24% Black participants; 56% females), AF was associated with greater cognitive decline over 20 years (global cognitive *Z* score, 0.115 [95% CI, 0.014–0.215]). Risk of dementia was also elevated in participants with AF compared with those without (HR, 1.23 [95% CI, 1.04–1.45]).[63] Among 25 980 adults in REGARDS, those with AF at baseline declined in mean word list learning score over 10 years of follow-up (decline in mean score from 16.3 [SD, 0.15] to 16.0 [SD, 0.23]), whereas those without AF at baseline increased in mean word list learning score (increase in mean score from 16.3 [SD, 0.05] to 16.9 [SD, 0.06]; *P*=0.03 for AF versus no AF); however, there were no significant differences in trajectories of semantic fluency, word list delayed recall, or Montreal Cognitive Assessment score.[64] In a meta-analysis of 18 studies including 3.5 million participants with >900 000 cases of incident dementia, AF was associated with 41% higher (28%–54%) hazard of dementia ($I^2$=94% indicating high heterogeneity, although 15 of 18 study-specific HRs fell between 1.10 and 2.00).[65]
- Evidence for the possible benefits of anticoagulant therapy to mitigate this risk relationship is conflicting, with some studies reporting benefits and others not.[66,67] In SNAC-K, AF was associated with increased risk of all-cause as well as vascular and mixed dementia (HR, 1.40 [95% CI, 1.11–1.77] and 1.88 [95% CI, 1.09–3.23], respectively); however, anticoagulant users with AF were less likely to develop dementia (HR, 0.40 [95% CI, 0.18–0.92]) compared with nonusers with AF.[66] In a meta-analysis of 9 studies including 613 920 patients with AF, anticoagulant treatment was associated with 28% lower (14%–40% lower) risk of dementia compared with no treatment, albeit with high heterogeneity of study-specific findings ($I^2$=97%).[68] However, in a study of 407 871 older adults enrolled in the US Veterans Health Administration, AF was associated with increased risk of dementia (OR, 1.14 [95% CI, 1.07–1.22]); anticoagulant use among those with AF also was associated with increased risk of dementia (OR, 1.44 [95% CI, 1.27–1.63]).[67]

- Among 39 200 new users of oral anticoagulants in the General Practice Research Database in the United Kingdom with 1258 cases of incident dementia, treatment with DOACs was associated with 16% lower hazard of dementia (95% CI, 2%–27% lower) and 26% lower hazard of MCI (95% CI, 16%–35% lower) than treatment with vitamin K antagonists.[69] Among 53 236 new users of oral anticoagulants in the Korean National Health Insurance Service database identified in 2013 to 2016 with 2194 cases of incident dementia through the end of 2016, treatment with DOACs was associated with 22% lower hazard of dementia (95% CI, 10%–31% lower) than treatment with warfarin.[70] However, in another analysis among 72 846 new users of oral anticoagulants in the Korean National Health Insurance Service database identified in 2014 to 2017 with 4437 cases of incident dementia through the end of 2018, treatment with DOACs compared with warfarin was not associated with dementia risk (HR, 0.99 [95% CI, 0.93–1.06]).[71] Among 12 068 patients with AF in the Taiwan National Health Insurance Research database, treatment with DOACs was associated with 18% lower hazard (8%–27% lower) of dementia than treatment with warfarin.[72] Last, in a meta-analysis of 9 studies including 611 069 participants, treatment with DOACs was associated with 44% lower odds (85% CI, 6%–66% lower) of incident dementia than treatment with warfarin.[73]
- In a systematic review of 10 studies with 15 886 patients treated with catheter ablation and 42 684 patients treated with medical therapy (rate or rhythm control), 4 studies reported risk of dementia with the pooled-effect estimate suggesting a decreased risk of incident dementia among those who underwent ablation (HR, 0.60 [95% CI, 0.42–0.88]).[74] These results, however, are limited by an inability to assess for publication bias because of the small number of studies included.

### *Coronary Disease*

- Regarding coronary revascularization procedures, the evidence for an association between either CABG or PCI and later-life dementia is contradictory, although most studies do not suggest an association. One RCT did not suggest a difference in cognitive decline between PCI or CABG after 7.5 years of follow-up.[75] Among 1680 participants (mean age, 75 years at the time of procedure) in the HRS, there was also no significant difference in the rate of memory decline between those undergoing PCI and those undergoing CABG.[76] In CHS, there was an association between CABG and all-cause dementia (HR, 1.93 [95% CI, 1.36–2.74]) compared with those without a history of CABG.[77] Fewer studies have investigated PCI versus medical therapy and the risk of dementia, with 1 cohort study suggesting a lower risk of dementia in the PCI group (HR, 0.65 [95% CI, 0.46–0.84]) compared with the medically managed group.[78]
- Among a prospective cohort of 3146 participants in the CARDIA study (mean age, 55; 57% females, 48% Black), premature CVD (≤60 years of age) was associated with worse midlife global cognition (−0.22 [95% CI, −0.37 to −0.08]), verbal memory (−0.28 [95% CI, −0.44 to −0.12]), processing speed (−0.46 [95% CI, −0.62 to −0.31]), and executive function (−0.38 [95% CI, −0.55 to −0.22]).[79] Early CVD was also associated with greater brain MRI WMH and lower white matter integrity, as well as accelerated cognitive decline over 5 years (aOR, 3.07 [95% CI, 1.56–5.71]).
- In a study from the NCDR Chest Pain–MI Registry of 43 812 participants >65 years of age with MI, MCI was found in 3.9% of those presenting with an STEMI and in 5.7% of those presenting with an NSTEMI.[80] After adjustment for potential confounders, MCI was associated with a higher risk of all-cause in-hospital mortality (STEMI cohort: OR, 1.3 [95% CI, 1.1–1.5]; NSTEMI cohort: OR, 1.3 [95% CI, 1.2–1.5]). In addition, among those presenting with STEMI, PCI use was relatively similar in those with MCI (92.8%) and those without cognitive impairment (92.1%), but fibrinolytic use was lower in those with MCI (27.4%) than in those without cognitive impairment (40.9%). Last, among patients with NSTEMI, rates of angiography, PCI, and CABG were 50.3%, 27.3%, and 3.3% in those with MCI compared with 84.7%, 49.4%, and 10.9% in those without cognitive impairment.

### *Subclinical Cardiac Disease*

- Subclinical measures of cardiac dysfunction also may be associated with brain health outcomes. In particular, LV hypertrophy, measured by LV mass index, has been associated with increased risk of cognitive decline and dementia and worse white matter structure in late life.[81,82]
- In MESA (N=4999; mean age, 61 years; 47% males; 26% Black, 22% Hispanic, and 13% Chinese participants; median follow-up, 12 years), both LV mass index and ratio of LV mass to volume were associated with increased risk of dementia (HR, 1.01 [95% CI, 1.00–1.02] and 2.37 [95% CI, 1.25–4.43], respectively).[82] LV hypertrophy and remodeling also were associated with worse global cognition, processing speed, and executive function. Studies suggest that this association is also significant for cognitive and brain MRI outcomes in middle-aged adults.[83]
- In ARIC (N=5078), a state of atrial cardiopathy was associated with an increased risk of dementia (HR,

1.35 [95% CI, 1.16–1.58]), and only a small portion of the effect was mediated by either AF (4%; *P*=0.005) or ischemic stroke (9%; *P*=0.048).[84]

### *Poststroke*

***See Chapter 15 (Stroke [Cerebrovascular Diseases]).***

### *Diabetes*

- Diabetes is associated with risk of both vascular dementia and AD. In a meta-analysis of 14 studies (N=2 310 330, with 102 174 patients with dementia), diabetes was associated with an independent increased risk of any dementia in both females (pooled RR, 1.62 [95% CI, 1.45–1.80]) and males (pooled RR, 1.58 [95% CI, 1.38–1.81]).[85] The risk of vascular dementia was 2.34 (95% CI, 1.86–2.94) in females and 1.73 (95% CI, 1.61–1.85) in males; the risk of nonvascular dementia was 1.53 (95% CI, 1.35–1.73) in females and 1.49 (95% CI, 1.31–1.69) in males. Among 63 117 postmenopausal females in the WHI observational study in the United States with 8340 cases of incident AD over a median follow-up of 20 years, diabetes was associated with 22% higher hazard (95% CI, 13%–31% higher) of AD. Incidence of AD was 8.5 cases per 1000 person-years (95% CI, 8.0–9.0) for females who had diabetes versus 7.1 cases per 1000 person-years (95% CI, 6.9–7.2) for females without diabetes.[86]
- In a mendelian randomization study of 115 875 adults, the risk ratio for 1–mmol/L (18–mg/dL) higher plasma glucose level and risk of dementia was 2.40 (95% CI, 1.18–4.89). The results were not significant for vascular dementia or AD.[87]
- Other studies also have demonstrated an association between elevated glucose levels in early adulthood to midlife and worse midlife cognitive outcomes among participants without diabetes.[42,88,89]
- HbA1c variability may be an indicator of increased risk for worse cognitive outcomes. In a study that pooled cohort data from the HRS and ELSA (N=6237; mean age, 63 years; 58% females; median follow-up, 11 years), the highest quartile of HbA1c variability compared with the lowest quartile was associated with greater decline in memory (β=–0.094 SD/y [95% CI, –0.185 to –0.003]) and executive function (–0.083 SD/y [95% CI, –0.125 to –0.041]). This association was significant even among those without diabetes.[90] In a meta-analysis of 5 longitudinal studies including >500 000 participants with diabetes with a mean follow-up of 6 years, risk of dementia was 6% higher (95% CI, 0.3%–12% higher) per increment in visit-to-visit HbA1c coefficient of variation across studies and 19% higher (95% CI, 6%–32% higher) per increment in visit-to-visit HbA1c SD across studies.[91]
- A history of hypoglycemia is also associated with worse brain health outcomes. In ARIC (N=580), there was a significant cross-sectional association between hypoglycemia and reduced total brain volume (β=–0.308 [95% CI, –0.612 to –0.004]). In a prospective analysis (N=1263; median follow-up, 14 years), hypoglycemia was associated with increased risk of developing dementia (RR, 2.54 [95% CI, 1.78–3.63]).[92] In a meta-analysis of 9 studies of older adults treated with glucose-lowering drugs, experiencing hypoglycemic episodes was associated with 50% higher odds (95% CI, 29%–74% higher) of dementia.[93] In another meta-analysis of 10 studies including >1.4 million participants with type 2 diabetes, hypoglycemic episodes were associated with 44% higher risk (95% CI, 26%–65% higher) of dementia.[94]
- Investigators have observed associations between lower fasting insulin and risk of dementia. In the PPSW (N=1212 females without diabetes; mean age, 48 years), fasting serum insulin at baseline was categorized into tertiles. Among those in the lowest tertile of fasting insulin, there was an increased risk of dementia over 34 years (HR, 2.34 [95% CI, 1.52–3.58]) compared with those with fasting insulin in the middle tertile.[95]
- Diabetes is associated with worse cognitive functioning and faster cognitive decline. In cross-sectional analysis of UK Biobank participants, 914 participants with type 2 diabetes scored significantly lower than matched healthy participants on measures of executive function, processing speed, abstract reasoning, and numeric memory; they scored similarly on a measure of reaction time (Chart 16-1B).[96] In meta-analyses of 34 studies conducted by the same authors, 4735 participants with type 2 diabetes scored significantly lower than 17 496 healthy participants on 10 of 11 cognitive domains assessed (Chart 161C).[96] In longitudinal analysis of ELSA participants with a median follow-up of 13 years, 576 participants experiencing incident diabetes declined faster on measures of global cognition (0.035 SD/y faster [95% CI, 0.015–0.054]), orientation (0.031 SD/y faster [95% CI, 0.002–0.060]), memory (0.016 SD/y faster [95% CI, 0.003–0.029]), and executive function (0.027 SD/y faster [95% CI, 0.013–0.042]) after diabetes onset than participants without diabetes.[97]
- Late-life diabetes, poor glycemic control among those with diabetes, and diabetes duration (≥5 years) were also associated with greater risk of MCI/dementia in ARIC (HR, 1.14 [95% CI, 1.00–1.31], 1.31 [95% CI, 1.05–1.63], and 1.59 [95% CI, 1.23–2.07], respectively). Late-life higher HbA1c (>7.5%, 58 mmol/mol) and lower HbA1c (<5.8%, 40 mmol/mol) were also associated with increased

risk of MCI/dementia compared with HbA1c in the midrange.[98]

### Chronic Kidney Disease

- Among 90 369 adults in the CGPS, of whom 2468 developed dementia over 15 years of follow-up, age- and sex-standardized percentile of eGFR below the median versus above was associated with 9% higher risk of dementia (95% CI, 1%–18% higher).[99] In a meta-analysis of >460 000 Scandinavian adults conducted by the same authors, there was a dose-response pattern: Risk of dementia was 1.14 times as high (95% CI, 1.06–1.22) for eGFR 60 to 90 mL·min$^{-1}$·1.73 m$^{-2}$, 1.31 times as high (95% CI, 0.92–1.87) for eGFR 30 to 59 mL·min$^{-1}$·1.73 m$^{-2}$, and 1.91 times as high (95% CI, 1.21–3.01) for eGFR <30 mL·min$^{-1}$·1.73 m$^{-2}$ relative to eGFR >90 mL·min$^{-1}$·1.73 m$^{-2}$.[99]
- Among 6050 adults in the Whitehall II Study, of whom 306 developed dementia over a mean 10 years of follow-up, eGFR <60 mL·min$^{-1}$·1.73 m$^{-2}$ at baseline was associated with 37% higher risk of dementia (95% CI, 1%–85% higher), and decline in eGFR of ≥4 mL·min$^{-1}$·1.73 m$^{-2}$ over ≈4 years was associated with 37% higher risk of subsequent dementia (95% CI, 2%–85% higher).[100]
- Albuminuria and eGFR, defined by cystatin C and β-2-microglobulin, were associated with increased risk of dementia on average 12 years later in ARIC (N=9967 without dementia, ESRD, or stroke; mean age, 63 years; 20% Black participants; 57% female).[101]
- In a meta-analysis of 16 studies (some longitudinal and some cross-sectional) including >120 000 participants, of whom 5488 had or developed cognitive impairment and 1266 had or developed dementia, albuminuria was associated with 1.18 times the odds of cognitive impairment (95% CI, 1.09–1.27), 1.32 times the odds of dementia (95% CI, 1.10–1.58), 1.33 times the odds of AD (95% CI, 1.06–1.67), and 2.32 times the odds of vascular dementia (95% CI, 1.59–3.38).[102]
- Among 10 567 older adults undergoing hemodialysis with 1302 cases of incident dementia over a median follow-up of 3.8 years, patients in the highest quartile of dialysis adequacy had 31% lower hazard of dementia (HR, 0.69 [95% CI, 0.58–0.82]) and 31% lower hazard of AD (HR, 0.69 [95% CI, 0.57–0.84]) than patients in the lowest quartile of dialysis adequacy.[103]

### Obesity

- Midlife overweight and obesity are associated with increased risk of cognitive impairment and dementia. In a meta-analysis of 11 longitudinal studies including >64 000 participants, midlife overweight compared with normal weight was associated with 1.14 times the risk of cognitive impairment and dementia (95% CI, 0.98–1.32), 1.64 times the risk of AD (95% CI, 1.23–2.18), and 1.49 times the risk of vascular dementia (95% CI, 1.06–2.10); midlife obesity compared with normal weight was associated with 1.31 times the risk of cognitive impairment and dementia (95% CI, 1.02–1.68), 2.23 times the risk of AD (95% CI, 1.58–3.14), and 3.18 times the risk of vascular dementia (95% CI, 1.81–5.57).[104] In NOMAS, abdominal adiposity, measured as waist-hip ratio, in middle-aged adults was associated with cognitive decline over 6 years. For each increase in SD for waist-hip ratio, the associated decline in global cognition was equivalent to a 2.6-year increase in age. There was also a significant association with decline in processing speed and executive function.[105] In a separate analysis of NOMAS cohort data, BMI and WC were associated with reduced cortical thickness on brain MRI at follow-up.[106]
- In 9652 participants from the UK Biobank (mean age, 55 years; 48% males), BMI, waist-hip ratio, and fat mass were cross-sectionally associated with worse gray matter volume (β per 1 SD of measure=−4113 [95% CI, −4862 to −3364], −4272 [95% CI,−5280 to −3264], and −4590 [95% CI, −5386 to −3793], respectively).[107] In a systematic review of 34 studies, of which 30 were cross-sectional and 4 were prospective, obesity was associated with lower gray matter volume or cortical thickness in most studies; no quantitative meta-analysis was conducted because of the heterogeneity of obesity measures (BMI, WC, waist-to-hip ratio, plasma leptin levels) and of brain MRI measures used in the included studies.[108]
- The evidence for obesity and BMI in late life is less clear,[109] with some studies suggesting that obesity is protective or that weight loss may be a prodrome of late-life dementia.[110,111]
- In the Whitehall II Study (N=10 308; age, 35–55 years at baseline; 33% females), obesity at 50 years of age, but not at 60 or 70 years of age, was associated with increased risk of dementia (HR, 1.93 [95% CI, 1.35–2.75]).[110] In a subanalysis, the trajectory of BMI among those with dementia was higher than in participants without dementia 28 and 16 years before dementia diagnosis, whereas BMI was lower among those with dementia 8 years before diagnosis.
- In an analysis combining data from 39 cohort studies (N=1 349 857 dementia-free participants; mean follow-up, 16 years [range, 4–38 years]), the HR for each 5-unit increase in BMI increased as the time between BMI assessment and dementia diagnosis increased (BMI assessed <10 years before dementia diagnosis: HR, 0.71 [95% CI, 0.66–0.77]; BMI

assessed 10–20 years before dementia diagnosis: HR, 0.94 [95% CI, 0.89–0.99]; BMI assessed >20 years before dementia diagnosis: HR, 1.16 [95% CI, 1.05–1.27]).[112]

- Among 7885 adults ≥60 years of age with normal cognition at baseline in the MHAS, of whom 506 developed cognitive impairment over 6 years of follow-up, overweight and obesity were associated with higher risk of cognitive impairment only when combined with diabetes. Relative to normal weight without diabetes, overweight without diabetes (RR, 0.86 [95% CI, 0.67–1.11]) and obesity without diabetes (RR, 0.88 [95% CI, 0.63–1.20]) were not associated with higher risk of dementia, but normal BMI with diabetes (RR, 2.01 [95% CI, 1.40–2.87]), overweight with diabetes (RR, 1.42 [95% CI, 1.02–1.97]), and obesity with diabetes (RR, 1.70 [95% CI, 1.16–2.48]) were associated with higher dementia risk.[113]
- In a prospective cohort study (MARS and MAP; N=2134; mean age, 78 years; 33% Black participants; 75% females), lower BMI in late life was associated with greater decline in global cognition, semantic memory, and episodic memory ($P<0.01$ for all) over a mean of 6 years of follow-up. There was no association with decline in working memory, perceptual speed, or visuospatial function.[114]

### SDB/Sleep Apnea

#### (See also Chapter 13 [Sleep].)

- In a meta-analysis of 18 longitudinal studies (N=246 786 participants), SDB (including self-reported or objective snoring, sleep apnea, or OSA) was associated with all-cause dementia (pooled RR, 1.18 [95% CI, 1.02–1.36]), AD (pooled RR, 1.20 [95% CI, 1.03–1.41]), and vascular dementia (pooled RR, 1.23 [95% CI, 1.04–1.46]).[115]
- In another meta-analysis of 6 longitudinal studies (follow-up between 3 and 15 years), SDB (defined as AHI ≥15 or based on *ICD-9* codes) was associated with increased risk of cognitive decline and dementia (RR, 1.26 [95% CI, 1.05–1.50]). The study also reported cross-sectional associations (7 studies) between SDB and worse global cognition and executive function.[116]
- Greater OSA severity, based on AHI parameters, was associated with decreased cerebrospinal fluid β-amyloid$_{42}$ over 2 years in a community-based sample of adults with normal cognition (N=208; 62% females).[117] There was also a trend, although nonsignificant, between OSA severity and cortical Pittsburgh compound B–positron emission tomography uptake.
- Sleep apnea, assessed by AHI or oxygen desaturation index, was cross-sectionally associated with greater predicted brain age, a calculated score based on patterns of 169 regions of brain volume, in SHIP (N=690; mean age, 53 years; 49% females)[118] and with brain WMH, most notably periventricular frontal and dorsal WMH volumes (N=529 participants; age, 52 years; 53% females).[119]
- In a retrospective study of Medicare beneficiaries with OSA (*ICD-9* codes; N=53 321 adults ≥65 years of age; 41% females), the odds of incident AD and dementia not otherwise specified over 3 years were lower among older adults prescribed treatment for positive airway pressure therapy (OR, 0.65 [95% CI, 0.56–0.76] and 0.69 [95% CI, 0.5–0.85]).[120]
- In a meta-analysis of 9 RCTs (N=1901), CPAP treatment was not associated with benefits for cognition; however, study designs were heterogeneous, and all of the interventions were ≤1 year.[121]

### Smoking

- Smoking is a risk factor for dementia and poor cognitive outcomes, and studies suggest that quitting smoking is beneficial for brain health.[122–124]
- In an analysis from the NACC UDS, current smoking was associated with incident dementia (HR, 1.88 [95% CI, 1.08–3.27]) compared with nonsmoking. Participants who quit within the past 10 years compared with nonsmokers were not more likely to develop dementia.[123]
- Early adult trajectories of smoking are also associated with worse cognitive outcomes. In CARDIA (N=3364; mean age at cognitive assessment, 50 years; 46% Black participants; 56% female), investigators identified 5 smoking trajectories over 25 years from early adulthood to midlife: 19% quitters, 40% minimal-stable, 20% moderate-stable, 15% heavy-stable, and 5% heavy-declining smokers. Compared with nonsmokers, heavy-stable smokers had worse performance on processing speed, executive function, and memory at midlife (OR, 2.22 [95% CI, 1.53–3.22], 1.58 [95% CI, 1.05–2.36], and 1.48 [95% CI, 1.05–2.10], respectively). Heavy-declining and moderate-stable smokers also had worse processing speed (OR, 1.95 [95% CI, 1.06–3.68] and 1.56 [95% CI, 1.11–2.19]). Minimal stable smokers and quitters were not more likely than nonsmokers to have worse cognitive performance at midlife.[122]
- Among 2993 participants in the Framingham Offspring Study, those exposed to >1 pack/d of secondhand smoke during the first 18 years of life had 2.86 times the risk of dementia (HR, 2.86 [95% CI, 1.00–4.09]) and 3.13 times the risk of AD (HR, 3.13 [95% CI, 1.80–5.42]) compared with those with no exposure to secondhand smoke.[125]

### Cardiovascular Risk Factor Burden

#### (See Table 16-1)

- The AHA's ideal CVH metrics are associated with reduced cognitive decline. In a meta-analysis of 14

studies including >300 000 participants, of whom 8006 experienced incident dementia, a 1-point increment in Life's Simple 7 CVH score was associated with 6% lower rate of dementia (95% CI, 4%–8% lower).[126] The inverse relationship of higher CVH score with dementia risk was more pronounced for midlife CVH than for late-life CVH. These results are consistent with findings in ARIC showing that ideal midlife vascular risk factors were associated with less cognitive decline over 20 years.[127]

- Ideal CVH metrics at 50 years of age were similarly associated with lower incidence of dementia over 25 years of follow-up in the Whitehall II Study.[128] Those with poor CVH (scores 0–6) had 3.2 cases of dementia per 1000 person-years (95% CI, 2.5–4.0); those with intermediate CVH (scores 7–11) had 1.5 fewer cases per 1000 person-years (95% CI, 0.7–2.3 fewer); and those with optimal CVH (scores 12–14) had 1.9 fewer cases per 1000 person-years (95% CI, 1.1–2.8 fewer), with an HR for dementia of 0.89 per 1-point increment in CVH score (95% CI, 0.85–0.95).
- In the 3C Study of 6626 older adults (mean age, 74 years; 63% female), 37% had 0 to 2 ideal CVH factors, 57% had 3 to 4 ideal factors, and 7% had 5 to 7 ideal factors. Ideal CVH was associated with lower risk of developing dementia (HR, 0.90 [95% CI, 0.84–0.97] per each additional ideal CVH metric) and with better global cognition after 8.5 years of follow-up.[129]
- Among 229 976 participants in the UK Biobank with 2143 cases of incident dementia over a median follow-up of 9 years, each 1-point increment in Life's Simple 7 score was associated with 11% lower hazard of dementia (HR, 0.89 [95% CI, 0.88–0.91]).[130] Each 1-point increment in the biological component score (based on BP, cholesterol, and glucose) was associated with 7% lower hazard of dementia (HR, 0.93 [95% CI, 0.89–0.96]). However, a 1-point increment in the lifestyle component score (based on smoking, BMI, diet, and PA) was not associated with dementia (HR, 0.99 [95% CI, 0.96–1.02]).
- Conversely, greater cardiovascular risk factor burden is associated with increased risk of cognitive decline and dementia.[131,132]
- In CARDIA,[131] Framingham 10-Year Coronary Heart Disease Risk Score ≥10 was associated with accelerated cognitive decline 5 years later in midlife (OR, 2.29 [95% CI, 1.21–4.34]).
- In the Harvard Aging Brain Study,[133] greater Framingham 10-Year Cardiovascular Disease Risk Score was associated with greater late-life cognitive decline (−0.064 [95% CI, −0.094 to −0.033]) over almost 4 years. There was also a significant interactive effect between cardiovascular risk and amyloid burden (β=−0.040 [95% CI, −0.062 to −0.018]).
- In the Insight 46 cohort, higher Framingham 10-Year Cardiovascular Disease Risk Score in early adulthood (36 years of age) also was associated with lower late-life total brain volume (β per 1% increase in risk score=−3.6 mL [95% CI, −7.0 to −0.3]) and higher WMH volume (exponentiated β [mean ratio] per 1% increase in risk score=1.09 [95% CI, 1.01–1.18]).[134] The association between vascular risk score and markers of brain health was strongest in early adulthood compared with midlife and late life.
- In the HRS, cognitive impairment-free life expectancy at 55 years of age was estimated as 23.0 years (95% CI, 22.6–23.4) for participants with no hypertension, HD, diabetes, or stroke; 21.2 years (95% CI, 20.9–21.5) for those with any 1 of those conditions; 18.1 years (95% CI, 17.7–18.4) for those with any 2 conditions; and 14.0 years (95% CI, 13.5–14.5) for those with any 3 or all 4 conditions.[135] The association of CVD burden with lower cognitive impairment-free life expectancy was also observed at 65, 75, and 85 years of age with lower absolute life expectancies (Table 16-1).

## Social Determinants of Health/Health Equity

### *Race and Ethnicity*

- A retrospective analysis of the BRFSS 2016 data found significant differences in subjective cognitive decline across all racial and ethnic groups compared with White adults in the 20 843 respondents who had reported being diagnosed with stroke.[136] Compared with White adults, adults from racial and ethnic underrepresented groups were more likely to report worsening confusion or memory loss that contributed to not participating in everyday activities or difficulty with work, volunteer, and social activities outside of the home at least some of the time. Binary logistic regression adjusted for sex, age, education, income, and comorbidities found that Black adults (OR, 1.59 [95% CI, 1.54–1.63]) and Hispanic adults (OR, 2.30 [95% CI, 2.19–2.42]) had significantly higher odds compared with White adults of giving up day-to-day household activities or chores as a result of confusion or memory loss. Black adults (OR, 2.94 [95% CI, 2.85–3.03]) and Hispanic adults (OR, 4.03 [95% CI, 3.83–4.24]) also reported higher odds of needing assistance with everyday activities compared with White adults.
- An analysis of statewide encounter-level data for all hospital discharges in South Carolina between 2000 and 2012 included 68 758 individuals with a diagnosis of stroke before 2010.[137] The analysis identified individuals subsequently diagnosed with any of 5 categories of dementia. Adjusted Cox proportional hazards models showed that Black race was associated with increased risk for all-cause

dementia after incident stroke (HR, 1.55 [95% CI, 1.48–1.63]) and ranged from an HR of 1.37 (95% CI, 1.28–1.47) for AD to an HR of 1.95 (95% CI, 1.80–2.11) for vascular dementia.

### Sexual Orientation and Gender Identity

- Among 108 152 NHIS participants ≥45 years of age, 2421 individuals identified as gay, lesbian, bisexual, or something else, and 105 731 identified as straight.[138] Difficulty remembering or concentrating (subjective cognitive impairment) was reported by 24.5% (95% CI, 21.6%–27.8%) of sexual minority individuals compared with 19.1% (95% CI, 18.6%–19.6%) of straight individuals (OR, 1.5 [95% CI, 1.3–1.8], adjusted for age, income, education, race and ethnicity, and survey year). Frequency, severity, and extent of this subjective cognitive impairment were all reported more often by sexual minority individuals. Being "limited in any way" due to difficulty remembering or periods of confusion was reported by 7.3% (95% CI, 6.1%–8.7%) of sexual minority individuals compared with 5.4% (95% CI, 5.2–5.6) of straight individuals (OR, 1.7 [95% CI, 1.4–2.1]).
- Among 452 transgender adults ≥50 years of age identified in the OneFlorida Clinical Research Consortium, 3.5% had been diagnosed with ADRD compared with 2.2% of age- and race and ethnicity–matched cis-gender adults ($P$=0.07).[139]

### Education

- A meta-analysis looked at factors predicting reversion from MCI to normal cognition.[140] The analysis included 17 studies with 6829 participants. An overall reversion rate from MCI to normal cognition of 27.6% was found, and several factors positively predicted reversion, including higher education (standardized mean difference, 0.34 [95% CI, 0.12–0.56]).
- In a meta-analysis of 31 studies conducted in Latin America, prevalence of dementia among participants without formal education was 21.4%, whereas prevalence of dementia among participants with at least 1 year of formal education was 9.9%.[141]
- In a meta-analysis of 39 prospective studies including >1.4 million individuals, lowest education level (ie, quintile) was associated with 22% higher risk for cognitive impairment and dementia (95% CI, 10%–25% higher) relative to highest education level; lowest education versus highest education was also associated with higher risk for all-cause dementia (RR, 1.66 [95% CI, 1.20–2.32]).[142]
- PARs for established potentially modifiable risk factors for dementia among different groups were calculated using data from the SADHS 2016 study. The risk factor contributing the greatest PAR was low education (weighted PAR, 12% [95% CI, 7%–18%]). The PAR for low education differed by wealth strata but not sex ($P$ for interaction with sex=0.1880, $P$ for interaction with wealth <0.0000).[143]

### Occupation

- An observational study collected occupational information on 2121 patients with dementia (57% male) from the Amsterdam Dementia Cohort with a mean 67±8 years of age.[144] The sample included patients with AD (n=1467), frontotemporal dementia (n=281), vascular dementia (n=98), Lewy body disease (n=174), and progressive supranuclear palsy/corticobasal degeneration (n=101). Patients were categorized into 11 occupational classes. Significant differences in distribution of dementia types were seen across occupation groups ($P$<0.001). Unadjusted logistic regression showed that transportation/logistics occupations were significantly related to vascular dementia (OR, 3.41; $P$<0.01) and AD (OR, 0.43; $P$<0.001), whereas health care/welfare occupations were significantly associated with AD (OR, 1.74; $P$<0.01).
- Among 10 195 adults in studies included in the COSMIC collaboration, high occupational complexity (eg, managers and professionals) versus low (eg, individuals performing simple and routine manual tasks) was associated with 19% longer dementia-free survival time (95% CI, 5%–33% longer).[145] Intermediate occupational complexity (eg, clerical and craft jobs) versus low was associated with 7% longer dementia-free survival time (95% CI, 1% lower–16% higher).
- Among 8941 ELSA participants, low occupational attainment (routine/manual) was associated with 1.60 times the risk of dementia (95% CI, 1.23–2.09) and intermediate occupational attainment with 1.53 times the risk of dementia (95% CI, 1.15–2.06) compared with high occupational attainment (managerial or professional) after adjustment for age and sex.[146]
- In a meta-analysis of 39 prospective studies including >1.4 million individuals, lowest occupation level (ie, quintile) was not significantly associated with risk for cognitive impairment and dementia (RR, 1.06 [95% CI, 0.83–1.36]) relative to highest occupation level or with risk for all-cause dementia (RR, 1.03 [95% CI, 0.77–1.36]).[142]

### Income/Wealth

- In a meta-analysis of 39 prospective studies including >1.4 million individuals, lowest income level (ie, quintile) was associated with 21% higher risk for cognitive impairment and dementia (95% CI, 4%–41% higher) relative to highest income level; lowest income versus highest was not significantly associated with risk for all-cause dementia (RR, 1.19 [95% CI, 0.78–1.82]).[142]

- Among 8941 ELSA participants, self-reported household wealth was measured as the total value of home (minus outstanding mortgage), physical items such as jewelry, business assets such as investments, and financial assets, including cash and savings (minus debts and loans).[146] The lowest tertile of wealth was associated with 1.63 times the risk of dementia (95% CI, 1.26–2.12) and middle tertile of wealth with 1.22 times the risk of dementia (95% CI, 0.93–1.60) compared with the highest wealth tertile.

### *Composite Socioeconomic Status*

- Composite SES is a measure that incorporates education, occupation, and income levels into an index, with higher values indicating higher SES. In a meta-analysis of 39 prospective studies including >1.4 million individuals, lowest composite SES level (ie, quintile) was associated with 1.75 times the risk for cognitive impairment and dementia (95% CI, 1.37–2.23) relative to highest composite SES level and with 2.00 times the risk for all-cause dementia (95% CI, 1.27–3.15]).[142]

### *Geography/Dementia Belt/Rural-Urban*

- Among 152 444 HRS participants ≥50 years of age, compared with living in an urban county that had maintained or increased population size over the previous 20 years, living in a rural county that had maintained or increased population size was associated with 0.22 points lower TICS score ($P<0.01$), and living in a rural county that had decreased in population size was associated with 0.36 points lower TICS score ($P<0.01$).[147]
- In a US nationwide ecological study of Medicare beneficiaries from 2008 to 2015, county-level annual prevalence of AD/ADRD was ≈0.5 to 1.0 cases per 100 population lower in rural counties than in urban counties, whereas county-level annual incidence of AD/ADRD was ≈0.4 new cases per 100 population higher in rural counties than in urban counties, adjusted for county-level demographic and health care factors.[148]

## Risk Prediction

### *Polygenic Risk Scores*

- According to genetic data from 60 801 cases of CAD and 17 008 cases of LOAD, each increment in PRS for CAD was associated with 7% higher odds of LOAD (95% CI, 1%–15%).[149] This association was no longer present after removal of the *APOE* locus from the PRS.
- All-cause dementia GRSs have been used to examine whether lifestyle factors can offset high dementia genetic risk.[150] In a study of N=196 383 participants, although a healthy lifestyle was associated with lower risk of incident dementia among participants with low or high genetic risk, no significant interaction between dementia genetic risk and lifestyle factors on incident dementia was detected ($P=0.99$).
- A PRS for AD developed from GWASs in a European population was associated with risk of AD in a sample of 1634 Korean participants, of whom 716 had AD (OR of AD per increment in PRS, 1.95 [95% CI, 1.40–2.72]), suggesting that GRSs for AD may be transferable across different ethnic populations.[151]

### *Risk Scores That Emphasize Vascular Risk Factors*

- The LIBRA index for predicting dementia includes depression, diabetes, PA, hypertension, obesity, smoking, hypercholesterolemia, CHD, and mild to moderate alcohol use. Among 1024 adults in the Finnish CAIDE study, higher LIBRA score in midlife was associated with a 27% higher incidence of dementia (95% CI, 13%–43%), but a higher LIBRA score in late life was not associated with dementia risk (HR, 1.02 [95% CI, 0.84–1.24]).[152]
- Among 4392 adults in MESA, 3 vascular risk scores at baseline—CAIDE score, Framingham Stroke Risk Profile score, and ASCVD-PCE score—were each associated with lower mean scores on 3 cognitive measures obtained 10 years later: CASI, Digit Symbol Coding, and Digit Span.[153] For example, mean CASI score was 2.41 points lower (95% CI, 2.19–2.64), mean Digit Symbol Coding score was 7.46 points lower (95% CI, 6.97–7.95), and mean Digit Span score was 0.95 points lower (95% CI, 0.83–1.07) per 1-SD increment in CAIDE score. These associations varied by race and ethnicity. For example, the association of SD increment in baseline CAIDE score with mean CASI score 10 years later was 1.61 points lower in White individuals (95% CI, 1.28–1.95), 2.52 points lower in Chinese American individuals (95% CI, 1.81–3.24), 2.30 points lower in African American individuals (95% CI, 1.84–2.77), and 3.28 points lower in Hispanic individuals (95% CI, 2.82–3.74).
- Among 34 083 female and 39 998 male patients with AF with no history of dementia, $CHA_2DS_2$-VASc scores ≥3 (versus ≤1) were associated with 7.8 times the risk of dementia in females (95% CI, 5.9–10.2) and 4.8 times the risk of dementia in males (95% CI, 4.2–5.4). Similarly, the blood biomarker–based Intermountain Mortality Risk Score (high versus low) was associated with 3.1 times the risk of dementia in females (95% CI, 2.7–3.5) and 2.7 times the risk of dementia in males (95% CI, 2.4–3.1).[154]

## Subclinical/Unrecognized Disease

- Among 896 people in WHICAP without MCI or dementia, an MRI index of cerebrovascular and

neurodegenerative pathology, including WMHs, infarcts, hippocampal volumes, and cortical thicknesses, was associated with a higher incidence of MCI or LOAD (HR per 1 SD of MRI score, 1.68 [95% CI, 1.44–1.96]).[155]

- In a meta-analysis of 3 population-based cohort studies (Rotterdam Study, FHS, and AGES Reykjavik Study), the presence of cortical microbleeds on MRI was associated with a higher risk for incident all-cause dementia (unadjusted OR, 2.01 [95% CI, 0.92–4.36]; aHR, 1.35 [95% CI, 1.00–1.82]).[156]
- Among 152 patients diagnosed with MCI and cerebral small-vessel disease, 41 (27%) had ≥1 cerebral microbleeds.[157] Total number of cerebral microbleeds was correlated with lower scores on measures of attention/executive function (Spearman $\rho$=–0.282; $P$=0.003) and fluency (Spearman $\rho$=–0.166; $P$=0.041) but not with memory (Spearman $\rho$=–0.055; $P$=0.505) or global cognitive ability (Spearman $\rho$=–0.57; $P$=0.487).
- In a meta-analysis of 9 studies, covert vascular brain injury was associated with decline in cognitive dysfunction on the MMSE (standardized mean difference, –0.47 [95% CI, –0.72 to –0.22]).[158] In the same meta-analysis, among 4 studies, covert vascular brain injury was associated with cognitive dysfunction on the Montreal Cognitive Assessment Scale (standardized mean difference, –3.36 [95% CI, –5.90 to –0.82]).
- Among 282 patients with AD (mean age, 73 years; 54% female), annual change in Clinical Dementia Rating Sum of Boxes scores was not significantly associated with any MRI findings after adjustment for age and sex, including presence of cortical infarcts (annual change, 0.7 points [95% CI, –0.5 to 1.9]), lacunes (–0.2 [95% CI, –0.9 to 0.5]), any infarcts (0.0 [95% CI, –0.6 to 0.7]), WMH Fazekas 3 (–0.3 [95% CI, –0.9 to 0.3]), and WMH Fazekas 2 or 3 (–0.2 [95% CI, –0.8 to 0.4]).[159]
- Greater arterial stiffness, measured as PWV, is another vascular risk factor consistently associated with worse measures of brain health. In a meta-analysis of 9 longitudinal studies, greater arterial stiffness was associated with worse global cognition (effect size, –0.21 [95% CI, –0.36 to –0.06]), executive function (effect size, –0.12 [95% CI, –0.22 to –0.02]), and memory (effect size, –0.05 [95% CI, –0.12 to 0.03]).[160]
- Among 630 participants without dementia in the Alzheimer's Disease Neuroimaging Initiative who underwent an assessment for neuropsychiatric symptoms with the Neuropsychiatric Inventory and 3-T MRI at baseline (n=631) and follow-up (n=616), a higher burden of cerebral small-vessel disease was associated with neuropsychiatric symptoms in follow-up.[161] Lacunar infarcts predicted hyperactivity ($P$=0.0092), psychosis ($P$=0.0402), affective symptoms ($P$=0.0156), and apathy ($P$≤0.0001). WMHs were associated with hyperactivity ($P$=0.0377) and apathy ($P$=0.0343), whereas cerebral microbleeds correlated with apathy ($P$=0.0141).
- Among 4399 cognitively unimpaired adults 65 to 85 years of age enrolled in the Anti-Amyloid Treatment in Asymptomatic Alzheimer Disease Study, the amyloid-$\beta$ standard uptake value ratio on positron emission tomography imaging was associated with anxiety scores on the State Trait Anxiety Inventory (range 6–24) but not depression scores on the Geriatric Depression Scale.[162] For each 0.5-point increase in cortical amyloid-$\beta$ standard uptake value ratio, the mean anxiety score increased by 0.25 points (95% CI, 0.04–0.53).
- Lighter sleep, as characterized by longer N1 sleep and shorter slow-wave sleep, is associated with higher burden of enlarged perivascular spaces, representing impaired perivascular drainage. Among 552 dementia- and stroke-free participants from the FHS, longer N1 sleep duration on polysomnography was associated with higher enlarged perivascular spaces burden in the centrum semiovale on brain MRI (OR of higher burden per minute of N1 sleep, 1.03 [95% CI, 1.10–1.05]), and longer N3 sleep duration was associated with lower enlarged perivascular spaces burden in the centrum semiovale (OR, 0.99 [95% CI, 0.98–1.00]).[163] These findings suggest that sleep architecture may be involved in glymphatic clearance and cerebral small-vessel disease.
- Transcranial magnetic stimulation applied to the primary motor cortex and coupled with electromyography provides a subclinical measure of cortical excitability and plasticity. In a meta-analysis of the value of transcranial magnetic stimulation–derived excitability and plasticity measures to distinguish AD, MCI, and normal cognition, 61 studies (n=2728 participants) included 1454 patients with AD, 163 patients with MCI, and 1111 cognitively normal individuals.[164] Patients with AD had significantly lower resting motor threshold (Cohen d=1.05 [$P$<0.0001]), lower active motor threshold (Cohen d=0.77 [$P$<0.0001]), lower short latency afferent inhibition (Cohen d=1.89 [$P$<0.0001]), lower short-latency intracortical inhibition (Cohen d=0.68 [$P$<0.01]), and lower long-term potentiation-like plasticity (Cohen d=1.20 [$P$<0.0001]) compared with cognitively normal individuals. Patients with MCI had lower resting motor threshold (Cohen d=0.39 [$P$<0.005]) and lower long-term potentiation-like plasticity (Cohen d=0.86 [$P$<0.05]) compared with cognitively normal individuals.
- In the Baltimore Longitudinal Study of Aging, subclinical hearing loss or imperfect hearing

(pure-tone average ≤25 dB) was associated with cognitive decline and risk of incident MCI/dementia.[165] Among participants ≥50 years of age (n=263) followed up for a mean of 11.7 years, after adjustment for age, sex, education, vascular burden, and race, a 10-dB increase in hearing loss was associated with an annual decline of −0.02 SD (95% CI, −0.03 to −0.01) in testing of letter fluency. There was no significant relationship of hearing to incident MCI or dementia.

- Among 623 community-dwelling adults from the Whitehall II Imaging Substudy who underwent multimodal MRI, higher mean arterial pressure throughout midlife (β=3.36 [95% CI, 0.42–6.30]) and faster cognitive decline in letter fluency (β=−0.07 [95% CI, −0.13 to −0.01]) and verbal reasoning (β=−0.05 [95% CI, −0.11 to −0.001]) were associated with severe small-vessel disease burden in older age.[166]
- In a study that combined longitudinal data from 3 clinical trials (B-Vitamin Atherosclerosis Intervention Trial, Women's Isoflavone Soy Health Trial, and the Early Versus Late Intervention Trial With Estradiol), among participants (308 males and 1187 females; mean age, 61 years) free of CVD and diabetes, participants underwent the same standardized protocol for ultrasound measurement of carotid IMT, as well as cognitive assessment, at baseline and 2.5 years. Although no associations were found between carotid IMT and cognitive function at baseline or at 2.5 years, there was a weak inverse association between carotid IMT at baseline and change in global cognition assessed over 2.5 years (β [SE]=−0.056 [0.028] units per 0.1 mm carotid IMT [95% CI, −0.110 to −0.001]; *P*=0.046).[167] When analysis was stratified by <65 and ≥65 years of age, the inverse association remained statistically significant for participants in the older age group.
- In a single-center study, among 288 Chinese patients (mean age, 80.5 years; 60.4% females) with AD, subclinical epileptiform discharge on scalp electroencephalography was present in 57 patients (19.8%).[168] Subclinical epileptiform discharge was associated with greater decline in CASI (−9.32 versus −3.52 points; *P*=0.0001) and MMSE (−2.52 versus −1.12 points; *P*=0.0042) scores at 1 year.

## Genetics and Family History

- AD is highly heritable with a complex genetic cause. According to data from 11 884 twin pairs >65 years of age from the Swedish Twin Registry, AD heritability was estimated to range from 58% to 79%.[169]
- Rare forms of early-onset autosomal dominant AD may reflect highly penetrant variations in *APP*, *PSEN1*, or *PSEN2*.[170]
- Cerebral autosomal dominant arteriopathy with subcortical infarct and leukoencephalopathy and familial cerebral amyloid angiopathy are 2 rare, highly heritable forms of vascular dementia that show autosomal dominant inheritance patterns.[171,172] Missense variations in *NOTCH3* are largely responsible for cerebral autosomal dominant arteriopathy with subcortical infarct and leukoencephalopathy, whereas variations in *APP*, *CST3*, or *ITM2B* underlie familial cerebral amyloid angiopathy.
- The heritability of sporadic vascular dementia is estimated to be very low (<1%).[173]

### *APOE*

- The *APOE* ε4 allele is an established AD genetic risk factor, lowering age at onset and increasing AD lifetime risk in a dose-dependent manner.[174]
- The *APOE* ε4 allele also is associated with vascular dementia risk.[175] Among 549 cases of vascular dementia and 552 controls without dementia in Europe, having ≥1 *APOE* ε4 alleles was associated with 1.85 times the odds of vascular dementia (95% CI, 1.35–2.52), and having ≥1 *APOE* ε2 alleles was associated with 0.67 times the odds of vascular dementia (95% CI, 0.46–0.98).
- The frequency of the *APOE* ε4 allele shows marked variation (range, 3%–49%) across diverse ancestral populations.[176]
- Among 8263 Latino people in the United States, prevalence of ≥1 *APOE* ε4 alleles (associated with higher risk for LOAD) varied by genetically determined ancestry group: 11.0% (95% CI, 9.6%–12.5%) in Central American individuals, 12.6% (95% CI, 11.5%–13.7%) in Cuban individuals, 17.5% (95% CI, 15.5%–19.4%) in Dominican individuals, 11.0% (95% CI, 10.2%–11.8%) in Mexican individuals, 13.3% (95% CI, 12.1%–14.6%) in Puerto Rican individuals, and 11.2% (95% CI, 9.4%–13.0%) in South American individuals.[177] Prevalence of ≥1 *APOE* ε2 alleles (associated with lower risk for LOAD) was highest in Dominican individuals (8.6% [95% CI, 7.2%–10.1%]) and lowest in Mexican individuals (2.9% [95% CI, 2.4%–3.3%]).

### *Other Dementia Loci*

- In total, AD GWASs have mapped 40 AD susceptibility loci, which harbor 89 unique lead variants.[178] Twenty-four of these loci have been replicated at genome-wide significance, and functional genomics studies suggest *APOE*, *CR1*, *BIN1*, *TREM2*, *CLU*, *SORL1*, *ADAM10*, *ABCA7*, *CD33*, *SPI1*, and *PILRA* as the most likely causal genes.
- To date, the largest GWAS of clinically diagnosed AD was performed by the International Genomics of Alzheimer's Project Consortium.[179] With a final n=35 274 cases and n=59 163 controls, this study identified 25 AD loci, 5 of which were novel.

Pathway analyses implicated tau binding proteins and amyloid precursor protein metabolism in LOAD, suggesting a shared genetic architecture with early-onset autosomal dominant AD.

- Although not examining clinically diagnosed AD, other GWASs have examined AD proxy traits. As an example, a GWAS of 116 196 UK Biobank participants compared participants who reported having a parent with AD (proxy cases) with control subjects who reported having no parent with AD.[180] These findings also were meta-analyzed with published GWASs. When analyzed alone, this study replicated previous associations with *APOE.* When pooled with published GWASs, this study identified 4 novel loci ($P<5\times10^{-8}$) on chromosomes 5 (near *HBEFGF*), 10 (near *ECHDC3*), 15 (near *SPPL2A*), and 17 (near *SCIMP*).
- GWASs that combined clinically diagnosed with "proxy" AD cases have been performed. For example, a study of n=111 326 clinical diagnosed or proxy AD cases and n=677 663 controls identified 75 loci, including 42 new loci.[181] In addition to confirming involvement of amyloid/tau pathways, this study suggested new mechanisms, including the tumor necrosis factor-α pathway. These results also were used to develop new GRSs to predict AD/dementia incidence or progression from MCI to AD/dementia.

## Prevention

### Exercise

- A 2019 randomized, parallel-group, community-based clinical trial of 132 multiracial, multiethnic, cognitively normal individuals (mean age, 40 years) with below-median aerobic capacity in New York found that aerobic exercise, compared with stretching and toning, for 6 months improved executive function with greater improvement as age increased (increase at 40 years of age, 0.228 SD [95% CI, 0.007–0.448]; increase at 60 years of age, 0.596 SD [95% CI, 0.219–0.973]) and less improvement among those with ≥1 *APOE* ε4 alleles.[182]
- In a trial of adults ≥65 years of age with subjective cognitive concerns (N=585), participants were randomized to exercise training, mindfulness-based stress reduction, both exercise training and mindfulness-based stress reduction, or health education. At both 6 and 18 months, there was no difference in executive function or episodic memory between the intervention groups.[183]
- Meta-analyses examining RCTs indicate that PA interventions benefit cognition in both AD (7 RCTs; N=501; with improvement on the MMSE, 0.458 [95% CI, 0.097–0.819]) and MCI (15 RCTs; N=1156; improvement on the MMSE, 0.631 [95% CI, 0.244–1.018]).[184]

### BP Control

- Among 9361 participants (SPRINT) with hypertension and high cardiovascular risk in the United States and Puerto Rico (mean age, 67.9 years; 35% females; 58% White, 30% Black, 10% Hispanic individuals), targeting an SBP <120 mm Hg compared with targeting an SBP <140 mm Hg for a median of 3.34 years reduced the risk of MCI (14.6 versus 18.3 cases per 1000 person-years; HR, 0.81 [95% CI, 0.69–0.95]) and the combined rate of MCI or probable dementia (20.2 versus 24.1 cases per 1000 person-years; HR, 0.85 [95% CI, 0.74–0.97]) but not the risk of adjudicated probable dementia (7.2 versus 8.6 cases per 1000 person-years; HR, 0.83 [95% CI, 0.67–1.04]) over a total median follow-up of 5.11 years.[185] A secondary analysis from SPRINT suggests that antihypertensive treatment regimens that stimulate angiotensin II receptors were associated with reduced risk of cognitive impairment compared with angiotensin inhibitor–only regimens (HR for amnestic MCI, 0.74 [95% CI, 0.64–0.87]; HR for probable dementia, 0.80 [95% CI, 0.57–1.14]).[186]
- A post hoc analysis from the PreDIVA trial (54% females; mean age, 74.5 years) also found that angiotensin II–stimulating antihypertensive medications were significantly associated with reduced risk of dementia (HR, 0.86 [95% CI, 0.64–1.16]) compared with angiotensin II–inhibiting medications.[187]
- In a systematic review of 15 prospective cohort studies and 7 randomized control trials (N=649 790), treatment with calcium channel blockers and angiotensin II receptor blockers was associated with a reduced risk of incident dementia compared with other antihypertensive classes.[188] For calcium channel blockers, the HR versus ACE inhibitors was 0.84 (95% CI, 0.74–0.95), the HR versus β-blockers was 0.83 (95% CI, 0.81–0.97), and the HR versus diuretics was 0.89 (95% CI, 0.78–1.01). For angiotensin II receptor blockers, the HR versus ACE inhibitors was 0.88 (95% CI, 0.81–0.97), the HR versus β-blockers was 0.87 (95% CI, 0.77–0.99), and the HR versus diuretics was 0.93 (95% CI, 0.83–1.05).
- In a randomized clinical trial of older adults with MCI and hypertension (N=176; mean age, 66 years; 57% females; 64% Black individuals), participants treated with candesartan over 1 year had better outcomes on executive function (−0.03 [95% CI, −0.08 to 0.03]) compared with those treated with lisinopril.[189]
- In a subset of participants in The International Polycap Study 3 who underwent cognitive assessment (N=2098; mean±SD age, 70.1±4.5 years),

treatment with a polypill (antihypertensives and a statin), aspirin alone, or polypill plus aspirin over 5 years did not reduce the risk of cognitive decline or dementia compared with treatment with placebo.[190]

- In a meta-analysis of 12 RCTs (>92 000 participants; mean age, 69 years; 42% females), BP lowering with antihypertensive agents compared with control was associated with a lower risk of incident dementia or cognitive impairment (7.0% versus 7.5% of patients over a mean trial follow-up of 4.1 years; OR, 0.93 [95% CI, 0.88–0.98]; absolute risk reduction, 0.39% [95% CI, 0.09%–0.68%]; $I^2$=0.0%).[191]
- In a meta-analysis of 5 RCTs (N=28 008; mean age, 69.1 years; median follow-up, 4.3 years; HYVET, SYST-EUR, PROGRESS, ADVANCE, and SHEP), antihypertensive treatment was associated with reduced risk of incident dementia (aOR, 0.87 [95% CI, 0.75–0.99]).[192]
- A 2021 Cochrane review of hypertension treatment in adults without prior cerebrovascular disease reported low-certainty evidence for a small benefit in cognition (4 placebo-controlled trials; mean difference on MMSE score, 0.20 [95% CI, 0.10–0.29]) but no significant benefit for dementia (5 placebo-controlled trials).[193]

### Blood Lipid Control/Statin Therapy

- A secondary analysis of the HPS suggests that statin therapy for 5 years in adults with vascular disease or diabetes (mean age, 63 years; 25% females) resulted in 2.0% of participants avoiding a nonfatal stroke or TIA and 2.4% avoiding a nonfatal cardiac event, which yielded an expected reduction in cognitive aging of 0.15 years (95% CI, 0.11–0.19).[194]
- In an observational study of 18 846 older adults (median age, 74 years; 56% females) with no history of cardiovascular events, statin therapy was not associated with risk of dementia, MCI, or cognitive decline.[195]
- A meta-analysis of 14 double-blind trials (4 phase 2 and 10 phase 3) for the PCSK9 inhibitor alirocumab found low incidence of neurocognitive adverse events, with no significant differences between the alirocumab and control groups and no association between neurocognitive adverse events and LDL-C <25 mg/dL.[196] Another meta-analysis of 35 RCTs for alirocumab and evolocumab similarly found no significant associations between PCSK9 inhibitor use and neurocognitive adverse events (OR, 1.12 [95% CI, 0.88–1.42]).[197]
- A randomized placebo-controlled trial of evolocumab in addition to statin therapy (N=1204; age, 40–85 years) found no significant differences in cognitive function between the evolocumab group and the placebo group.[198] Another RCT (N=22 655) involving evolocumab added to statin therapy found no significant effect on self-reported cognition, even among patients who had LDL-C <20 mg/dL.[199]
- A meta-analysis of 33 RCTs found no association between lipid-lowering treatments (PCSK9 inhibitors, statins, and ezetimibe) and cognitive impairment and no significant effects of low LDL-C levels on cognitive disorder likelihood or global cognitive performance.[200]

### Aspirin Therapy

- In a randomized placebo-controlled trial, the ASPREE study, rates of incident dementia, probable AD, and MCI did not differ between the low-dose daily aspirin treatment group and the placebo group after almost 5 years of follow-up (N= 19 114; age, 65–98 years; 44% male).[201]

### Glycemic Control

- In adults ≥60 years of age with type 1 diabetes, continuous glucose monitoring compared with standard blood glucose monitoring resulted in a small but statistically significant reduction in hypoglycemia but no differences in cognitive outcomes over 6 months.[202]
- A meta-analysis of RCTs found that intensive glucose control compared with conventional glucose control may delay cognitive decline slightly in patients with type 2 diabetes (4 cohorts with N=5444; β=−0.03 [95% CI, −0.05 to −0.02]).[203]

### Multidomain Prevention Strategies

- In the 4-year DR's EXTRA trial (N=1401; mean age, 66.5 years), there was a trend toward better cognition in older adults randomized to a combined aerobic exercise and healthy diet intervention compared with the control group (global cognition [CERAD-TS] increase, 1.4 points [95% CI, 0.1–2.7]; $P$=0.06).[204] Effects were not significant for the resistance exercise alone, aerobic exercise alone, diet alone, or combined resistance exercise and diet groups.
- A pooled analysis of 2 multidomain intervention trials focused on cardiovascular and lifestyle strategies (MAPT and PreDIVA; N=4162 participants; median age, 74 years) found no significant overall association between multidomain prevention and cognitive decline.[205] Cognitive benefits were observed among participants with lower baseline cognitive function (MMSE score <26; n=250; mean difference in change, 0.84 [95% CI, 0.15–1.54]; $P$<0.001]).
- A 2021 Cochrane review of RCTs found no conclusive evidence that multidomain interventions reduce the incidence of dementia in older adults (2 RCTs; n=7256); however, there was high-certainty evidence for a small effect on cognition (3 RCTs; n=4617; mean difference on composite cognitive

*Z* score based on neuropsychological test battery, 0.03 [95% CI, 0.01–0.06]).[206]

- A meta-analysis of RCTs for older adults with MCI (28 RCTs; N=2711; mean±SD age, 71.6±3.4 years; mean±SD duration of intervention, 19.8±14.6 weeks) suggests that compared with single-domain interventions, multidomain interventions, targeting at least 2 nonpharmacological strategies, benefit cognition, including global cognition (20 RCTs; SMD, 0.41 [95% CI, 0.23–0.59]), executive function (17 RCTs; SMD, 0.20 [95% CI, 0.04–0.36]), memory (15 RCTs; SMD, 0.29 [95% CI, 0.14–0.45]), and verbal fluency (8 RCTs; SMD, 0.30 [95% CI, 0.12–0.49]) but not attention (6 RCTs; SMD, 0.13 [95% CI, −0.15 to 0.41]) or processing speed (10 RCTs; SMD, 0.46 [95% CI, −0.04 to 0.96]).[207]
- Among 221 Black participants with MCI (mean age, 75.8 years; 79% females), behavioral activation, which aimed to increase cognitive, physical, and social activity, compared with supportive therapy, an attention control treatment, reduced the 2-year incidence of memory decline (absolute difference, 7.1%; RR, 0.12 [95% CI, 0.02–0.74]; *P*=0.02).[208] Compared with supportive therapy, behavioral activation also was associated with improvement in executive function and preservation of everyday function.
- Observational studies suggest that preventing stroke is one of the most effective strategies for preventing dementia. In the Oxford Vascular Study (N=2305), the 1-year incidence of dementia was 47 times higher among those with major stroke (1-year standardized morbidity ratio, 47.3 [95% CI, 35.9–61.2]), almost 6 times higher among those with minor stroke (1-year standardized morbidity ratio, 5.8 [95% CI, 4.4–7.5]), and 3.5 times higher in those with TIA (1-year standardized morbidity ratio, 3.5 [95% CI, 2.5–4.8]) compared with age- and sex-matched incidence in the UK population.[209]

## Mortality

## (See Table 16-2)

- In 2021 (unpublished NHLBI tabulations using CDC WONDER[210] and the NVSS[211]):
  - On average, every 1 minute 53 seconds, someone died of dementia.
  - Dementia accounted for ≈1 of every 12 deaths in the United States.
  - The number of deaths with dementia as an underlying cause was 279 704 (Table 16-2); the age-adjusted death rate for dementia as an underlying cause of death was 72.4 per 100 000, whereas the age-adjusted rate for any mention of dementia as a cause of death was 114.7 per 100 000.
  - More females than males die of dementia each year because of the higher prevalence of elderly females compared with males. Females accounted for 67.0% of US dementia deaths in 2021.
- Conclusions about changes in dementia death rates from 2011 to 2021 are as follows[210]:
  - The age-adjusted dementia death rate increased 17.2% (from 61.8 per 100 000 to 72.4 per 100 000), whereas the actual number of dementia deaths increased 31.4% (from 212 876 to 279 704 deaths).
  - Age-adjusted dementia death rates increased 12.4% for males and 21.0% for females.
- A mortality risk score for people having probable dementia was developed among 4267 HRS participants who had probable dementia with a mean 82 years of age and median follow-up of 3.9 years; it was then externally validated in NHATS participants.[212] In the external validation, the risk score had an AUC of 73% (95% CI, 70%–76%) for predicting death within 1 year and an AUC of 74% (95% CI, 71%–76%) for predicting death within 5 years. Factors included in this mortality risk score model were age, sex, BMI, smoking status, activities of daily living dependency count, instrumental activity of daily living difficulty count, difficulty walking several blocks, participation in vigorous PA, and chronic conditions (cancer, HD, diabetes, lung disease).
- Among 5989 NHANES participants surveyed in 1999 to 2014 with mortality follow-up to 2015, lower cognitive test scores were associated with higher all-cause mortality rates.[213] For example, a 1-SD decrement on the Digit Symbol Substitution Test was associated with 36% higher (95% CI, 25%–48% higher) mortality rate. There were differences by education level. Among individuals with less than high school education, mortality rates were 46% higher (95% CI, 9%–97% higher) per 1-SD decrement in animal fluency, 34% higher (95% CI, 7%–67% higher) per 1-SD decrement in word list learning, and 38% higher (95% CI, 5%–82% higher) per 1-SD decrement in word list delayed recall; those associations were not observed for individuals with high school diploma or higher education. Similarly, SD decrements in animal fluency, word list learning, and word list delayed recall were associated with higher mortality among low-income individuals but not high-income individuals.

### *Mortality in Hospitalized Patients*

- In a 5-year retrospective review of 9519 adult patients with trauma, 195 (2.0%) who had a diagnosis of dementia at an American College of Surgeons–verified level I trauma center,[214] patients with dementia (n=195) were matched

with dementia-free patients (n=195) and compared on mortality, ICU length of stay, and hospital length of stay. The comorbidities and complications were similar between the groups (11.8% versus 12.4%). Mortality was 5.1% in both the dementia and control groups. The study found that dementia did not increase the risk of mortality in patients with trauma.

- In a cohort of >1 million Medicare beneficiaries hospitalized in 2016, of whom 211 698 had diagnosed dementia, those with dementia were more likely to die (5.7%) than those without dementia (3.1%) within 30 days after discharge (aOR, 1.21 [95% CI, 1.17–1.24]).[215]
- In an analysis of 3.7 million hospitalizations of adults ≥65 years of age throughout Italy, of whom 278 149 were patients diagnosed with dementia, those with dementia were more likely to die while in the hospital than those without dementia (age-, sex-, and comorbidity-adjusted OR, 1.98 [95% CI, 1.95–2.00]).[216] Among patients with dementia, the comorbidities most strongly associated with higher risk for in-hospital mortality were HF, pneumonia, and kidney disease.

## Complications

- In a national cohort of Medicare fee-for-service beneficiaries ≥65 years of age with newly diagnosed ADRD (n=2 667 987) linked to the National Death Index, the rate of suicide was 26.42 per 100 000 person-years.[217] The overall standardized mortality ratio for suicide was 1.53 (95% CI, 1.42–1.65). The highest risk for suicide was among those 65 to 74 years of age (SMR, 3.40 [95% CI, 2.94–3.86]) and during the first 90 days after diagnosis. Rural residence and recent mental health, substance use, or chronic pain conditions were associated with increased suicide risk.
- In a meta-analysis of 24 studies of polysomnographic changes in patients with AD compared with healthy control subjects, patients with AD had significant reductions in total sleep time (SMD, −0.60 [95% CI, −0.86 to −0.34]), sleep efficiency (SMD, −0.96 [95% CI, −1.36 to −0.57]), and percentage of slow-wave sleep (SMD, −0.86 [95% CI, −1.14 to −0.58]) and rapid eye movement sleep (SMD, −0.77 [95% CI, −1.14 to −0.40]), as well as increases in sleep latency (SMD, 0.45 [95% CI, 0.29–0.61], wake time after sleep onset (SMD, 0.74 [95% CI, 0.38–1.10]), number of awakenings (SMD, 0.55 [95% CI, 0.25–0.86]), and rapid eye movement latency (SMD, 0.35 [95% CI, 0.13–0.58]).[218] Decreased slow-wave sleep and rapid eye movement sleep were significantly associated with the severity of cognitive impairment.
- In a secondary analysis of baseline data from a cluster randomized trial among hospitalized individuals with dementia, increased daytime PA was associated with greater sleep duration (β=0.16 [95% CI, 0.11–0.72]) and sleep efficiency (β=0.16 [95% CI, 0.02–0.15]) and less sleep fragmentation (β=−0.22 [95% CI, −0.25 to −0.08]).[219] Higher behavioral and psychological symptoms of dementia were significantly associated with prolonged sleep latency (β=0.13 [95% CI, 0.10–2.75]).
- In a meta-analysis of 16 studies of patients ≥65 years of age living with dementia in acute care, community, and residential care settings, the prevalence of frailty (variously defined) ranged from 50.8% to 91.8% in acute care settings across studies (overall 77.6% in 6 studies for which detailed data were available).[220] The prevalence of frailty in the community-dwelling setting ranged from 24.3% to 98.9% (overall 94.2% in 9 studies for which detailed data were available, which was driven largely by 1 UK study of 22 710 participants with dementia and included mild degrees of frailty as well).[221]
- In a 3-year longitudinal population-based study among 192 drug-naive patients with newly diagnosed PD and 172 control subjects without PD matched for age, sex, and education, frailty at baseline, measured with the frailty index, was higher among patients with PD (0.21±0.10) than control subjects (0.11±0.07; $P<0.001$).[222] One-third of patients with PD had high frailty (frailty index>0.25) compared with 5% of control subjects. Patients with PD with greater frailty were more likely to develop dementia by 3 years after adjustment for age and sex (OR, 2.91 [95% CI, 1.54–5.99]).
- Among 53 studies (N=196 491 patients) included in a systematic review and meta-analysis, preoperative cognitive impairment was associated with a significant risk of delirium in patients ≥60 years of age after noncardiac surgery (25.1% versus 10.3%; OR, 3.84 [95% CI, 2.35–6.26]).[223] Cognitive impairment was also associated with an increased risk of discharge to assisted care (44.7% versus 38.3%; OR, 1.74 [95% CI, 1.05–2.89]) and postoperative complications (40.7% versus 18.8%; OR, 1.85 [95% CI, 1.37–2.49]).
- In a retrospective cohort study using electronic health records linked to fee-for-service Medicare claims (n=6779 patients), patients with dementia undergoing high-risk surgery (n=536, 7.9%) were at increased risk of postoperative complications (OR, 1.49 [95% CI, 1.23–1.81]) and 90-day mortality (OR, 1.44 [95% CI, 1.09–1.91]) compared with those without dementia.[224]
- In a registry-based longitudinal study in Sweden, among 23 759 patients >50 years of age with a nonpathological hip fracture previously able to walk,

25% of patients with dementia lost their ability to walk compared with 7% of those with no cognitive dysfunction.[225] After adjustment for several other risk factors, dementia was associated with an increased risk of loss of walking ability at 4 months (OR, 1.80 [95% CI, 1.57–2.06]).

- Among 11 studies (N=9504) in individuals with MCI, apathy was associated with an increased risk of conversion to dementia (HR, 1.54 [95% CI, 1.29–1.84]).[226]
- In a meta-analysis of 11 case-control and case series studies, orthostatic hypotension was present in 28% (95% CI, 17%–40%) of 500 patients with AD.[227] AD was associated with higher odds of orthostatic hypotension compared with healthy controls (OR, 2.53 [95% CI, 1.10–5.86[).
- In a prospective, multicenter, observational study among patients recently diagnosed with prodromal AD (n=50) or dementia due to AD (n=127), the prevalence of nutritional impairment based on the Mini Nutritional Assessment test was 28.2%.[228] A larger proportion of patients with progression was observed among those with nutritional impairment (50%) than among those with normal nutritional status (29%; $P<0.05$). More severe cognitive impairment (OR, 2.1 [95% CI, 1.03–4.4]) and nutritional impairment (OR, 2.4 [95% CI, 1.1–5.1]) independently predicted disease progression.
- In a multicenter observational cross-sectional study in patients with Huntington disease (N=158), 90.5% of patients had ≥1 dysphagia symptoms.[229] The prevalence of fear of choking in patients was 45.7%.
- In a retrospective cohort study (n=8640 patients with dementia without prior periodontitis and 8640 propensity score–matched control individuals without dementia), 2670 patients with dementia developed periodontitis.[230] The risk of periodontitis was significantly higher in those with dementia compared with those without dementia (aHR, 1.92 [95% CI, 1.77–2.08]).
- In a series of meta-analyses of the prevalence of uncontrolled episodes of crying and laughing (pseudobulbar affect) in patients with neurodegenerative disorders, the prevalence of pseudobulbar affect was highest in amyotrophic lateral sclerosis (38.5% [95% CI, 31%–45%]).[231] The prevalence in patients with PD ranged between 1% and 31% across studies, with an overall meta-analysis prevalence of 16.5%. Pseudobulbar affect prevalence in AD was 16.4% (95% CI, 7%–25%).
- In a study from the French Dijon Stroke Registry of 1048 patients with ischemic stroke, prestroke MCI or dementia was associated with more severe stroke assessed with the NIHSS compared with no cognitive impairment (aOR for MCI, 1.52 [95% CI, 1.02–2.28]; aOR for dementia, 2.16 [95% CI, 1.45–3.22]).[232]
- In a meta-analysis of 29 studies including 61 824 individuals with AD followed up for incident stroke, incidence of total stroke (20 studies) was 15.4 per 1000 person-years (95% CI, 10.6–20.3), incidence of ischemic stroke (11 studies) was 13.0 per 1000 person-years (95% CI, 7.6–18.5), and incidence of ICH (16 studies) was 3.4 per 1000 person-years (95% CI, 2.3–4.6).[233] Individuals with AD compared with controls without AD (3 studies) had 1.31 times the incidence of total stroke (95% CI, 1.07–1.59), 1.22 times the incidence of ischemic stroke (95% CI, 0.95–1.57), and 1.67 times the incidence of ICH (95% CI, 1.43–1.96).
- Among 3111 community-dwelling older adults in the Taiwan Longitudinal Study on Aging, prevalence of disability in instrumental activities of daily living was 71.8% among participants who had cognitive impairment without stroke, 56.8% among participants who had stroke without cognitive impairment, and 91.5% among participants who had cognitive impairment and stroke compared with 24.2% among participants who were cognitively intact with no stroke ($P<0.001$).[234]

## Health Care Use

- In Japan, among 8897 patients discharged from a general acute care hospital who had undergone cognitive screening before admission, having moderate cognitive impairment was associated with 1.42 times (95% CI, 1.01–2.00) higher risk for readmission within 90 days and having severe cognitive impairment was associated with 2.21 times (95% CI, 1.21–4.06) higher risk for readmission within 90 days compared with normal cognitive screening.[235]
- Among 490 community-dwelling people living with dementia with a family caregiver in the Baltimore, MD, area, 34.4% were hospitalized at least once in the course of 12 months.[236] Infection (22.4%), falls (16.5%), and cardiovascular/pulmonary (12.4%) were the leading reasons for hospitalization.
- Use of hospice care during the last 6 months of life with dementia varies by race, sex, and level of education. Among 5058 participants in HRS with linked Medicare claims who were diagnosed with dementia and died between 2000 and 2016, NH Black individuals had 35% lower odds (95% CI, 22%–45% lower) of using hospice care than NH White individuals.[237] Females had 19% higher odds (95% CI, 5%–35% higher) of using hospice care than males. Individuals with high school education had 17% higher odds (95% CI, 1%–36% higher) and those with more than high school education had 32% higher odds (95% CI, 13%–54% higher)

of using hospice care compared with those with less than high school education.

- Use of ED care and inpatient hospitalization during the last 6 months of life with dementia varies by race and ethnicity. Among 5058 participants in HRS with linked Medicare claims who were diagnosed with dementia and died between 2000 and 2016, ED care was used by 79.7% of Black individuals and 76.8% of Hispanic individuals compared with 70.7% of White individuals ($P<0.001$).[237] Inpatient hospitalization occurred for 77.3% of Black individuals and 77.0% of Hispanic individuals compared with 67.5% of White individuals ($P<0.001$). In addition, completing advance care planning was lower among Black individuals (20.7%) and Hispanic individuals (21.4%) than among White individuals (57.1%); having written instructions to choose all care possible to prolong life was higher among Black individuals (20.8%) and Hispanic individuals (18.4%) than among White individuals (3.9%).
- In Italy, among 108 patients with cognitive impairment who were contacted by video call for a telemedicine neurological evaluation, 74 (68.5%) successfully connected for the televisit, and 34 (31.5%) were unable to connect for the televisit.[238] Successful connection for the televisit was higher (86%) when a child or grandchild of the patient was present than in the absence of a child or grandchild (49%).
- Patients with stroke with preexisting cognitive impairment or dementia may receive different care compared with cognitively normal patients with stroke. Among 836 adults with AIS in the Brain Attack Surveillance in Corpus Christi project, having preexisting dementia compared with being cognitively normal was associated with lower odds of receiving antithrombotic therapy by day 2 (OR, 0.39 [95% CI, 0.16–0.96]) and echocardiogram (OR, 0.42 [95% CI, 0.26–0.67]).[239] Preexisting MCI compared with normal cognition was associated with lower odds of receiving intravenous tPA (OR, 0.36 [95% CI, 0.14–0.96]), rehabilitation assessment (OR, 0.28 [95% CI, 0.10–0.79]), and echocardiogram (OR, 0.48 [95% CI, 0.32–0.73]). A composite quality measure of care received compared with care eligible to receive was not significantly associated with dementia (OR, 0.79 [95% CI, 0.55–1.12]) or with MCI (OR, 1.06 [95% CI, 0.77–1.45]). Among 7070 patients with acute stroke in the Australian Stroke Foundation national audit, those with dementia were more likely to receive no rehabilitation (OR, 1.88 [95% CI, 1.25–2.83]) and to be discharged to residential care (OR, 2.36 [95% CI, 1.50–3.72]).[240]
- A structured dementia care program was examined with regard to health care use and cost outcomes.[241] The program included structured needs assessments of patients and caregivers, individualized care plans, coordination with primary care, referrals to community organizations for dementia-related services and support, and continuous access to clinicians for assistance and advice. Compared with community control subjects (n=2163), those in the program (n=1083) were less likely to be admitted to a long-term care facility (HR, 0.60 [95% CI, 0.59–0.61]). There were no differences between groups in terms of hospitalizations, ED visits, or 30-day readmissions.

## Cost

- Estimated US spending on dementias more than doubled from $38.6 billion (95% CI, $34.1–$42.8 billion) in 1996 to $79.2 billion (95% CI, $67.6–$90.8 billion) in 2016. Spending on dementias was among the top 10 health care costs in the United States in 2016.[242]
- Among 3619 HRS participants with incident dementia, during the first 8 years after diagnosis, mean estimated total out-of-pocket spending on medical costs was $22 795 (95% CI, $21 236–$24 398), which was $8751 more (95% CI, $7354–$10 217) than the expected mean 8-year total out-of-pocket spending without dementia of $14 044 (95% CI, $13 544–$14 597).[243] Additional out-of-pocket spending attributed to dementia was much higher for NH White individuals (mean, $16 766 [95% CI, $14 305–$19 380]) than for Black or Hispanic individuals (mean, $853 [95% CI, −$441 to $2209]) and was higher for females (mean, $13 706 [95% CI, $11 393–$16 322]) than for males (mean $5744 [95% CI, $3815–$7801]). Additional out-of-pocket spending attributed to dementia and the race, ethnicity, and sex differences were due largely to out-of-pocket nursing home costs.
- Inpatient hospitalization costs during the last 6 months of life with dementia vary by race and ethnicity. Among 5058 participants in HRS with linked Medicare claims who were diagnosed with dementia and died between 2000 and 2016, mean inpatient hospitalization costs were $23 279 for Black individuals (95% CI, $20 690–$25 868) and $23 471 for Hispanic individuals (95% CI, $19 532–$27 410) compared with $14 609 for White individuals (95% CI, $13 800–$15 418).[237]
- Among an estimated 690 000 people with dementia in England, 565 000 received unpaid care, received community care, or lived in a care home (assisted living residence or nursing home).[244] Total annual cost of dementia care in England was estimated to be £24.2 billion in 2015, of which 42% (£10.1 billion) was attributable to unpaid care. Social care costs (£10.2 billion) were 3 times larger than health

care costs (£3.8 billion), and £6.2 billion of the total social care costs was met by users themselves and their families, with £4.0 billion (39.4%) funded by the government. The economic impact of dementia weighs more heavily on the social care than on the health care sector and on people with more severe dementia.

- A structured dementia care program was examined with regard to health care use and cost outcomes.[241] The total cost of care to Medicare, excluding program costs, was $601 less per patient per quarter (95% CI, $5–$1198). After accounting for the estimated program costs of $317 per patient per quarter, the program was cost neutral for Medicare, with an estimated net cost of −$284 (95% CI, −$881 to $312) per program participant per quarter.
- Among 2779 HRS participants with incident dementia, mean Medicare spending in the quarter during which the diagnosis occurred was $13794, which was $8400 more ($P<0.001$) than mean Medicare spending of $5394 in the quarter before the diagnosis.[245] The additional costs in the quarter containing the diagnosis were not significantly different (all group differences $P>0.1$) for females (+$7899) versus males (+$9248), for NH Black individuals (+$8709) versus NH White individuals (+$8388), for college graduates (+$7265) versus those with less than college graduation (+$8639), and for those living in rural areas (+$8849) versus those living in nonrural areas (+$8666).

## Global Burden

All prevalence and mortality estimates cited here are courtesy of the GBD Study 2021 based on 204 countries and territories and pertain to all types of dementia combined.[246]

### *Prevalence: GBD Study 2021*

#### *(See Table 16-3 and Chart 16-2)*

- There were 56.85 (95% UI, 49.56–64.08) million prevalent cases of AD and other dementias in 2021, with 20.75 (95% UI, 17.96–23.69) million among males and 36.10 (95% UI, 31.67–40.61) million among females (Table 16-3).
- In 2021, the highest age-standardized prevalence rates of AD and other dementias were found in East Asia followed by high-income North America, North Africa and the Middle East, tropical Latin America, and central sub-Saharan Africa (Chart 16-2).

### *Mortality: GBD Study 2021*

#### *(See Table 16-3 and Chart 16-3)*

- There were 1.90 (95% UI, 0.51–4.78) million deaths due to AD and other dementias in 2021 (Table 16-3).
- In 2021, mortality rates estimated for AD and other dementias were highest in central sub-Saharan Africa. Mortality was lowest in Andean and central Latin America (Chart 16-3).

## COVID-19

- In a meta-analysis of 19 studies of post–COVID-19 syndrome (long COVID) with 11324 participants with COVID-19, prevalence of cognitive dysfunction was assessed ≥3 months after COVID-19 onset.[247] Prevalence of memory issues (5 studies; 5268 participants) was 27% (95% CI, 18%–36%); prevalence of attention disorder (3 studies; 1207 participants) was 22% (95% CI, 10%–34%); and prevalence of brain fog (3 studies; 4329 participants) was 32% (95% CI, 9%–55%). In another meta-analysis of 43 studies, prevalence of cognitive impairment ≥12 weeks after COVID-19 diagnosis was 22% (95% CI, 17%–28%).[248]
- In a study of 263 older adults in France who had cognitive measures obtained longitudinally for up to 15 years before the COVID-19 pandemic and during the COVID-19 pandemic, decline in global cognitive ability accelerated during the pandemic ($\beta=-0.289$ [$P<0.001$]), suggesting that the circumstances of the pandemic such as isolation and loneliness may contribute to cognitive decline.[249]
- In a study of 401 UK Biobank participants who had brain imaging before and after COVID-19 infection and 385 control subjects who had brain imaging at 2 time points on average 2 years apart without COVID-19 infection, those who had COVID-19 experienced 7.8% greater increase in time to complete Trails A (uncorrected $P=0.0002$; family-wise error–corrected $P=0.005$) and 12.2% greater increase in time to complete Trails B (uncorrected $P=0.0007$; family-wise error–corrected $P=0.002$) relative to control subjects without COVID-19. Those with COVID-19 also had significantly reduced gray matter thickness in certain regions, changes in tissue damage biomarker levels, and reduced global brain size, suggesting that COVID-19 infection affected brain structure.[250]
- In a cohort study evaluating cognitive decline during the first year after COVID-19 infection among 1438 COVID-19 survivors and 438 uninfected spouses, the authors found that 12.5% of those with COVID-19 had incident cognitive impairment within 12 months.[251] Compared with uninfected spouses and with adjustment for demographics and comorbidities, survivors of severe COVID-19 had 4.87 times the odds of cognitive decline at 6 months followed by remaining stable through 12 months (95% CI, 3.30–7.20), 7.58 times the odds of cognitive decline only at 12 months after being stable at 6 months

(95% CI, 3.58–16.03), and 19.00 times the odds of progressive cognitive decline at both 6 and 12 months (95% CI, 9.14–39.51).

- Dementia is a risk factor for mortality in patients with COVID-19. In a meta-analysis of 3 studies including 130 patients with COVID-19 with dementia and 805 patients with COVID-19 without dementia, having dementia was associated with 3.69 times the odds of mortality (95% CI, 1.99–6.83).[252] Mortality among 223 patients with COVID-19 >50 years of age in South Korea who had underlying dementia was 33.6% compared with 20.2% among 223 propensity-matched patients with COVID-19 who did not have dementia (aOR, 3.05 [95% CI, 1.80–5.30]); dementia was also associated with requiring a ventilator (24.1% versus 22.0% without dementia; $P<0.001$).[253] In a meta-analysis of 10 studies including 56577 patients with COVID-19 with 10% prevalence of dementia, having dementia was associated with 1.80 times the adjusted odds of death (95% CI, 1.45–2.24).[254]
- Pandemic conditions were associated with excess mortality among people with dementia. In a meta-analysis of 11 studies of people with dementia who did not have COVID-19, the mortality rate during the pandemic period was 1.25 times as high as in the prepandemic period (95% CI, 1.21–1.29).[255] Mortality among residents of assisted living facilities increased during the pandemic. In a study of 273601 Medicare beneficiaries living in assisted living facilities in 2020, compared with 286350 such beneficiaries in 2019, excess weekly mortality in 2020 versus 2019 was higher among those with dementia by an additional 33.4 deaths per 100000 per week (95% CI, 25.9–40.9) compared with the excess weekly mortality among those not having dementia (Chart 16-4).[256]
- COVID-19 is also a risk factor for subsequent dementia. Among 7133 COVID-19 survivors and 299444 control subjects without COVID-19 in the Korean National Health Insurance Service database, all free of dementia at baseline, COVID-19 survivors had 1.39 times the hazard of new-onset dementia compared with people without COVID-19 (95% CI, 1.05–1.85).[257] Among > 6 million individuals in the TriNetX Analytics Platform, people with COVID-19 died at 1.69 times the rate of those without COVID-19 (95% CI, 1.53–1.72).[258] A systematic review and meta-analysis of the impact of dementia on the clinical outcomes of COVID-19 used 10 studies including 119218 individuals.[259] The review found that overall the incidence of dementia in patients with COVID-19 was 9% (95% CI, 6%–13%). In the meta-analysis of 9 studies, the mortality rate in individuals with dementia after being infected with COVID-19 was significantly higher than in those without dementia (OR, 5.17 [95% CI, 2.31–11.59]).

**Table 16-1. Health Expectancies by Number of Cardiovascular Conditions Across Age Groups, HRS in the United States, 1996 to 2014**

| | No. of cardiovascular conditions* | | | |
|---|---|---|---|---|
| | 0; y (95% CI) | 1; y (95% CI) | 2; y (95% CI) | ≥3; y (95% CI) |
| At 55 y of age | | | | |
| CIFLE | 23.0 (22.6–23.4) | 21.2 (20.9–21.5) | 18.1 (17.7–18.4) | 14.0 (13.5–14.5) |
| CILE | 6.7 (6.4–7.0) | 6.2 (6.0–6.4) | 5.5 (5.3–5.8) | 4.6 (4.2–5.0) |
| TLE | 29.7 (29.3–30.2) | 27.4 (27.0–27.8) | 23.6 (23.1–24.0) | 18.6 (18.0–19.2) |
| At 65 y of age | | | | |
| CIFLE | 15.0 (14.6–15.3) | 13.3 (13.1–13.6) | 10.9 (10.7–11.2) | 7.9 (7.6–8.3) |
| CILE | 6.4 (6.1–6.7) | 5.8 (5.6–6.0) | 5.2 (5.0–5.4) | 4.3 (4.0–4.6) |
| TLE | 21.3 (20.9–21.8) | 19.2 (18.9–19.5) | 16.1 (15.8–16.4) | 12.2 (11.9–12.6) |
| At 75 y of age | | | | |
| CIFLE | 8.4 (8.1–8.6) | 7.1 (6.9–7.3) | 5.6 (5.4–5.7) | 3.7 (3.5–3.9) |
| CILE | 5.7 (5.4–5.9) | 5.1 (4.9–5.3) | 4.5 (4.3–4.6) | 3.7 (3.5–3.9) |
| TLE | 14.0 (13.7–14.4) | 12.2 (12.0–12.5) | 10.0 (9.8–10.3) | 7.4 (7.1–7.6) |
| At 85 y of age | | | | |
| CIFLE | 3.8 (3.6–4.0) | 3.1 (2.9–3.2) | 2.3 (2.1–2.4) | 1.4 (1.2–1.5) |
| CILE | 4.5 (4.3–4.7) | 3.9 (3.8–4.1) | 3.4 (3.3–3.6) | 2.7 (2.5–2.8) |
| TLE | 8.3 (8.0–8.6) | 7.0 (6.8–7.2) | 5.7 (5.5–5.8) | 4.1 (3.9–4.2) |

CIFLE indicates cognitive impairment-free life expectancy; CILE, cognitive impairment life expectancy; HRS, Health and Retirement Study; and TLE, total life expectancy.

*Cardiovascular conditions included hypertension, heart disease, diabetes, and stroke.

Source: Adapted from Zheng et al.[135] with permission. Copyright © 2021 Oxford University Press.

**Table 16-2. Dementia Mortality in the United States**

| Population group | Mortality, 2021: all ages* |
|---|---|
| Both sexes | 279 704 |
| Males | 92 303 (33.0%)† |
| Females | 187 401 (67.0%)† |
| NH White males | 76 082 |
| NH White females | 153 117 |
| NH Black males | 7506 |
| NH Black females | 16 179 |
| Hispanic males | 5815 |
| Hispanic females | 12 061 |
| NH Asian males | 2189‡ |
| NH Asian females | 4604‡ |
| NH American Indian or Alaska Native | 874 |
| NH Native Hawaiian or Other Pacific Islander | 170 |

Data represent underlying cause of death only using *ICD-10* codes F01, F03, and G30 through G31. (*ICD-10* codes F00 and F02 are not listed as underlying or multiple causes of death in the NVSS.)

ICD-10 indicates *International Classification of Diseases, 10th Revision*; NH, non-Hispanic; and NVSS, National Vital Statistics System.

*Mortality for American Indian or Alaska Native and Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native, Asian and Pacific Islander, and Hispanic decedents, as well as undercounts of these groups in censuses.

†These percentages represent the portion of total mortality that is for males vs females.

‡Includes Chinese, Filipino, Japanese, and other Asian people.

Source: Mortality: Unpublished National Heart, Lung, and Blood Institute tabulation using NVSS.[211]

**Table 16-3. Global Mortality and Prevalence of AD and Other Dementias, by Sex, 2021**

| | Both sexes | | Male | | Female | |
|---|---|---|---|---|---|---|
| | Deaths (95% UI) | Prevalence (95% UI) | Deaths (95% UI) | Prevalence (95% UI) | Deaths (95% UI) | Prevalence (95% UI) |
| Total number (millions), 2021 | 1.90 (0.51 to 4.78) | 56.85 (49.56 to 64.08) | 0.61 (0.15 to 1.67) | 20.75 (17.96 to 23.69) | 1.30 (0.35 to 3.11) | 36.10 (31.67 to 40.61) |
| Percent change in total number, 1990–2021 | 189.11 (173.25 to 215.55) | 160.69 (155.42 to 165.51) | 210.67 (189.33 to 235.71) | 170.95 (164.12 to 176.73) | 180.00 (160.49 to 210.78) | 155.14 (150.65 to 159.95) |
| Percent change in total number, 2010–2021 | 49.79 (44.37 to 57.45) | 45.46 (44.02 to 46.90) | 53.73 (46.24 to 62.92) | 47.13 (45.53 to 48.75) | 48.01 (40.87 to 56.99) | 44.51 (42.89 to 45.96) |
| Rate per 100 000, age-standardized, 2021 | 23.98 (6.39 to 59.89) | 703.17 (614.51 to 790.43) | 19.11 (4.85 to 51.59) | 597.08 (520.52 to 676.88) | 27.07 (7.38 to 65.08) | 779.97 (683.92 to 876.91) |
| Percent change in rate, age standardized, 1990–2021 | −5.99 (−9.16 to −0.81) | 3.16 (1.59 to 4.23) | −6.00 (−10.19 to −0.64) | 3.07 (0.96 to 4.35) | −3.92 (−8.90 to 3.00) | 4.51 (3.19 to 5.57) |
| Percent change in rate, age standardized, 2010–2021 | −4.26 (−7.33 to −0.23) | 2.99 (2.15 to 3.79) | −4.03 (−7.74 to 1.11) | 2.98 (2.13 to 3.76) | −3.38 (−7.19 to 1.32) | 3.49 (2.52 to 4.37) |

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

AD indicates Alzheimer disease; GBD, Global Burden of Disease; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[246]

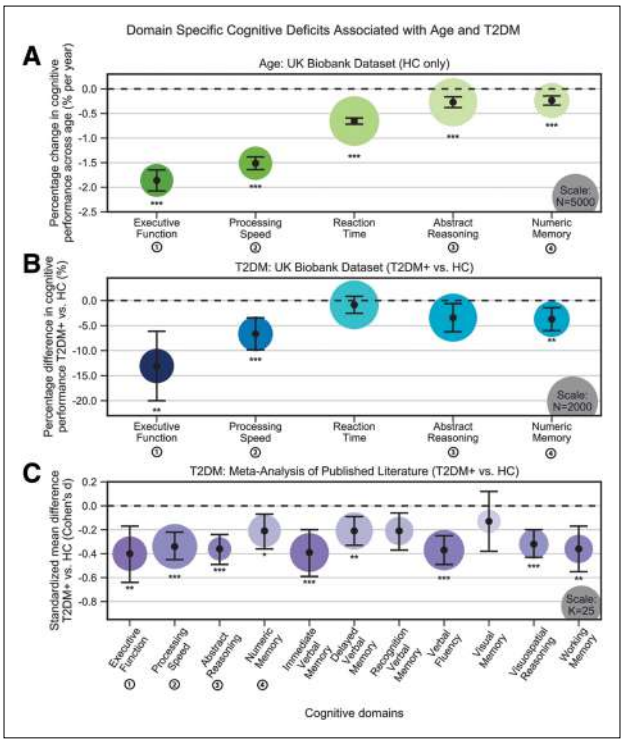



**Chart 16-1. Domain-specific cognitive deficits associated with age and type 2 diabetes.**

**A**, In the UK Biobank, among participants without type 2 diabetes, age was associated with statistically significant deficits in executive function, processing speed, abstract reasoning, numeric memory, and reaction time. **B**, In the UK Biobank, type 2 diabetes was associated with statistically significant deficits in executive function, processing speed, abstract reasoning, and numeric memory but not in reaction time. **C**, In meta-analysis of published literature, type 2 diabetes was associated with statistically significant deficits in executive function, processing speed, abstract reasoning, numeric memory, immediate verbal memory, delayed verbal memory, recognition verbal memory, verbal fluency, visuospatial reasoning, and working memory but not in visual memory. Error bars are 95% CI. **P*≤0.05, ***P*≤0.01, ****P*≤0.001, Bonferroni corrected.

HC indicates healthy controls; and T2DM, type 2 diabetes.

Source: Reprinted from Antal et al.[96] This article is distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use and redistribution provided that the original author and source are credited.

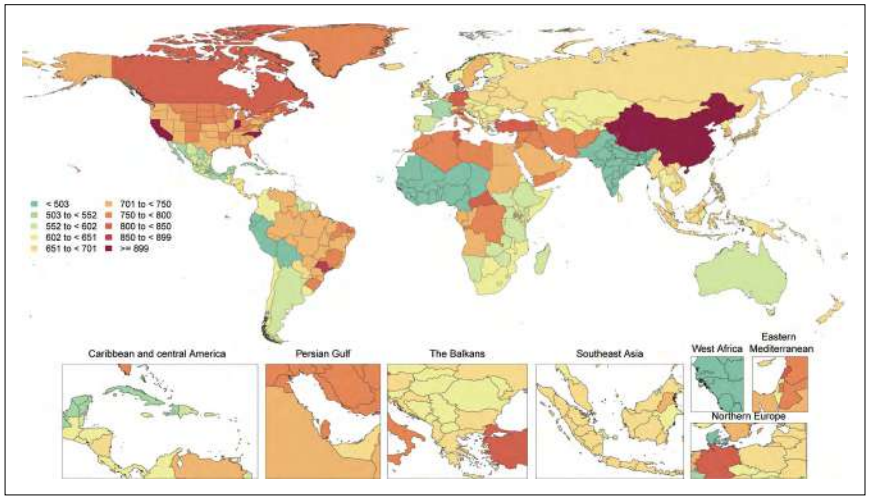



**Chart 16-2. Age-standardized global prevalence rates of AD and other dementias per 100 000, both sexes, 2021.**

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

AD indicates Alzheimer disease; and GBD, Global Burden of Disease.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[246]

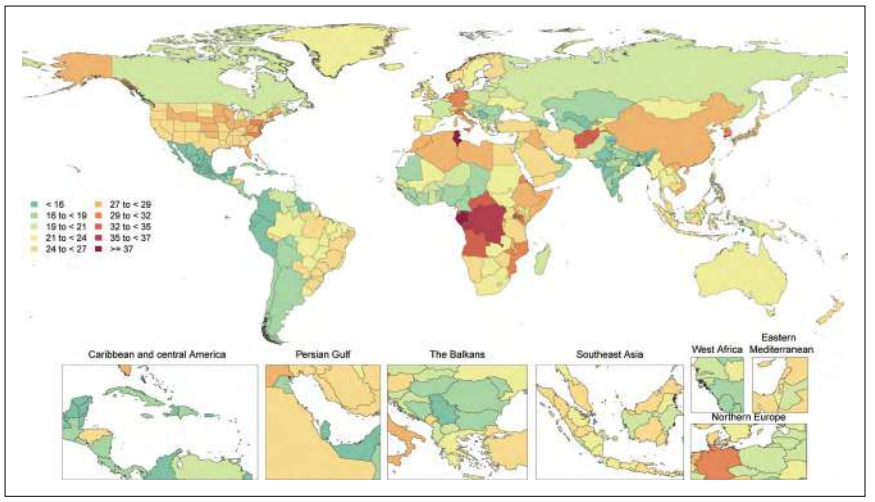



**Chart 16-3. Age-standardized global mortality rates of AD and other dementias per 100 000, both sexes, 2021.**

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.
AD indicates Alzheimer disease; and GBD, Global Burden of Disease.
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[246]

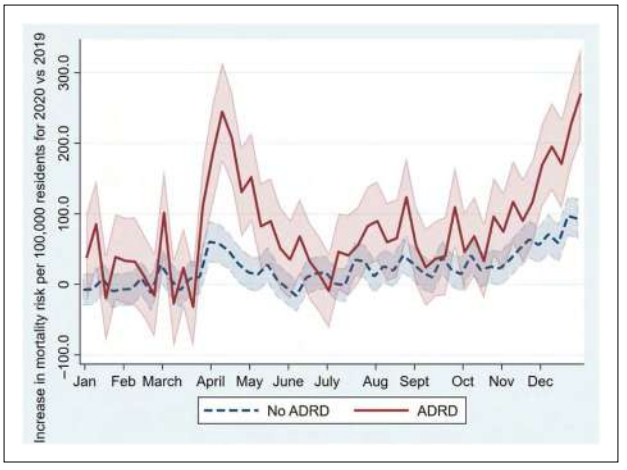



**Chart 16-4. Unadjusted weekly rate of excess all-cause mortality per 100 000 assisted living residents during COVID-19 comparing those with ADRD and those without ADRD.**

Weekly unadjusted excess all-cause mortality was calculated using the Centers for Medicare & Medicaid Services Vital Status file. The calendar week began on January 1 of each year. Assisted living residents with Medicare Advantage and residents in small assisted living communities (<25 beds) were excluded. Minnesota and Connecticut were excluded because of their different licensing structures. Shaded areas represent CIs.
ADRD indicates Alzheimer disease and related dementias; and COVID-19, coronavirus disease 2019.
Source: Reprinted from Hua et al.[256] Copyright 2022, with permission from AMDA — The Society for Post-Acute and Long-Term Care Medicine.

## REFERENCES


1. Gorelick PB, Furie KL, Iadecola C, Smith EE, Waddy SP, Lloyd-Jones DM, Bae HJ, Bauman MA, Dichgans M, Duncan PW, et al; on behalf of the American Heart Association/American Stroke Association. Defining optimal brain health in adults: a presidential advisory from the American Heart Association/American Stroke Association. *Stroke*. 2017;48:e284–e303. doi: 10.1161/STR.0000000000000148
2. Jicha GA, Parisi JE, Dickson DW, Johnson K, Cha R, Ivnik RJ, Tangalos EG, Boeve BF, Knopman DS, Braak H, et al. Neuropathologic outcome of mild cognitive impairment following progression to clinical dementia. *Arch Neurol*. 2006;63:674–681. doi: 10.1001/archneur.63.5.674
3. Wolters FJ, Ikram MA. Epidemiology of vascular dementia. *Arterioscler Thromb Vasc Biol*. 2019;39:1542–1549. doi: 10.1161/ATVBAHA.119.311908
4. Kapasi A, DeCarli C, Schneider JA. Impact of multiple pathologies on the threshold for clinically overt dementia. *Acta Neuropathol*. 2017;134:171–186. doi: 10.1007/s00401-017-1717-7
5. GBD 2016 Dementia Collaborators. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. 2019;18:88–106. doi: 10.1016/S1474-4422(18)30403-4
6. National Institute of Neurological Disorders. Focus on Alzheimer's disease and related dementia. Accessed April 21, 2023. https://ninds.nih.gov/Current-Research/Focus-Disorders/Alzheimers-Related-Dementias
7. Hudomiet P, Hurd MD, Rohwedder S. Dementia prevalence in the United States in 2000 and 2012: estimates based on a nationally representative study. *J Gerontol B Psychol Sci Soc Sci*. 2018;73:S10–S19. doi: 10.1093/geronb/gbx169
8. Feigin VL, Vos T, Alahdab F, Amit AML, Barnighausen TW, Beghi E, Beheshti M, Chavan PP, Criqui MH, Desai R, et al; GBD 2017 US Neurological Disorders Collaborators. Burden of neurological disorders across the US from 1990-2017: a Global Burden of Disease Study. *JAMA Neurol*. 2021;78:165–176. doi: 10.1001/jamaneurol.2020.4152
9. Matthews KA, Xu W, Gaglioti AH, Holt JB, Croft JB, Mack D, McGuire LC. Racial and ethnic estimates of Alzheimer's disease and related dementias in the United States (2015-2060) in adults aged >/=65 years. *Alzheimers Dement*. 2019;15:17–24. doi: 10.1016/j.jalz.2018.06.3063
10. Lennon JC, Aita SL, Bene VAD, Rhoads T, Resch ZJ, Eloi JM, Walker KA. Black and White individuals differ in dementia prevalence, risk factors, and symptomatic presentation. *Alzheimers Dement*. 2022;18:1461–1471. doi: 10.1002/alz.12509
11. Prince MJ. World Alzheimer report 2015—the global impact of dementia: an analysis of prevalence, incidence, cost and trends. 2015. Accessed April 20, 2023. https://alzint.org/u/WorldAlzheimerReport2015.pdf
12. Wimo A, Guerchet M, Ali GC, Wu YT, Prina AM, Winblad B, Jonsson L, Liu Z, Prince M. The worldwide costs of dementia 2015 and comparisons with 2010. *Alzheimers Dement*. 2017;13:1–7. doi: 10.1016/j.jalz.2016.07.150
13. Mattap SM, Mohan D, McGrattan AM, Allotey P, Stephan BC, Reidpath DD, Siervo M, Robinson L, Chaiyakunapruk N. The economic burden of dementia in low- and middle-income countries (LMICs): a systematic review. *BMJ Glob Health*. 2022;7:e007409. doi: 10.1136/bmjgh-2021-007409
14. Brookmeyer R, Abdalla N, Kawas CH, Corrada MM. Forecasting the prevalence of preclinical and clinical Alzheimer's disease in the United States. *Alzheimers Dement*. 2018;14:121–129. doi: 10.1016/j.jalz.2017.10.009
15. 2021 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2021;17:327–406. doi: 10.1002/alz.12328
16. Chang Wong E, Chang Chui H. Vascular cognitive impairment and dementia. *Continuum (Minneap Minn)*. 2022;28:750–780. doi: 10.1212/CON.0000000000001124
17. Davis MA, Lee KA, Harris M, Ha J, Langa KM, Bynum JPW, Hoffman GJ. Time to dementia diagnosis by race: a retrospective cohort study. *J Am Geriatr Soc*. 2022;70:3250–3259. doi: 10.1111/jgs.18078
18. Kornblith E, Bahorik A, Boscardin WJ, Xia F, Barnes DE, Yaffe K. Association of race and ethnicity with incidence of dementia among older adults. *JAMA*. 2022;327:1488–1495. doi: 10.1001/jama.2022.3550
19. Du XL, Song L, Schulz PE, Xu H, Chan W. Risk of developing Alzheimer's disease and related dementias in association with cardiovascular disease, stroke, hypertension, and diabetes in a large cohort of women with breast cancer and with up to 26 years of follow-up. *J Alzheimers Dis*. 2022;87:415–432. doi: 10.3233/JAD-215657
20. Rajan KB, Weuve J, Barnes LL, Wilson RS, Evans DA. Prevalence and incidence of clinically diagnosed Alzheimer's disease dementia from 1994 to 2012 in a population study. *Alzheimers Dement*. 2019;15:1–7. doi: 10.1016/j.jalz.2018.07.216
21. Yeverino-Castro SG, Mejia-Arango S, Mimenza-Alvarado AJ, Cantu-Brito C, Avila-Funes JA, Aguilar-Navarro SG. Prevalence and incidence of possible vascular dementia among Mexican older adults: analysis of the Mexican Health and Aging Study. *PLoS One*. 2021;16:e0253856. doi: 10.1371/journal.pone.0253856
22. Yoshida D, Ohara T, Hata J, Shibata M, Hirakawa Y, Honda T, Furuta Y, Oishi E, Sakata S, Kanba S, et al. Lifetime cumulative incidence of dementia in a community-dwelling elderly population in Japan. *Neurology*. 2020;95:e508–e518. doi: 10.1212/WNL.0000000000009917
23. Lucca U, Tettamanti M, Tiraboschi P, Logroscino G, Landi C, Sacco L, Garri M, Ammesso S, Biotti A, Gargantini E, et al. Incidence of dementia in the oldest-old and its relationship with age: the Monzino 80-Plus population-based study. *Alzheimers Dement*. 2020;16:472–481. doi: 10.1016/j.jalz.2019.09.083
24. Klijs B, Mitratza M, Harteloh PPM, Moll van Charante EP, Richard E, Nielen MMJ, Kunst AE. Estimating the lifetime risk of dementia using nationwide individually linked cause-of-death and health register data. *Int J Epidemiol*. 2021;50:809–816. doi: 10.1093/ije/dyaa219
25. Chene G, Beiser A, Au R, Preis SR, Wolf PA, Dufouil C, Seshadri S. Gender and incidence of dementia in the Framingham Heart Study from mid-adult life. *Alzheimers Dement*. 2015;11:310–320. doi: 10.1016/j.jalz.2013.10.005
26. GBD 2019 Collaborators. Global mortality from dementia: application of a new method and results from the Global Burden of Disease Study 2019. *Alzheimers Dement (N Y)*. 2021;7:e12200. doi: 10.1002/trc2.12200
27. Morovatdar N, Avan A, Azarpazhooh MR, Di Napoli M, Stranges S, Kapral MK, Rezayat AA, Shariatzadeh A, Abootalebi S, Mokhber N, et al. Secular trends of ischaemic heart disease, stroke, and dementia in high-income countries from 1990 to 2017: the Global Burden of Disease Study 2017. *Neurol Sci*. 2022;43:255–264. doi: 10.1007/s10072-021-05259-2
28. GBD 2019 Dementia Forecasting Collaborators. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. *Lancet Public Health*. 2022;7:e105–e125. doi: 10.1016/S2468-2667(21)00249-8
29. Hudomiet P, Hurd MD, Rohwedder S. Trends in inequalities in the prevalence of dementia in the United States. *Proc Natl Acad Sci USA*. 2022;119:e2212205119. doi: 10.1073/pnas.2212205119
30. Ding M, Qiu C, Rizzuto D, Grande G, Fratiglioni L. Tracing temporal trends in dementia incidence over 25 years in central Stockholm, Sweden. *Alzheimers Dement*. 2020;16:770–778. doi: 10.1002/alz.12073
31. Hegelund ER, Mehta AJ, Mortensen LH, Westendorp RGJ. The plasticity of late-onset dementia: A nationwide cohort study in Denmark. *Alzheimers Dement*. 2022;18:1287–1295. doi: 10.1002/alz.12469
32. Wolters FJ, Chibnik LB, Waziry R, Anderson R, Berr C, Beiser A, Bis JC, Blacker D, Bos D, Brayne C, et al. Twenty-seven-year time trends in dementia incidence in Europe and the United States: the Alzheimer Cohorts Consortium. *Neurology*. 2020;95:e519–e531. doi: 10.1212/WNL.0000000000010022
33. Gao S, Burney HN, Callahan CM, Purnell CE, Hendrie HC. Incidence of dementia and Alzheimer disease over time: a meta-analysis. *J Am Geriatr Soc*. 2019;67:1361–1369. doi: 10.1111/jgs.16027
34. Power MC, Bennett EE, Turner RW, Dowling NM, Ciarleglio A, Glymour MM, Gianattasio KZ. Trends in relative incidence and prevalence of dementia across non-Hispanic Black and White individuals in the United States, 2000-2016. *JAMA Neurol*. 2021;78:275–284. doi: 10.1001/jamaneurol.2020.4471
35. Yoseph M, Paddick SM, Gray WK, Andrea D, Barber R, Colgan A, Dotchin C, Urasa S, Kisoli A, Kissima J, et al. Prevalence estimates of dementia in older adults in rural Kilimanjaro 2009-2010 and 2018-2019: is there evidence of changing prevalence? *Int J Geriatr Psychiatry*. 2021;36:950–959. doi: 10.1002/gps.5498
36. Akinyemi RO, Yaria J, Ojagbemi A, Guerchet M, Okubadejo N, Njamnshi AK, Sarfo FS, Akpalu A, Ogbole G, Ayantayo T, et al; African Dementia Consortium (AfDC). Dementia in Africa: Current evidence, knowledge gaps, and future directions. *Alzheimers Dement*. 2022;18:790–809. doi: 10.1002/alz.12432
37. Wu H, Le Couteur DG, Hilmer SN. Mortality trends of stroke and dementia: changing landscapes and new challenges. *J Am Geriatr Soc*. 2021;69:2888–2898. doi: 10.1111/jgs.17322
38. Satizabal CL, Beiser AS, Chouraki V, Chene G, Dufouil C, Seshadri S. Incidence of dementia over three decades in the Framingham Heart Study. *N Engl J Med*. 2016;374:523–532. doi: 10.1056/NEJMoa1504327

39. Ou Y-N, Tan C-C, Shen X-N, Xu W, Hou X-H, Dong Q, Tan L, Yu J-T. Blood pressure and risks of cognitive impairment and dementia. *Hypertension*. 2020;76:217–225. doi: 10.1161/HYPERTENSIONAHA.120.14993
40. Abell JG, Kivimäki M, Dugravot A, Tabak AG, Fayosse A, Shipley M, Sabia S, Singh-Manoux A. Association between systolic blood pressure and dementia in the Whitehall II cohort study: role of age, duration, and threshold used to define hypertension. *Eur Heart J*. 2018;39:3119–3125. doi: 10.1093/eurheartj/ehy288
41. Zhou H, Zhu Z, Liu C, Bai Y, Zhan Q, Huang X, Zeng Q, Ren H, Xu D. Effect of hypertension duration and blood pressure control during early adulthood on cognitive function in middle age. *J Alzheimers Dis*. 2022;85:779–789. doi: 10.3233/JAD-215070
42. Yaffe K, Vittinghoff E, Hoang T, Matthews K, Golden SH, Al Hazzouri AZ. Cardiovascular risk factors across the life course and cognitive decline: a pooled cohort study. *Neurology*. 2021;96:e2212–e2219. doi: 10.1212/WNL.0000000000011747
43. Samara AA, Liampas I, Dadouli K, Siokas V, Zintzaras E, Stefanidis I, Daponte A, Sotiriou S, Dardiotis E. Preeclampsia, gestational hypertension and incident dementia: a systematic review and meta-analysis of published evidence. *Pregnancy Hypertens*. 2022;30:192–197. doi: 10.1016/j.preghy.2022.10.008
44. Lane CA, Barnes J, Nicholas JM, Sudre CH, Cash DM, Parker TD, Malone IB, Lu K, James S-N, Keshavan A, et al. Associations between blood pressure across adulthood and late-life brain structure and pathology in the neuroscience substudy of the 1946 British Birth Cohort (Insight 46): an epidemiological study. *Lancet Neurol*. 2019;18:942–952. doi: 10.1016/S1474-4422(19)30228-5
45. Sánchez-Nieto JM, Rivera-Sánchez UD, Mendoza-Núñez VM. Relationship between arterial hypertension with cognitive performance in elderly: systematic review and meta-analysis. *Brain Sci*. 2021;11:1445. doi: 10.3390/brainsci11111445
46. Legdeur N, Heymans MW, Comijs HC, Huisman M, Maier AB, Visser PJ. Age dependency of risk factors for cognitive decline. *BMC Geriatr*. 2018;18:187. doi: 10.1186/s12877-018-0876-2
47. Deckers K, Köhler S, van Boxtel M, Verhey F, Brayne C, Fleming J. Lack of associations between modifiable risk factors and dementia in the very old: findings from the Cambridge City over-75s cohort study. *Aging Mental Health*. 2018;22:1272–1278. doi: 10.1080/13607863.2017.1280767
48. van Dalen JW, Brayne C, Crane PK, Fratiglioni L, Larson EB, Lobo A, Lobo E, Marcum ZA, Moll van Charante EP, Qiu C, et al. Association of systolic blood pressure with dementia risk and the role of age, U-shaped associations, and mortality. *JAMA Intern Med*. 2022;182:142–152. doi: 10.1001/jamainternmed.2021.7009
49. Nasrallah IM, Gaussoin SA, Pomponio R, Dolui S, Erus G, Wright CB, Launer LJ, Detre JA, Wolk DA, Davatzikos C, et al; SPRINT Research Group. Association of intensive vs standard blood pressure control with magnetic resonance imaging biomarkers of Alzheimer disease: secondary analysis of the SPRINT MIND randomized trial. *JAMA Neurol*. 2021;78:568–577. doi: 10.1001/jamaneurol.2021.0178
50. Rouch L, Cestac P, Sallerin B, Piccoli M, Benattar-Zibi L, Bertin P, Berrut G, Corruble E, Derumeaux G, Falissard B, et al; S.AGES Investigators. Visit-to-visit blood pressure variability is associated with cognitive decline and incident dementia: the S.AGES cohort. *Hypertension*. 2020;76:1280–1288. doi: 10.1161/HYPERTENSIONAHA.119.14553
51. Li C, Ma Y, Hua R, Yang Z, Zhong B, Wang H, Xie W. Dose-response relationship between long-term blood pressure variability and cognitive decline. *Stroke*. 2021;52:3249–3257. doi: 10.1161/STROKEAHA.120.033697
52. Ernst ME, Ryan J, Chowdhury EK, Margolis KL, Beilin LJ, Reid CM, Nelson MR, Woods RL, Shah RC, Orchard SG, et al. Long-term blood pressure variability and risk of cognitive decline and dementia among older adults. *J Am Heart Assoc*. 2021;10:e019613. doi: 10.1161/JAHA.120.019613
53. Ma Y, Blacker D, Viswanathan A, van Veluw SJ, Bos D, Vernooij MW, Hyman BT, Tzourio C, Das S, Hofman A. Visit-to-visit blood pressure variability, neuropathology, and cognitive decline. *Neurology*. 2021;96:e2812–e2823. doi: 10.1212/WNL.0000000000012065
54. Gao H, Wang K, Ahmadizar F, Zhuang J, Jiang Y, Zhang L, Gu J, Zhao W, Xia ZL. Associations of changes in late-life blood pressure with cognitive impairment among older population in China. *BMC Geriatr*. 2021;21:536. doi: 10.1186/s12877-021-02479-1
55. Walker KA, Sharrett AR, Wu A, Schneider ALC, Albert M, Lutsey PL, Bandeen-Roche K, Coresh J, Gross AL, Windham BG. Association of midlife to late-life blood pressure patterns with incident dementia. *JAMA*. 2019;322:535–545. doi: 10.1001/jama.2019.10575
56. Peters R, Anstey KJ, Booth A, Beckett N, Warwick J, Antikainen R, Rockwood K, Peters J, Bulpitt CJ. Orthostatic hypotension and symptomatic subclinical orthostatic hypotension increase risk of cognitive impairment: an integrated evidence review and analysis of a large older adult hypertensive cohort. *Eur Heart J*. 2018;39:3135–3143. doi: 10.1093/eurheartj/ehy418
57. Cui C, Sekikawa A, Kuller LH, Lopez OL, Newman AB, Kuipers AL, Mackey RH. Aortic stiffness is associated with increased risk of incident dementia in older adults. *J Alzheimers Dis*. 2018;66:297–306. doi: 10.3233/JAD-180449
58. Hughes TM, Wagenknecht LE, Craft S, Mintz A, Heiss G, Palta P, Wong D, Zhou Y, Knopman D, Mosley TH, et al. Arterial stiffness and dementia pathology: Atherosclerosis Risk in Communities (ARIC)-PET Study. *Neurology*. 2018;90:e1248–e1256. doi: 10.1212/WNL.0000000000005259
59. Levine DA, Gross AL, Briceno EM, Tilton N, Kabeto MU, Hingtgen SM, Giordani BJ, Sussman JB, Hayward RA, Burke JF, et al. Association between blood pressure and later-life cognition among Black and White individuals. *JAMA Neurol*. 2020;77:810–819. doi: 10.1001/jamaneurol.2020.0568
60. Hammond CA, Blades NJ, Chaudhry SI, Dodson JA, Longstreth WT Jr, Heckbert WSR , Psaty BM, Arnold AM, Dublin S, Sitlani CM, et al. Long-term cognitive decline after newly diagnosed heart failure: longitudinal analysis in the CHS (Cardiovascular Health Study). *Circ Heart Fail*. 2018;11:e004476. doi: 10.1161/CIRCHEARTFAILURE.117.004476
61. Wolters FJ, Segufa RA, Darweesh SKL, Bos D, Ikram MA, Sabayan B, Hofman A, Sedaghat S. Coronary heart disease, heart failure, and the risk of dementia: a systematic review and meta-analysis. *Alzheimers Dement*. 2018;14:1493–1504. doi: 10.1016/j.jalz.2018.01.007
62. Manemann SM, Knopman DS, St Sauver J, Bielinski SJ, Chamberlain AM, Weston SA, Jiang R, Roger VL. Alzheimer's disease and related dementias and heart failure: a community study. *J Am Geriatr Soc*. 2022;70:1664–1672. doi: 10.1111/jgs.17752
63. Bekwelem W, Norby FL, Agarwal SK, Matsushita K, Coresh J, Alonso A, Chen LY. Association of peripheral artery disease with incident atrial fibrillation: the ARIC (Atherosclerosis Risk in Communities) study. *J Am Heart Assoc*. 2018;7:e007452. doi: 10.1161/JAHA.117.007452
64. Bailey MJ, Soliman EZ, McClure LA, Howard G, Howard VJ, Judd SE, Unverzagt FW, Wadley V, Sachs BC, Hughes TM. Relation of atrial fibrillation to cognitive decline (from the REasons for Geographic and Racial Differences in Stroke [REGARDS] study). *Am J Cardiol*. 2021;148:60–68. doi: 10.1016/j.amjcard.2021.02.036
65. Zuin M, Roncon L, Passaro A, Bosi C, Cervellati C, Zuliani G. Risk of dementia in patients with atrial fibrillation: short versus long follow-up: a systematic review and meta-analysis. *Int J Geriatr Psychiatry*. 2021;36:1488–1500. doi: 10.1002/gps.5582
66. Ding M, Fratiglioni L, Johnell K, Santoni G, Fastbom J, Ljungman P, Marengoni A, Qiu C. Atrial fibrillation, antithrombotic treatment, and cognitive aging: a population-based study. *Neurology*. 2018;91:e1732–e1740. doi: 10.1212/WNL.0000000000006456
67. Rouch L, Xia F, Bahorik A, Olgin J, Yaffe K. Atrial fibrillation is associated with greater risk of dementia in older veterans. *Am J Geriatr Psychiatry*. 2021;29:1092–1098. doi: 10.1016/j.jagp.2021.02.038
68. Lin M, Han W, Zhong J, Wu L. A systematic review and meta-analysis to determine the effect of oral anticoagulants on incidence of dementia in patients with atrial fibrillation. *Int J Clin Pract*. 2021;75:e14269. doi: 10.1111/ijcp.14269
69. Cadogan SL, Powell E, Wing K, Wong AY, Smeeth L, Warren-Gash C. Anticoagulant prescribing for atrial fibrillation and risk of incident dementia. *Heart*. 2021;107:1898–1904. doi: 10.1136/heartjnl-2021-319672
70. Kim D, Yang PS, Jang E, Yu HT, Kim TH, Uhm JS, Kim JY, Sung JH, Pak HN, Lee MH, et al. Association of anticoagulant therapy with risk of dementia among patients with atrial fibrillation. *Europace*. 2021;23:184–195. doi: 10.1093/europace/euaa192
71. Lee SR, Choi EK, Park SH, Jung JH, Han KD, Oh S, Lip GYH. Comparing warfarin and 4 direct oral anticoagulants for the risk of dementia in patients with atrial fibrillation. *Stroke*. 2021;52:3459–3468. doi: 10.1161/STROKEAHA.120.033338
72. Hsu JY, Liu PP, Liu AB, Lin SM, Huang HK, Loh CH. Lower risk of dementia in patients with atrial fibrillation taking non-vitamin K antagonist oral anticoagulants: a nationwide population-based cohort study. *J Am Heart Assoc*. 2021;10:e016437. doi: 10.1161/JAHA.120.016437
73. Lee ZX, Ang E, Lim XT, Arain SJ. Association of risk of dementia with direct oral anticoagulants versus warfarin use in patients with non-valvular atrial fibrillation: a systematic review and meta-analysis. *J Cardiovasc Pharmacol*. 2021;77:22–31. doi: 10.1097/FJC.0000000000000925
74. Bodagh N, Yap R, Kotadia I, Sim I, Bhalla A, Somerville P, O'Neill M, Williams SE. Impact of catheter ablation versus medical therapy on cognitive

function in atrial fibrillation: a systematic review. *J Interv Card Electrophysiol*. 2022;65:271–286. doi: 10.1007/s10840-022-01196-y
75. Sauer AC, Nathoe HM, Hendrikse J, Peelen LM, Regieli J, Veldhuijzen DS, Kalkman CJ, Grobbee DE, Doevendans PA, van Dijk D, et al. Cognitive outcomes 7.5 years after angioplasty compared with off-pump coronary bypass surgery. *Ann Thorac Surg*. 2013;96:1294–1300. doi: 10.1016/j.athoracsur.2013.05.001
76. Whitlock EL, Diaz-Ramirez LG, Smith AK, Boscardin WJ, Covinsky KE, Avidan MS, Glymour MM. Association of coronary artery bypass grafting vs percutaneous coronary intervention with memory decline in older adults undergoing coronary revascularization. *JAMA*. 2021;325:1955–1964. doi: 10.1001/jama.2021.5150
77. Kuzma E, Airdrie J, Littlejohns TJ, Lourida I, Thompson-Coon J, Lang IA, Scrobotovici M, Thacker EL, Fitzpatrick A, Kuller LH, et al. Coronary artery bypass graft surgery and dementia risk in the Cardiovascular Health Study. *Alzheimer Dis Assoc Disord*. 2017;31:120–127. doi: 10.1097/WAD.0000000000000191
78. Mutch WA, Fransoo RR, Campbell BI, Chateau DG, Sirski M, Warrian RK. Dementia and depression with ischemic heart disease: a population-based longitudinal study comparing interventional approaches to medical management. *PLoS One*. 2011;6:e17457. doi: 10.1371/journal.pone.0017457
79. Jiang X, Lewis CE, Allen NB, Sidney S, Yaffe K. Premature cardiovascular disease and brain health in midlife: the CARDIA study. *Neurology*. 2023;100:e1454–e1463. doi: 10.1212/WNL.0000000000206825
80. Bagai A, Chen AY, Udell JA, Dodson JA, McManus DD, Maurer MS, Enriquez JR, Hochman J, Goyal A, Henry TD, et al. Association of cognitive impairment with treatment and outcomes in older myocardial infarction patients: a report from the NCDR Chest Pain-MI Registry. *J Am Heart Assoc*. 2019;8:e012929. doi: 10.1161/JAHA.119.012929
81. Norby FL, Chen LY, Soliman EZ, Gottesman RF, Mosley TH, Alonso A. Association of left ventricular hypertrophy with cognitive decline and dementia risk over 20 years: the Atherosclerosis Risk In Communities-Neurocognitive Study (ARIC-NCS). *Am Heart J*. 2018;204:58–67. doi: 10.1016/j.ahj.2018.07.007
82. Moazzami K, Ostovaneh MR, Ambale Venkatesh B, Habibi M, Yoneyama K, Wu C, Liu K, Pimenta I, Fitzpatrick A, Shea S, et al. Left Ventricular hypertrophy and remodeling and risk of cognitive impairment and dementia: MESA (Multi-Ethnic Study of Atherosclerosis). *Hypertension*. 2018;71:429–436. doi: 10.1161/HYPERTENSIONAHA.117.10289
83. Razavi AC, Fernandez C, He J, Kelly TN, Krousel-Wood M, Whelton SP, Carmichael OT, Bazzano LA. Left ventricular mass index is associated with cognitive function in middle-age: Bogalusa Heart Study. *Circ Cardiovasc Imaging*. 2020;13:e010335. doi: 10.1161/CIRCIMAGING.119.010335
84. Johansen MC, Wang W, Zhang M, Knopman DS, Ndumele C, Mosley TH, Selvin E, Shah AM, Solomon SD, Gottesman RF, et al. Risk of dementia associated with atrial cardiopathy: the ARIC study. *J Am Heart Assoc*. 2022;11:e025646. doi: 10.1161/JAHA.121.025646
85. Ninomiya T. Epidemiological evidence of the relationship between diabetes and dementia. *Adv Exp Med Biol*. 2019;1128:13–25. doi: 10.1007/978-981-13-3540-2_2
86. Liu L, Gracely EJ, Yin X, Eisen HJ. Impact of diabetes mellitus and cardiometabolic syndrome on the risk of Alzheimer's disease among postmenopausal women. *World J Diabetes*. 2021;12:69–83. doi: 10.4239/wjd.v12.i1.69
87. Benn M, Nordestgaard BG, Tybjærg-Hansen A, Frikke-Schmidt R. Impact of glucose on risk of dementia: mendelian randomisation studies in 115,875 individuals. *Diabetologia*. 2020;63:1151–1161. doi: 10.1007/s00125-020-05124-5
88. Carmichael O, Stuchlik P, Pillai S, Biessels G-J, Dhullipudi R, Madden-Rusnak A, Martin S, Hsia DS, Fonseca V, Bazzano L. High-normal adolescent fasting plasma glucose is associated with poorer midlife brain health: Bogalusa Heart Study. *J Clin Endocrinol Metab*. 2019;104:4492–4500. doi: 10.1210/jc.2018-02750
89. Cohen-Manheim I, Sinnreich R, Doniger GM, Simon ES, Pinchas-Mizrachi R, Kark JD. Fasting plasma glucose in young adults free of diabetes is associated with cognitive function in midlife. *Eur J Public Health*. 2018;28:496–503. doi: 10.1093/eurpub/ckx194
90. Yu ZB, Zhu Y, Li D, Wu MY, Tang ML, Wang JB, Chen K. Association between visit-to-visit variability of HbA(1c) and cognitive decline: a pooled analysis of two prospective population-based cohorts. *Diabetologia*. 2020;63:85–94. doi: 10.1007/s00125-019-04986-8
91. Song J, Bai H, Xu H, Xing Y, Chen S. HbA1c variability and the risk of dementia in patients with diabetes: a meta-analysis. *Int J Clin Pract*. 2022;2022:7706330. doi: 10.1155/2022/7706330
92. Lee AK, Rawlings AM, Lee CJ, Gross AL, Huang ES, Sharrett AR, Coresh J, Selvin E. Severe hypoglycaemia, mild cognitive impairment, dementia and brain volumes in older adults with type 2 diabetes: the Atherosclerosis Risk in Communities (ARIC) cohort study. *Diabetologia*. 2018;61:1956–1965. doi: 10.1007/s00125-018-4668-1
93. Mattishent K, Loke YK. Meta-analysis: association between hypoglycemia and serious adverse events in older patients treated with glucose-lowering agents. *Front Endocrinol*. 2021;12:571568. doi: 10.3389/fendo.2021.571568
94. Huang L, Zhu M, Ji J. Association between hypoglycemia and dementia in patients with diabetes: a systematic review and meta-analysis of 1.4 million patients. *Diabetol Metab Syndr*. 2022;14:31. doi: 10.1186/s13098-022-00799-9
95. Mehlig K, Lapidus L, Thelle DS, Waern M, Zetterberg H, Björkelund C, Skoog I, Lissner L. Low fasting serum insulin and dementia in nondiabetic women followed for 34 years. *Neurology*. 2018;91:e427–e435. doi: 10.1212/WNL.0000000000005911
96. Antal B, McMahon LP, Sultan SF, Lithen A, Wexler DJ, Dickerson B, Ratai EM, Mujica-Parodi LR. Type 2 diabetes mellitus accelerates brain aging and cognitive decline: complementary findings from UK Biobank and meta-analyses. *Elife*. 2022;11:e73138. doi: 10.7554/eLife.73138
97. Ji X, Gao H, Sun D, Zhuang J, Fang Y, Wang K, Ahmadizar F. Trajectories of cognition and daily functioning before and after incident diabetes. *Diabetes Care*. 2023;46:75–82. doi: 10.2337/dc22-1190
98. Rawlings AM, Sharrett AR, Albert MS, Coresh J, Windham BG, Power MC, Knopman DS, Walker K, Burgard S, Mosley TH, et al. The association of late-life diabetes status and hyperglycemia with incident mild cognitive impairment and dementia: the ARIC study. *Diabetes Care*. 2019;42:1248–1254. doi: 10.2337/dc19-0120
99. Kjaergaard AD, Ellervik C, Witte DR, Nordestgaard BG, Frikke-Schmidt R, Bojesen SE. Kidney function and risk of dementia: observational study, meta-analysis, and two-sample mendelian randomization study. *Eur J Epidemiol*. 2022;37:1273–1284. doi: 10.1007/s10654-022-00923-z
100. Singh-Manoux A, Oumarou-Ibrahim A, Machado-Fragua MD, Dumurgier J, Brunner EJ, Kivimaki M, Fayosse A, Sabia S. Association between kidney function and incidence of dementia: 10-year follow-up of the Whitehall II cohort study. *Age Ageing*. 2022;51:afab259. doi: 10.1093/ageing/afab259
101. Scheppach JB, Coresh J, Wu A, Gottesman RF, Mosley TH, Knopman DS, Grams ME, Sharrett AR, Koton S. Albuminuria and estimated GFR as risk factors for dementia in midlife and older age: findings from the ARIC study. *Am J Kidney Dis*. 2020;76:775–783. doi: 10.1053/j.ajkd.2020.03.015
102. Li H, Zhao S, Wang R, Gao B. The association between cognitive impairment/dementia and albuminuria: a systematic review and meta-analysis. *Clin Exp Nephrol*. 2022;26:45–53. doi: 10.1007/s10157-021-02127-3
103. Kim HW, Jhee JH, Joo YS, Yang KH, Jung JJ, Shin JH, Han SH, Yoo TH, Kang SW, Park JT. Dialysis adequacy and risk of dementia in elderly hemodialysis patients. *Front Med (Lausanne)*. 2021;8:769490. doi: 10.3389/fmed.2021.769490
104. Qu Y, Hu HY, Ou YN, Shen XN, Xu W, Wang ZT, Dong Q, Tan L, Yu JT. Association of body mass index with risk of cognitive impairment and dementia: a systematic review and meta-analysis of prospective studies. *Neurosci Biobehav Rev*. 2020;115:189–198. doi: 10.1016/j.neubiorev.2020.05.012
105. Gardener H, Caunca M, Dong C, Cheung YK, Rundek T, Elkind MSV, Wright CB, Sacco RL. Obesity measures in relation to cognition in the Northern Manhattan Study. *J Alzheimers Dis*. 2020;78:1653–1660. doi: 10.3233/JAD-201071
106. Caunca MR, Gardener H, Simonetto M, Cheung YK, Alperin N, Yoshita M, DeCarli C, Elkind MSV, Sacco RL, Wright CB, et al. Measures of obesity are associated with MRI markers of brain aging: the Northern Manhattan Study. *Neurology*. 2019;93:e791–e803. doi: 10.1212/WNL.0000000000007966
107. Hamer M, Batty GD. Association of body mass index and waist-to-hip ratio with brain structure: UK Biobank study. *Neurology*. 2019;92:e594–e600. doi: 10.1212/WNL.0000000000006879
108. Fernández-Andújar M, Morales-García E, García-Casares N. Obesity and gray matter volume assessed by neuroimaging: a systematic review. *Brain Sci*. 2021;11:999. doi: 10.3390/brainsci11080999
109. Danat IM, Clifford A, Partridge M, Zhou W, Bakre AT, Chen A, McFeeters D, Smith T, Wan Y, Copeland J, et al. Impacts of overweight and obesity in older age on the risk of dementia: a systematic literature review and a meta-analysis. *J Alzheimers Dis*. 2019;70:S87–S99. doi: 10.3233/JAD-180763
110. Singh-Manoux A, Dugravot A, Shipley M, Brunner EJ, Elbaz A, Sabia S, Kivimaki M. Obesity trajectories and risk of dementia: 28 years of

follow-up in the Whitehall II Study. *Alzheimers Dement*. 2018;14:178–186. doi: 10.1016/j.jalz.2017.06.2637
111. Lee CM, Woodward M, Batty GD, Beiser AS, Bell S, Berr C, Bjertness E, Chalmers J, Clarke R, Dartigues JF, et al. Association of anthropometry and weight change with risk of dementia and its major subtypes: a meta-analysis consisting 2.8 million adults with 57 294 cases of dementia. *Obes Rev*. 2020;21:e12989. doi: 10.1111/obr.12989
112. Kivimäki M, Luukkonen R, Batty GD, Ferrie JE, Pentti J, Nyberg ST, Shipley MJ, Alfredsson L, Fransson EI, Goldberg M, et al. Body mass index and risk of dementia: analysis of individual-level data from 1.3 million individuals. *Alzheimers Dement*. 2018;14:601–609. doi: 10.1016/j.jalz.2017.09.016
113. Milani SA, Lopez DS, Downer B, Samper-Ternent R, Wong R. Effects of diabetes and obesity on cognitive impairment and mortality in older Mexicans. *Arch Gerontol Geriatr*. 2022;99:104581. doi: 10.1016/j.archger.2021.104581
114. Arvanitakis Z, Capuano AW, Bennett DA, Barnes LL. Body mass index and decline in cognitive function in older Black and White persons. *J Gerontol Series A*. 2018;73:198–203. doi: 10.1093/gerona/glx152
115. Shi L, Chen S-J, Ma M-Y, Bao Y-P, Han Y, Wang Y-M, Shi J, Vitiello MV, Lu L. Sleep disturbances increase the risk of dementia: a systematic review and meta-analysis. *Sleep Med Rev*. 2018;40:4–16. doi: 10.1016/j.smrv.2017.06.010
116. Leng Y, McEvoy CT, Allen IE, Yaffe K. Association of sleep-disordered breathing with cognitive function and risk of cognitive impairment: a systematic review and meta-analysis. *JAMA Neurol*. 2017;74:1237–1245. doi: 10.1001/jamaneurol.2017.2180
117. Sharma RA, Varga AW, Bubu OM, Pirraglia E, Kam K, Parekh A, Wohlleber M, Miller MD, Andrade A, Lewis C, et al. Obstructive sleep apnea severity affects amyloid burden in cognitively normal elderly. a longitudinal study. *Am J Respir Crit Care Med*. 2018;197:933–943. doi: 10.1164/rccm.201704-0704OC
118. Weihs A, Frenzel S, Wittfeld K, Obst A, Stubbe B, Habes M, Szentkirályi A, Berger K, Fietze I, Penzel T, et al. Associations between sleep apnea and advanced brain aging in a large-scale population study. *Sleep*. 2021;44:zsaa204. doi: 10.1093/sleep/zsaa204
119. Zacharias HU, Weihs A, Habes M, Wittfeld K, Frenzel S, Rashid T, Stubbe B, Obst A, Szentkiralyi A, Bulow R, et al. Association between obstructive sleep apnea and brain white matter hyperintensities in a population-based cohort in Germany. *JAMA Netw Open*. 2021;4:e2128225. doi: 10.1001/jamanetworkopen.2021.28225
120. Dunietz GL, Chervin RD, Burke JF, Conceicao AS, Braley TJ. Obstructive sleep apnea treatment and dementia risk in older adults. *Sleep*. 2021;44:zsab076. doi: 10.1093/sleep/zsab076
121. Franks KH, Rowsthorn E, Nicolazzo J, Boland A, Lavale A, Baker J, Rajaratnam SMW, Cavuoto MG, Yiallourou SR, Naughton MT, et al. The treatment of sleep dysfunction to improve cognitive function: a meta-analysis of randomized controlled trials. *Sleep Med*. 2023;101:118–126. doi: 10.1016/j.sleep.2022.10.021
122. Bahorik AL, Sidney S, Kramer-Feldman J, Jacobs DR, Mathew AR, Reis JP, Yaffe K. Early to midlife smoking trajectories and cognitive function in middle-aged US adults: the CARDIA study. *J Gen Intern Med*. 2022;37:1023–1030. doi: 10.1007/s11606-020-06450-5
123. Johnson AL, Nystrom NC, Piper ME, Cook J, Norton DL, Zuelsdorff M, Wyman MF, Flowers Benton S, Lambrou NH, O'Hara J, et al. Cigarette smoking status, cigarette exposure, and duration of abstinence predicting incident dementia and death: a multistate model approach. *J Alzheimers Dis*. 2021;80:1013–1023. doi: 10.3233/JAD-201332
124. Deal JA, Power MC, Palta P, Alonso A, Schneider ALC, Perryman K, Bandeen-Roche K, Sharrett AR. Relationship of cigarette smoking and time of quitting with incident dementia and cognitive decline. *J Am Geriatr Soc*. 2020;68:337–345. doi: 10.1111/jgs.16228
125. Zhou S, Wang K. Childhood secondhand smoke exposure and risk of dementia, Alzheimer's disease and stroke in adulthood: a prospective cohort study. *J Prev Alzheimers Dis*. 2021;8:345–350. doi: 10.14283/jpad.2021.10
126. Wu J, Xiong Y, Xia X, Orsini N, Qiu C, Kivipelto M, Rizzuto D, Wang R. Can dementia risk be reduced by following the American Heart Association's Life's Simple 7? A systematic review and dose-response meta-analysis. *Ageing Res Rev*. 2023;83:101788. doi: 10.1016/j.arr.2022.101788
127. González HM, Tarraf W, Harrison K, Windham BG, Tingle J, Alonso A, Griswold M, Heiss G, Knopman D, Mosley TH. Midlife cardiovascular health and 20-year cognitive decline: Atherosclerosis Risk in Communities Study results. *Alzheimers Dement*. 2018;14:579–589. doi: 10.1016/j.jalz.2017.11.002
128. Sabia S, Fayosse A, Dumurgier J, Schnitzler A, Empana JP, Ebmeier KP, Dugravot A, Kivimaki M, Singh-Manoux A. Association of ideal cardiovascular health at age 50 with incidence of dementia: 25 year follow-up of Whitehall II cohort study. *BMJ*. 2019;366:l4414. doi: 10.1136/bmj.l4414
129. Samieri C, Perier M-C, Gaye B, Proust-Lima C, Helmer C, Dartigues J-F, Berr C, Tzourio C, Empana J-P. Association of cardiovascular health level in older age with cognitive decline and incident dementia. *JAMA*. 2018;320:657–664. doi: 10.1001/jama.2018.11499
130. Malik R, Georgakis MK, Neitzel J, Rannikmäe K, Ewers M, Seshadri S, Sudlow CLM, Dichgans M. Midlife vascular risk factors and risk of incident dementia: longitudinal cohort and mendelian randomization analyses in the UK Biobank. *Alzheimers Dement*. 2021;17:1422–1431. doi: 10.1002/alz.12320
131. Yaffe K, Bahorik AL, Hoang TD, Forrester S, Jacobs DR, Lewis CE, Lloyd-Jones DM, Sidney S, Reis JP. Cardiovascular risk factors and accelerated cognitive decline in midlife: the CARDIA study. *Neurology*. 2020;95:e839–e846. doi: 10.1212/WNL.0000000000010078
132. Fayosse A, Nguyen DP, Dugravot A, Dumurgier J, Tabak AG, Kivimäki M, Sabia S, Singh-Manoux A. Risk prediction models for dementia: role of age and cardiometabolic risk factors. *BMC Med*. 2020;18:107. doi: 10.1186/s12916-020-01578-x
133. Rabin JS, Schultz AP, Hedden T, Viswanathan A, Marshall GA, Kilpatrick E, Klein H, Buckley RF, Yang HS, Properzi M, et al. Interactive associations of vascular risk and β-amyloid burden with cognitive decline in clinically normal elderly individuals: findings from the Harvard Aging Brain Study. *JAMA Neurol*. 2018;75:1124–1131. doi: 10.1001/jamaneurol.2018.1123
134. Lane CA, Barnes J, Nicholas JM, Sudre CH, Cash DM, Malone IB, Parker TD, Keshavan A, Buchanan SM, Keuss SE, et al. Associations between vascular risk across adulthood and brain pathology in late life: evidence from a British birth cohort. *JAMA Neurol*. 2020;77:175–183. doi: 10.1001/jamaneurol.2019.3774
135. Zheng L, Matthews FE, Anstey KJ. Cognitive health expectancies of cardiovascular risk factors for cognitive decline and dementia. *Age Ageing*. 2021;50:169–175. doi: 10.1093/ageing/afaa111
136. Burns SP, Mueller M, Magwood G, White BM, Lackland D, Ellis C. Racial and ethnic differences in post-stroke subjective cognitive decline exist. *Disabil Health J*. 2019;12:87–92. doi: 10.1016/j.dhjo.2018.08.005
137. Clark DG, Boan AD, Sims-Robinson C, Adams RJ, Amella EJ, Benitez A, Lackland DT, Ovbiagele B. Differential impact of index stroke on dementia risk in African-Americans compared to Whites. *J Stroke Cerebrovasc Dis*. 2018;27:2725–2730. doi: 10.1016/j.jstrokecerebrovasdis.2018.05.048
138. Fredriksen-Goldsen KI, Jung H, Kim HJ, Petros R, Emlet C. Disparities in subjective cognitive impairment by sexual orientation and gender in a national population based study of U.S. adults, 2013-2018. *J Aging Health*. 2022;34:519–528. doi: 10.1177/08982643211046466
139. Guo Y, Li Q, Yang X, Jaffee MS, Wu Y, Wang F, Bian J. Prevalence of Alzheimer's and related dementia diseases and risk factors among transgender adults, Florida, 2012–2020. *Am J Public Health*. 2022;112:754–757. doi: 10.2105/AJPH.2022.306720
140. Xue H, Hou P, Li Y, Mao X, Wu L, Liu Y. Factors for predicting reversion from mild cognitive impairment to normal cognition: a meta-analysis. *Int J Geriatr Psychiatry*. 2019;34:1361–1368. doi: 10.1002/gps.5159
141. Ribeiro F, Teixeira-Santos AC, Caramelli P, Leist AK. Prevalence of dementia in Latin America and Caribbean countries: systematic review and meta-analyses exploring age, sex, rurality, and education as possible determinants. *Ageing Res Rev*. 2022;81:101703. doi: 10.1016/j.arr.2022.101703
142. Wang AY, Hu HY, Ou YN, Wang ZT, Ma YH, Tan L, Yu JT. Socioeconomic status and risks of cognitive impairment and dementia: a systematic review and meta-analysis of 39 prospective studies. *J Prev Alzheimer's Dis*. 2023;10:83–94. doi: 10.14283/jpad.2022.81
143. Bobrow K, Hoang T, Barnes DE, Gardner RC, Allen IE, Yaffe K. The effect of sex and wealth on population attributable risk factors for dementia in South Africa. *Front Neurol*. 2021;12:766705. doi: 10.3389/fneur.2021.766705
144. van Loenhoud AC, de Boer C, Wols K, Pijnenburg YA, Lemstra AW, Bouwman FH, Prins ND, Scheltens P, Ossenkoppele R, van der Flier WM. High occurrence of transportation and logistics occupations among vascular dementia patients: an observational study. *Alzheimers Res Ther*. 2019;11:112. doi: 10.1186/s13195-019-0570-4
145. Hyun J, Hall CB, Katz MJ, Derby CA, Lipnicki DM, Crawford JD, Guaita A, Vaccaro R, Davin A, Kim KW, et al; Cohort Studies of Memory in an International Consortium (COSMIC). Education, occupational complexity, and incident dementia: a COSMIC collaborative cohort study. *J Alzheimers Dis*. 2022;85:179–196. doi: 10.3233/JAD-210627

146. Geraets AFJ, Leist AK. Sex/gender and socioeconomic differences in modifiable risk factors for dementia. *Sci Rep*. 2023;13:80. doi: 10.1038/s41598-022-27368-4
147. Glauber R. Rural depopulation and the rural-urban gap in cognitive functioning among older adults. *J Rural Health*. 2022;38:696–704. doi: 10.1111/jrh.12650
148. Rahman M, White EM, Mills C, Thomas KS, Jutkowitz E. Rural-urban differences in diagnostic incidence and prevalence of Alzheimer's disease and related dementias. *Alzheimers Dement*. 2021;17:1213–1230. doi: 10.1002/alz.12285
149. Grace C, Clarke R, Goel A, Farrall M, Watkins H, Hopewell JC. Lack of genetic support for shared aetiology of coronary artery disease and late-onset Alzheimer's disease. *Sci Rep*. 2018;8:7102. doi: 10.1038/s41598-018-25460-2
150. Lourida I, Hannon E, Littlejohns TJ, Langa KM, Hypponen E, Kuzma E, Llewellyn DJ. Association of lifestyle and genetic risk with incidence of dementia. *JAMA*. 2019;322:430–437. doi: 10.1001/jama.2019.9879
151. Jung SH, Kim HR, Chun MY, Jang H, Cho M, Kim B, Kim S, Jeong JH, Yoon SJ, Park KW, et al. Transferability of Alzheimer disease polygenic risk score across populations and its association with Alzheimer disease-related phenotypes. *JAMA Netw Open*. 2022;5:e2247162. doi: 10.1001/jamanetworkopen.2022.47162
152. Deckers K, Barbera M, Kohler S, Ngandu T, van Boxtel M, Rusanen M, Laatikainen T, Verhey F, Soininen H, Kivipelto M, et al. Long-term dementia risk prediction by the LIBRA score: a 30-year follow-up of the CAIDE study. *Int J Geriatr Psychiatry*. 2020;35:195–203. doi: 10.1002/gps.5235
153. Schaich CL, Yeboah J, Espeland MA, Baker LD, Ding J, Hayden KM, Sachs BC, Craft S, Rapp SR, Luchsinger JA, et al. Association of vascular risk scores and cognitive performance in a diverse cohort: the Multi-Ethnic Study of Atherosclerosis. *J Gerontol A Biol Sci Med Sci*. 2022;77:1208–1215. doi: 10.1093/gerona/glab189
154. Graves KG, May HT, Jacobs V, Knowlton KU, Muhlestein JB, Lappe DL, Anderson JL, Horne BD, Bunch TJ. $CHA_2DS_2$-VASc scores and Intermountain Mortality Risk Scores for the joint risk stratification of dementia among patients with atrial fibrillation. *Heart Rhythm*. 2019;16:3–9. doi: 10.1016/j.hrthm.2018.10.018
155. Brickman AM, Tosto G, Gutierrez J, Andrews H, Gu Y, Narkhede A, Rizvi B, Guzman V, Manly JJ, Vonsattel JP, et al. An MRI measure of degenerative and cerebrovascular pathology in Alzheimer disease. *Neurology*. 2018;91:e1402–e1412. doi: 10.1212/WNL.0000000000006310
156. Charidimou A, Shams S, Romero JR, Ding J, Veltkamp R, Horstmann S, Eiriksdottir G, van Buchem MA, Gudnason V, Himali JJ, et al. Clinical significance of cerebral microbleeds on MRI: a comprehensive meta-analysis of risk of intracerebral hemorrhage, ischemic stroke, mortality, and dementia in cohort studies (v1). *Int J Stroke*. 2018;13:454–468. doi: 10.1177/1747493017751931
157. Rass V, Schoenherr E, Ianosi BA, Lindner A, Kofler M, Schiefecker AJ, Lenhart L, Gaasch M, Pertl MT, Freyschlag CF, et al. Subarachnoid hemorrhage is followed by pituitary gland volume loss: a volumetric MRI observational study. *Neurocrit Care*. 2020;32:492–501. doi: 10.1007/s12028-019-00764-x
158. Lei C, Deng Q, Li H, Zhong L. Association between silent brain infarcts and cognitive function: a systematic review and meta-analysis. *J Stroke Cerebrovasc Dis*. 2019;28:2376–2387. doi: 10.1016/j.jstrokecerebrovasdis.2019.03.036
159. Eldholm RS, Persson K, Barca ML, Knapskog AB, Cavallin L, Engedal K, Selbaek G, Skovlund E, Saltvedt I. Association between vascular comorbidity and progression of Alzheimer's disease: a two-year observational study in Norwegian memory clinics. *BMC Geriatr*. 2018;18:120. doi: 10.1186/s12877-018-0813-4
160. Alvarez-Bueno C, Cunha PG, Martinez-Vizcaino V, Pozuelo-Carrascosa DP, Visier-Alfonso ME, Jimenez-Lopez E, Cavero-Redondo I. Arterial Stiffness and Cognition Among Adults: A Systematic Review and Meta-Analysis of Observational and Longitudinal Studies. *J Am Heart Assoc*. 2020;9:e014621–e014621. doi: 10.1161/JAHA.119.014621
161. Cao QL, Sun Y, Hu H, Wang ZT, Tan L, Yu JT; Alzheimer's Disease Neuroimaging Initiative. Association of cerebral small vessel disease burden with neuropsychiatric symptoms in non-demented elderly: a longitudinal study. *J Alzheimers Dis*. 2022;89:583–592. doi: 10.3233/JAD-220128
162. Lewis CK, Bernstein OM, Grill JD, Gillen DL, Sultzer DL. Anxiety and depressive symptoms and cortical amyloid-β burden in cognitively unimpaired older adults. *J Prev Alzheimers Dis*. 2022;9:286–296. doi: 10.14283/jpad.2022.13
163. Baril AA, Pinheiro AA, Himali JJ, Beiser A, Sanchez E, Pase MP, Seshadri S, Demissie S, Romero JR. Lighter sleep is associated with higher enlarged perivascular spaces burden in middle-aged and elderly individuals. *Sleep Med*. 2022;100:558–564. doi: 10.1016/j.sleep.2022.10.006
164. Chou YH, Sundman M, Ton That V, Green J, Trapani C. Cortical excitability and plasticity in Alzheimer's disease and mild cognitive impairment: A systematic review and meta-analysis of transcranial magnetic stimulation studies. *Ageing Res Rev*. 2022;79:101660. doi: 10.1016/j.arr.2022.101660
165. Irace AL, Armstrong NM, Deal JA, Chern A, Ferrucci L, Lin FR, Resnick SM, Golub JS. Longitudinal associations of subclinical hearing loss with cognitive decline. *J Gerontol A Biol Sci Med Sci*. 2022;77:623–631. doi: 10.1093/gerona/glab263
166. Jansen MG, Griffanti L, Mackay CE, Anatürk M, Melazzini L, Lange AG, Filippini N, Zsoldos E, Wiegertjes K, Leeuw FE, et al. Association of cerebral small vessel disease burden with brain structure and cognitive and vascular risk trajectories in mid-to-late life. *J Cereb Blood Flow Metab*. 2022;42:600–612. doi: 10.1177/0271678X211048411
167. Lin F, Pa J, Karim R, Hodis HN, Han SD, Henderson VW, St John JA, Mack WJ. Subclinical carotid artery atherosclerosis and cognitive function in older adults. *Alzheimers Res Ther*. 2022;14:63. doi: 10.1186/s13195-022-00997-7
168. Yeh WC, Hsu CY, Li KY, Chien CF, Huang LC, Yang YH. Association between subclinical epileptiform discharge and the severity of cognitive decline in Alzheimer's disease: a longitudinal cohort study. *J Alzheimers Dis*. 2022;90:305–312. doi: 10.3233/JAD-220567
169. Gatz M, Reynolds CA, Fratiglioni L, Johansson B, Mortimer JA, Berg S, Fiske A, Pedersen NL. Role of genes and environments for explaining Alzheimer disease. *Arch Gen Psychiatry*. 2006;63:168–174. doi: 10.1001/archpsyc.63.2.168
170. Lanoiselee HM, Nicolas G, Wallon D, Rovelet-Lecrux A, Lacour M, Rousseau S, Richard AC, Pasquier F, Rollin-Sillaire A, Martinaud O, et al; Collaborators of the CNR-MAJ Project. *APP*, *PSEN1*, and *PSEN2* mutations in early-onset Alzheimer disease: a genetic screening study of familial and sporadic cases. *PLoS Med*. 2017;14:e1002270. doi: 10.1371/journal.pmed.1002270
171. Joutel A, Corpechot C, Ducros A, Vahedi K, Chabriat H, Mouton P, Alamowitch S, Domenga V, Cecillion M, Marechal E, et al. Notch3 mutations in CADASIL, a hereditary adult-onset condition causing stroke and dementia. *Nature*. 1996;383:707–710. doi: 10.1038/383707a0
172. Maia LF, Mackenzie IR, Feldman HH. Clinical phenotypes of cerebral amyloid angiopathy. *J Neurol Sci*. 2007;257:23–30. doi: 10.1016/j.jns.2007.01.054
173. Bergem AL, Engedal K, Kringlen E. The role of heredity in late-onset Alzheimer disease and vascular dementia: a twin study. *Arch Gen Psychiatry*. 1997;54:264–270. doi: 10.1001/archpsyc.1997.01830150090013
174. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL, Pericak-Vance MA. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science*. 1993;261:921–923. doi: 10.1126/science.8346443
175. Skrobot OA, McKnight AJ, Passmore PA, Seripa D, Mecocci P, Panza F, Kalaria R, Wilcock G, Munafo M, Erkinjuntti T, et al; Environmental Risk for Alzheimer's Disease Consortium (GERAD1). A validation study of vascular cognitive impairment genetics meta-analysis findings in an independent collaborative cohort. *J Alzheimers Dis*. 2016;53:981–989. doi: 10.3233/JAD-150862
176. Abondio P, Sazzini M, Garagnani P, Boattini A, Monti D, Franceschi C, Luiselli D, Giuliani C. The genetic variability of APOE in different human populations and its implications for longevity. *Genes (Basel)*. 2019;10:222. doi: 10.3390/genes10030222
177. González HM, Tarraf W, Jian X, Vasquez PM, Kaplan R, Thyagarajan B, Daviglus M, Lamar M, Gallo LC, Zeng D, et al. Apolipoprotein E genotypes among diverse middle-aged and older Latinos: Study of Latinos-Investigation of Neurocognitive Aging results (HCHS/SOL). *Sci Rep*. 2018;8:17578. doi: 10.1038/s41598-018-35573-3
178. Andrews SJ, Fulton-Howard B, Goate A. Interpretation of risk loci from genome-wide association studies of Alzheimer's disease. *Lancet Neurol*. 2020;19:326–335. doi: 10.1016/S1474-4422(19)30435-1
179. Kunkle BW, Grenier-Boley B, Sims R, Bis JC, Damotte V, Naj AC, Boland A, Vronskaya M, van der Lee SJ, Amlie-Wolf A, et al; Alzheimer Disease Genetics Consortium (ADGC); European Alzheimer's Disease Initiative (EADI); Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium (CHARGE); Genetic and Environmental Risk in AD/Defining Genetic, Polygenic and Environmental Risk for Alzheimer's Disease Consortium (GERAD/PERADES). Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates Abeta, tau, immunity and lipid processing. *Nat Genet*. 2019;51:414–430.

180. Liu JZ, Erlich Y, Pickrell JK. Case-control association mapping by proxy using family history of disease. *Nat Genet*. 2017;49:325–331. doi: 10.1038/ng.3766
181. Bellenguez C, Kucukali F, Jansen IE, Kleineidam L, Moreno-Grau S, Amin N, Naj AC, Campos-Martin R, Grenier-Boley B, Andrade V, et al. New insights into the genetic etiology of Alzheimer's disease and related dementias. *Nat Genet*. 2022;54:412–436. doi: 10.1038/s41588-022-01024-z
182. Stern Y, MacKay-Brandt A, Lee S, McKinley P, McIntyre K, Razlighi Q, Agarunov E, Bartels M, Sloan RP. Effect of aerobic exercise on cognition in younger adults: a randomized clinical trial. *Neurology*. 2019;92:e905–e916. doi: 10.1212/WNL.0000000000007003
183. Lenze EJ, Voegtle M, Miller JP, Ances BM, Balota DA, Barch D, Depp CA, Diniz BS, Eyler LT, Foster ER, et al. Effects of mindfulness training and exercise on cognitive function in older adults: a randomized clinical trial. *JAMA*. 2022;328:2218–2229. doi: 10.1001/jama.2022.21680
184. Pisani S, Mueller C, Huntley J, Aarsland D, Kempton MJ. A meta-analysis of randomised controlled trials of physical activity in people with Alzheimer's disease and mild cognitive impairment with a comparison to donepezil. *Int J Geriatr Psychiatry*. 2021;36:1471–1487. doi: 10.1002/gps.5581
185. Williamson JD, Pajewski NM, Auchus AP, Bryan RN, Chelune G, Cheung AK, Cleveland ML, Coker LH, Crowe MG, Cushman WC, et al; SPRINT MIND Investigators for the SPRINT Research Group. Effect of intensive vs standard blood pressure control on probable dementia: a randomized clinical trial. *JAMA*. 2019;321:553–561. doi: 10.1001/jama.2018.21442
186. Marcum ZA, Cohen JB, Zhang C, Derington CG, Greene TH, Ghazi L, Herrick JS, King JB, Cheung AK, Bryan N, et al; Systolic Blood Pressure Intervention Trial (SPRINT) Research Group. Association of antihypertensives that stimulate vs inhibit types 2 and 4 angiotensin ii receptors with cognitive impairment. *JAMA Netw Open*. 2022;5:e2145319. doi: 10.1001/jamanetworkopen.2021.45319
187. van Dalen JW, Marcum ZA, Gray SL, Barthold D, Moll van Charante EP, van Gool WA, Crane PK, Larson EB, Richard E. Association of angiotensin II-stimulating antihypertensive use and dementia risk: post hoc analysis of the PreDIVA trial. *Neurology*. 2021;96:e67–e80. doi: 10.1212/WNL.0000000000010996
188. den Brok M, van Dalen JW, Abdulrahman H, Larson EB, van Middelaar T, van Gool WA, van Charante EPM, Richard E. Antihypertensive medication classes and the risk of dementia: a systematic review and network meta-analysis. *J Am Med Dir Assoc*. 2021;22:1386–1395.e15. doi: 10.1016/j.jamda.2020.12.019
189. Hajjar I, Okafor M, McDaniel D, Obideen M, Dee E, Shokouhi M, Quyyumi AA, Levey A, Goldstein F. Effects of candesartan vs lisinopril on neurocognitive function in older adults with executive mild cognitive impairment: a randomized clinical trial. *JAMA Netw Open*. 2020;3:e2012252. doi: 10.1001/jamanetworkopen.2020.12252
190. Bosch JJ, O'Donnell MJ, Gao P, Joseph P, Pais P, Xavier D, Dans A, Lopez Jaramillo P, Yusuf S. Effects of a polypill, aspirin, and the combination of both on cognitive and functional outcomes: a randomized clinical trial. *JAMA Neurol*. 2023;80:251–259. doi: 10.1001/jamaneurol.2022.5088
191. Hughes D, Judge C, Murphy R, Loughlin E, Costello M, Whiteley W, Bosch J, O'Donnell MJ, Canavan M. Association of blood pressure lowering with incident dementia or cognitive impairment: a systematic review and meta-analysis. *JAMA*. 2020;323:1934–1944. doi: 10.1001/jama.2020.4249
192. Peters R, Xu Y, Fitzgerald O, Aung HL, Beckett N, Bulpitt C, Chalmers J, Forette F, Gong J, Harris K, et al; Dementia rIsk REduCTion (DIRECT) Collaboration. Blood pressure lowering and prevention of dementia: an individual patient data meta-analysis. *Eur Heart J*. 2022;43:4980–4990. doi: 10.1093/eurheartj/ehac584
193. Cunningham EL, Todd SA, Passmore P, Bullock R, McGuinness B. Pharmacological treatment of hypertension in people without prior cerebrovascular disease for the prevention of cognitive impairment and dementia. *Cochrane Database Syst Rev*. 2021;5:CD004034. doi: 10.1002/14651858.CD004034.pub4
194. Offer A, Arnold M, Clarke R, Bennett D, Bowman L, Bulbulia R, Haynes R, Li J, Hopewell JC, Landray M, et al; Heart Protection Study (HPS), Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH), and Treatment of HDL (High-Density Lipoprotein) to Reduce the Incidence of Vascular Events (HPS2-THRIVE) Collaborative Group. Assessment of vascular event prevention and cognitive function among older adults with preexisting vascular disease or diabetes: a secondary analysis of 3 randomized clinical trials. *JAMA Netw Open*. 2019;2:e190223. doi: 10.1001/jamanetworkopen.2019.0223
195. Zhou Z, Ryan J, Ernst ME, Zoungas S, Tonkin AM, Woods RL, McNeil JJ, Reid CM, Curtis AJ, Wolfe R, et al; ASPREE Investigator Group. Effect of statin therapy on cognitive decline and incident dementia in older adults. *J Am Coll Cardiol*. 2021;77:3145–3156. doi: 10.1016/j.jacc.2021.04.075
196. Harvey PD, Sabbagh MN, Harrison JE, Ginsberg HN, Chapman MJ, Manvelian G, Moryusef A, Mandel J, Farnier M. No evidence of neurocognitive adverse events associated with alirocumab treatment in 3340 patients from 14 randomized phase 2 and 3 controlled trials: a meta-analysis of individual patient data. *Eur Heart J*. 2018;39:374–381. doi: 10.1093/eurheartj/ehx661
197. Karatasakis A, Danek BA, Karacsonyi J, Rangan BV, Roesle MK, Knickelbine T, Miedema MD, Khalili H, Ahmad Z, Abdullah S, et al. Effect of PCSK9 inhibitors on clinical outcomes in patients with hypercholesterolemia: a meta-analysis of 35 randomized controlled trials. *J Am Heart Assoc*. 2017;6:e006910. doi: 10.1161/JAHA.117.006910
198. Giugliano RP, Mach F, Zavitz K, Kurtz C, Im K, Kanevsky E, Schneider J, Wang H, Keech A, Pedersen TR, et al; EBBINGHAUS Investigators. Cognitive function in a randomized trial of evolocumab. *N Engl J Med*. 2017;377:633–643. doi: 10.1056/NEJMoa1701131
199. Gencer B, Mach F, Guo J, Im K, Ruzza A, Wang H, Kurtz CE, Pedersen TR, Keech AC, Ott BR, et al; FOURIER Investigators. Cognition after lowering LDL-cholesterol with evolocumab. *J Am Coll Cardiol*. 2020;75:2283–2293. doi: 10.1016/j.jacc.2020.03.039
200. Ying H, Wang J, Shen Z, Wang M, Zhou B. Impact of lowering low-density lipoprotein cholesterol with contemporary lipid-lowering medicines on cognitive function: a systematic review and meta-analysis. *Cardiovasc Drugs Ther*. 2021;35:153–166. doi: 10.1007/s10557-020-07045-2
201. Ryan J, Storey E, Murray AM, Woods RL, Wolfe R, Reid CM, Nelson MR, Chong TT, Williamson JD, Ward SA, et al; ASPREE Investigator Group. Randomized placebo-controlled trial of the effects of aspirin on dementia and cognitive decline. *Neurology*. 2020;95:e320–e331. doi: 10.1212/wnl.0000000000009277
202. Pratley RE, Kanapka LG, Rickels MR, Ahmann A, Aleppo G, Beck R, Bhargava A, Bode BW, Carlson A, Chaytor NS, et al; Wireless Innovation for Seniors With Diabetes Mellitus (WISDM) Study Group. Effect of continuous glucose monitoring on hypoglycemia in older adults with type 1 diabetes: a randomized clinical trial. *JAMA*. 2020;323:2397–2406. doi: 10.1001/jama.2020.6928
203. Tang X, Cardoso MA, Yang J, Zhou JB, Simo R. Impact of intensive glucose control on brain health: meta-analysis of cumulative data from 16,584 patients with type 2 diabetes mellitus. *Diabetes Ther*. 2021;12:765–779. doi: 10.1007/s13300-021-01009-x
204. Komulainen P, Tuomilehto J, Savonen K, Mannikko R, Hassinen M, Lakka TA, Hanninen T, Kiviniemi V, Jacobs DR, Kivipelto M, et al. Exercise, diet, and cognition in a 4-year randomized controlled trial: Dose-Responses to Exercise Training (DR's EXTRA). *Am J Clin Nutr*. 2021;113:1428–1439. doi: 10.1093/ajcn/nqab018
205. den Brok M, Hoevenaar-Blom MP, Coley N, Andrieu S, van Dalen J, Meiller Y, Guillemont J, Brayne C, van Gool WA, Moll van Charante EP, et al. The effect of multidomain interventions on global cognition, symptoms of depression and apathy: a pooled analysis of two randomized controlled trials. *J Prev Alzheimers Dis*. 2022;9:96–103. doi: 10.14283/jpad.2021.53
206. Hafdi M, Hoevenaar-Blom MP, Richard E. Multi-domain interventions for the prevention of dementia and cognitive decline. *Cochrane Database Syst Rev*. 2021;11:CD013572. doi: 10.1002/14651858.CD013572.pub2
207. Salzman T, Sarquis-Adamson Y, Son S, Montero-Odasso M, Fraser S. Associations of multidomain interventions with improvements in cognition in mild cognitive impairment: a systematic review and meta-analysis. *JAMA Netw Open*. 2022;5:e226744–e226744. doi: 10.1001/jamanetworkopen.2022.6744
208. Rovner BW, Casten RJ, Hegel MT, Leiby B. Preventing cognitive decline in Black individuals with mild cognitive impairment: a randomized clinical trial. *JAMA Neurol*. 2018;75:1487–1493. doi: 10.1001/jamaneurol.2018.2513
209. Pendlebury ST, Rothwell PM, Oxford Vascular Study. Incidence and prevalence of dementia associated with transient ischaemic attack and stroke: analysis of the population-based Oxford Vascular Study. *Lancet Neurol*. 2019;18:248–258. doi: 10.1016/S1474-4422(18)30442-3
210. Centers for Disease Control and Prevention and National Center for Health Statistics. Multiple cause of death, CDC WONDER online database. Accessed April 1, 2023. https://wonder.cdc.gov/mcd-icd10.html
211. Centers for Disease Control and Prevention and National Center for Health Statistics. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death micro-data files. Accessed April 8, 2023. https://cdc.gov/nchs/nvss/mortality_public_use_data.htm
212. Deardorff WJ, Barnes DE, Jeon SY, Boscardin WJ, Langa KM, Covinsky KE, Mitchell SL, Whitlock EL, Smith AK, Lee SJ. Development and external

validation of a mortality prediction model for community-dwelling older adults with dementia. *JAMA Intern Med*. 2022;182:1161–1170. doi: 10.1001/jamainternmed.2022.4326
213. Adjoian Mezzaca T, Dodds LV, Rundek T, Zeki Al Hazzouri A, Caunca MR, Gomes-Osman J, Loewenstein DA, Schneiderman N, Elfassy T. Associations between cognitive functioning and mortality in a population-based sample of older United States adults: differences by sex and education. *J Aging Health*. 2022;34:905–915. doi: 10.1177/08982643221076690
214. Jordan BC, Brungardt J, Reyes J, Helmer SD, Haan JM. Dementia as a predictor of mortality in adult trauma patients. *Am J Surg*. 2018;215:48–52. doi: 10.1016/j.amjsurg.2017.07.012
215. Anderson TS, Marcantonio ER, McCarthy EP, Ngo L, Schonberg MA, Herzig SJ. Association of diagnosed dementia with post-discharge mortality and readmission among hospitalized Medicare beneficiaries. *J Gen Intern Med*. 2022;37:4062–4070. doi: 10.1007/s11606-022-07549-7
216. Zuliani G, Gallerani M, Martellucci CA, Reverberi R, Brombo G, Cervellati C, Zuin M, Pistolesi C, Pedrini D, Flacco ME, et al. Dementia and in-hospital mortality: retrospective analysis of a nationwide administrative database of elderly subjects in Italy. *Aging Clin Exper Res*. 2022;34:1037–1045. doi: 10.1007/s40520-021-02021-8
217. Schmutte T, Olfson M, Maust DT, Xie M, Marcus SC. Suicide risk in first year after dementia diagnosis in older adults. *Alzheimers Dement*. 2022;18:262–271. doi: 10.1002/alz.12390
218. Zhang Y, Ren R, Yang L, Zhang H, Shi Y, Okhravi HR, Vitiello MV, Sanford LD, Tang X. Sleep in Alzheimer's disease: a systematic review and meta-analysis of polysomnographic findings. *Transl Psychiatry*. 2022;12:136. doi: 10.1038/s41398-022-01897-y
219. Kuzmik A, Boltz M, BeLue R, Galvin JE, Arendacs R, Resnick B. Factors associated with sleep quality in hospitalized persons with dementia. *Alzheimer Dis Assoc Disord*. 2022;36:253–258. doi: 10.1097/WAD.0000000000000502
220. Koria LG, Sawan MJ, Redston MR, Gnjidic D. The prevalence of frailty among older adults living with dementia: a systematic review. *J Am Med Dir Assoc*. 2022;23:1807–1814. doi: 10.1016/j.jamda.2022.01.084
221. Hippisley-Cox J, Coupland C. Development and validation of QMortality risk prediction algorithm to estimate short term risk of death and assess frailty: cohort study. *BMJ*. 2017;358:j4208. doi: 10.1136/bmj.j4208
222. Borda MG, Pérez-Zepeda MU, Jaramillo-Jimenez A, Chaudhuri KR, Tovar-Rios DA, Wallace L, Batzu L, Rockwood K, Tysnes OB, Aarsland D, et al. Frailty in Parkinson's disease and its association with early dementia: a longitudinal study. *Parkinsonism Relat Disord*. 2022;99:51–57. doi: 10.1016/j.parkreldis.2022.05.004
223. Chen L, Au E, Saripella A, Kapoor P, Yan E, Wong J, Tang-Wai DF, Gold D, Riazi S, Suen C, et al. Postoperative outcomes in older surgical patients with preoperative cognitive impairment: a systematic review and meta-analysis. *J Clin Anesth*. 2022;80:110883. doi: 10.1016/j.jclinane.2022.110883
224. Shah SK, Adler RR, Xiang L, Clark CJ, Cooper Z, Finlayson E, Kim DH, Lin KJ, Lipsitz SR, Weissman JS. Patients living with dementia have worse outcomes when undergoing high-risk procedures. *J Am Geriatr Soc*. 2022;70:2838–2846. doi: 10.1111/jgs.17893
225. Martinez-Carranza N, Lindqvist K, Modig K, Hedström M. Factors associated with non-walking 4 months after hip fracture: a prospective study of 23,759 fractures. *Injury*. 2022;53:2180–2183. doi: 10.1016/j.injury.2021.10.031
226. Fresnais D, Humble MB, Bejerot S, Meehan AD, Fure B. Apathy as a predictor for conversion from mild cognitive impairment to dementia: a systematic review and meta-analysis of longitudinal studies. *J Geriatr Psychiatry Neurol*. 2023;36:3–17. doi: 10.1177/08919887221093361
227. Isik AT, Erken N, Yavuz I, Kaya D, Ontan MS, Ates Bulut E, Dost FS. Orthostatic hypotension in patients with Alzheimer's disease: a meta-analysis of prospective studies. *Neurol Sci*. 2022;43:999–1006. doi: 10.1007/s10072-021-05450-5
228. Izquierdo Delgado E, Gutiérrez Ríos R, Andrés Calvo M, Repiso Gento I, Castrillo Sanz A, Rodríguez Herrero R, Rodríguez Sanz MF, Tola-Arribas MA. Nutritional status assessment in Alzheimer disease and its influence on disease progression. *Neurologia (Engl Ed)*. 2022;37:735–747. doi: 10.1016/j.nrleng.2019.11.006
229. Kalkers K, Schols JMGA, van Zwet EW, Roos RAC. Dysphagia, fear of choking and preventive measures in patients with Huntington's disease: the perspectives of patients and caregivers in long-term care. *J Nutr Health Aging*. 2022;26:332–338. doi: 10.1007/s12603-022-1743-6
230. Ma KS, Hasturk H, Carreras I, Dedeoglu A, Veeravalli JJ, Huang JY, Kantarci A, Wei JC. Dementia and the risk of periodontitis: a population-based cohort study. *J Dent Res*. 2022;101:270–277. doi: 10.1177/00220345211037220
231. Nabizadeh F, Nikfarjam M, Azami M, Sharifkazemi H, Sodeifian F. Pseudobulbar affect in neurodegenerative diseases: a systematic review and meta-analysis. *J Clin Neurosci*. 2022;100:100–107. doi: 10.1016/j.jocn.2022.04.009
232. Bejot Y, Duloquin G, Crespy V, Durier J, Garnier L, Graber M, Giroud M. Influence of preexisting cognitive impairment on clinical severity of ischemic stroke: the Dijon Stroke Registry. *Stroke*. 2020;51:1667–1673. doi: 10.1161/STROKEAHA.119.028845
233. Pinho J, Quintas-Neves M, Dogan I, Reetz K, Reich A, Costa AS. Incident stroke in patients with Alzheimer's disease: systematic review and meta-analysis. *Sci Rep*. 2021;11:16385. doi: 10.1038/s41598-021-95821-x
234. Lee PH, Yeh TT, Yen HY, Hsu WL, Chiu VJ, Lee SC. Impacts of stroke and cognitive impairment on activities of daily living in the Taiwan longitudinal study on aging. *Sci Rep*. 2021;11:12199. doi: 10.1038/s41598-021-91838-4
235. Mitsutake S, Ishizaki T, Tsuchiya-Ito R, Furuta K, Hatakeyama A, Sugiyama M, Toba K, Ito H. Association of cognitive impairment severity with potentially avoidable readmissions: a retrospective cohort study of 8897 older patients. *Alzheimer Dement*. 2021;13:e12147. doi: 10.1002/dad2.12147
236. Lee YJ, Johnston DM, Reuland M, Lyketsos CG, Samus Q, Amjad H. Reasons for hospitalization while receiving dementia care coordination through maximizing independence at home. *J Am Med Dir Assoc*. 2022;23:1573–1578.e2. doi: 10.1016/j.jamda.2021.12.044
237. Lin PJ, Zhu Y, Olchanski N, Cohen JT, Neumann PJ, Faul JD, Fillit HM, Freund KM. Racial and ethnic differences in hospice use and hospitalizations at end-of-life among Medicare beneficiaries with dementia. *JAMA Netw Open*. 2022;5:e2216260. doi: 10.1001/jamanetworkopen.2022.16260
238. Arighi A, Fumagalli GG, Carandini T, Pietroboni AM, De Riz MA, Galimberti D, Scarpini E. Facing the digital divide into a dementia clinic during COVID-19 pandemic: caregiver age matters. *Neurol Sci*. 2021;42:1247–1251. doi: 10.1007/s10072-020-05009-w
239. Levine DA, Galecki AT, Morgenstern LB, Zahuranec DB, Langa KM, Kabeto MU, Okullo D, Nallamothu BK, Giordani B, Reale BK, et al. Preexisting mild cognitive impairment, dementia, and receipt of treatments for acute ischemic stroke. *Stroke*. 2021;52:2134–2142. doi: 10.1161/STROKEAHA.120.032258
240. Callisaya ML, Purvis T, Lawler K, Brodtmann A, Cadilhac DA, Kilkenny MF. Dementia is associated with poorer quality of care and outcomes after stroke: an observational study. *J Gerontol A Biol Sci Med Sci*. 2021;76:851–858. doi: 10.1093/gerona/glaa139
241. Jennings LA, Laffan AM, Schlissel AC, Colligan E, Tan Z, Wenger NS, Reuben DB. Health care utilization and cost outcomes of a comprehensive dementia care program for Medicare beneficiaries. *JAMA Intern Med*. 2019;179:161–166. doi: 10.1001/jamainternmed.2018.5579
242. Dieleman JL, Cao J, Chapin A, Chen C, Li Z, Liu A, Horst C, Kaldjian A, Matyasz T, Scott KW, et al. US health care spending by payer and health condition, 1996-2016. *JAMA*. 2020;323:863–884. doi: 10.1001/jama.2020.0734
243. Oney M, White L, Coe NB. Out-of-pocket costs attributable to dementia: a longitudinal analysis. *J Am Geriatr Soc*. 2022;70:1538–1545. doi: 10.1111/jgs.17746
244. Wittenberg R, Knapp M, Hu B, Comas-Herrera A, King D, Rehill A, Shi C, Banerjee S, Patel A, Jagger C, et al. The costs of dementia in England. *Int J Geriatr Psychiatry*. 2019;34:1095–1103. doi: 10.1002/gps.5113
245. Hoffman GJ, Maust DT, Harris M, Ha J, Davis MA. Medicare spending associated with a dementia diagnosis among older adults. *J Am Geriatr Soc*. 2022;70:2592–2601. doi: 10.1111/jgs.17835
246. Global Burden of Disease Study and Institute for Health Metrics and Evaluation. University of Washington. Accessed August 2, 2023. http://ghdx.healthdata.org/
247. Premraj L, Kannapadi NV, Briggs J, Seal SM, Battaglini D, Fanning J, Suen J, Robba C, Fraser J, Cho SM. Mid and long-term neurological and neuropsychiatric manifestations of post-COVID-19 syndrome: a meta-analysis. *J Neurol Sci*. 2022;434:120162. doi: 10.1016/j.jns.2022.120162
248. Ceban F, Ling S, Lui LMW, Lee Y, Gill H, Teopiz KM, Rodrigues NB, Subramaniapillai M, Di Vincenzo JD, Cao B, et al. Fatigue and cognitive impairment in post-COVID-19 syndrome: a systematic review and meta-analysis. *Brain Behav Immun*. 2022;101:93–135. doi: 10.1016/j.bbi.2021.12.020
249. Amieva H, Retuerto N, Hernandez-Ruiz V, Meillon C, Dartigues JF, Peres K. Longitudinal study of cognitive decline before and after the COVID-19 pandemic: evidence from the PA-COVID survey. *Dement Geriatr Cogn Disord*. 2022;51:56–62. doi: 10.1159/000521999
250. Douaud G, Lee S, Alfaro-Almagro F, Arthofer C, Wang C, McCarthy P, Lange F, Andersson JLR, Griffanti L, Duff E, et al. SARS-CoV-2 is associated with

changes in brain structure in UK Biobank. *Nature*. 2022;604:697–707. doi: 10.1038/s41586-022-04569-5
251. Liu YH, Chen Y, Wang QH, Wang LR, Jiang L, Yang Y, Chen X, Li Y, Cen Y, Xu C, et al. One-year trajectory of cognitive changes in older survivors of COVID-19 in Wuhan, China: a longitudinal cohort study. *JAMA Neurol*. 2022;79:509–517. doi: 10.1001/jamaneurol.2022.0461
252. Damayanthi HDWT, Prabani KIP, Weerasekara I. Factors Associated for mortality of older people with COVID 19: a systematic review and meta-analysis. *Gerontol Geriatric Med*. 2021;7:23337214211057392. doi: 10.1177/23337214211057392
253. Wang SM, Park SH, Kim NY, Kang DW, Na HR, Um YH, Han S, Park SS, Lim HK. Association between dementia and clinical outcome after covid-19: a nationwide cohort study with propensity score matched control in South Korea. *Psychiatry Investig*. 2021;18:523–529. doi: 10.30773/pi.2021.0064
254. July J, Pranata R. Prevalence of dementia and its impact on mortality in patients with coronavirus disease 2019: a systematic review and meta-analysis. *Geriatr Gerontol Inter*. 2021;21:172–177. doi: 10.1111/ggi.14107
255. Axenhus M, Frederiksen KS, Zhou RZ, Waldemar G, Winblad B. The impact of the COVID-19 pandemic on mortality in people with dementia without COVID-19: a systematic review and meta-analysis. *BMC Geriatr*. 2022;22:878. doi: 10.1186/s12877-022-03602-6
256. Hua CL, Cornell PY, Zimmerman S, Carder P, Thomas KS. Excess mortality among assisted living residents with dementia during the COVID-19 pandemic. *J Am Med Dir Assoc*. 2022;23:1743–1749.e6. doi: 10.1016/j.jamda.2022.07.023
257. Park HY, Song IA, Oh TK. Dementia risk among coronavirus disease survivors: a nationwide cohort study in South Korea. *J Personalized Med*. 2021;11:1015. doi: 10.3390/jpm11101015
258. Wang L, Davis PB, Volkow ND, Berger NA, Kaelber DC, Xu R. Association of COVID-19 with new-onset Alzheimer's disease. *J Alzheimers Dis*. 2022;89:411–414. doi: 10.3233/JAD-220717
259. Liu N, Sun J, Wang X, Zhao M, Huang Q, Li H. The impact of dementia on the clinical outcome of COVID-19: a systematic review and meta-analysis. *J Alzheimers Dis*. 2020;78:1775–1782. doi: 10.3233/JAD-201016

# 17. CONGENITAL CARDIOVASCULAR DEFECTS AND KAWASAKI DISEASE

***See Tables 17-1 and 17-2 and Charts 17-1 through 17-7***

Click here to return to the Table of Contents

Click here to return to the Abbreviations

## Congenital Cardiovascular Defects

### *ICD-9 745 to 747; ICD-10 Q20 to Q28.*

CCDs, which arise from abnormal or incomplete formation of the heart, valves, and blood vessels, are one of the most common birth defects worldwide.[1–3] CCDs range in severity from minor abnormalities that spontaneously resolve or are hemodynamically insignificant to complex malformations, including absent, hypoplastic, or atretic portions of the heart. There is significant variability in the presentation of CCDs, resulting in heterogeneous morbidity, mortality, and health care costs across the life span. Some types of CCDs are associated with diminished quality of life,[4,5] on par with what is seen in other chronic pediatric health conditions,[6] as well as deficits in cognitive functioning[7,8] and neurodevelopmental outcomes.[9,10] However, health outcomes generally continue to improve for CCDs, including survival.[11]

### *Overall Life Span Prevalence*

It is estimated that 13.3 (95% CI, 11.5–15.4) million people globally were living with CCDs in 2019.[12] CCD prevalence increased by 28% between 1990 and 2019, driven largely by increases in the number of adolescents and younger adults (15–49 years of age increased by 42%) and middle-aged adults (50–69 years of age increased by 117%) living with CCDs.[12] The change was greatest in low- and middle-income countries, attributed to both increasing population growth and improving survival.

In 2017, the all-age prevalence of CCDs in the United States was estimated at 466 566 (95% CI, 429 140–505 806) individuals, with 279 320 (95% CI, 266 461–331 437; 60%) of these <20 years of age.[13] This figure represents a fairly drastic downshift from the 32nd Bethesda Conference estimate (2000 estimate, 800 000)[14] and estimates provided by the CDC (2010 estimate, 1.4 million adults and 1 million children),[15] reflecting a change in GBD Study modeling strategy. In prior estimates, every person born with a CCD, regardless of type or severity, was assumed to have a CCD across their life span. In 2017, the GBD Study took a more nuanced approach that allowed for "cure" of simple lesions such as ASDs that undergo spontaneous closure for which there was no known associated morbidity or mortality, thus lowering the overall population considered to be living with a CCD.[13] With the same modeling strategy, 2017 estimates place the global prevalence of CCDs at 157 per 100 000 (95% CI, 143–172), with the highest prevalence estimates in countries with a low sustainable development index (238 per 100 000 [95% CI, 216–261]) and the lowest in those with a high-middle or high sustainable development index (112 per 100 000 [95% CI, 102–114] and 135 per 100 000 [95% CI, 125–145], respectively).[13]

### *Birth Prevalence*

#### *(See Table 17-1)*

- In high-income North America, including the United States, the birth prevalence of CCDs is estimated to be 12.3 per 1000 (95% CI, 11.1–13.8) according to 1990 to 2017 data.[13]
- An estimated 1% or a minimum of 40 000 infants are expected to be affected by CCDs each year in the United States.[16] Of these, ≈25%, or 2.4 per 1000 live births, require invasive treatment in the first year of life (Table 17-1).

### *Birth Prevalence of Specific Defects*

- The National Birth Defects Prevention Network showed the average birth prevalence of 29 selected major birth defects from 39 population-based birth defects surveillance programs in the United States from 2010 to 2014.[17] These data indicated the following prevalence: atrioventricular septal defect (0.54 per 1000 births), coarctation of the aorta (0.56 per 1000 births), truncus arteriosus (0.067 per 1000 births), double-outlet right ventricle (0.17 per 1000 births), HLHS (0.26 per 1000 births), other single ventricle (0.079 per 1000 births), interrupted aortic arch (0.062 per 1000 births), pulmonary valve atresia/stenosis (0.97 per 1000 births), TOF (0.46 per 1000 births), total anomalous pulmonary venous connection (0.14 per 1000 births), and TGA (0.38 per 1000 births).
- Bicuspid aortic valve occurs in 13.7 of every 1000 people; these defects vary in severity, but aortic stenosis and regurgitation can progress throughout life.[16]

### *Risk Factors*

- Numerous nongenetic risk factors are thought to contribute to CCDs.[18]

The 2024 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2024. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

- Maternal exposure to first-trimester anesthesia (between 3 and 8 weeks after conception) may be associated with 1.50 times greater risk of CCDs at birth (95% CI, 1.11–2.03).[19]
- Maternal exposure to teratogens may be associated with CCDs at birth. In an Iranian cohort, exposure to teratogens in the first trimester of pregnancy (hair color, canned foods, detergents) increased the odds of CCDs (OR, 2.32 [95% CI, 1.68–3.20]).[20]

- Maternal lifestyle factors have been associated with increased risk of CCDs.
  - Periconceptional cigarette smoking[21–24] 1 month before conception through 3 months after conception is associated with an increased odds of ASD (OR, 1.7 [95% CI, 1.5–2.0]), truncus arteriosus (OR, 1.7 [95% CI, 1.0–2.7]), any septal defect (OR, 1.5 [95% CI, 1.3–1.7]), double-outlet right ventricle (OR, 1.3 [95% CI, 1.1–2.2]), perimembranous VSD (OR, 1.3, [95% CI, 1.0–1.4]), atrioventricular septal defect (OR, 1.3 [95% CI, 1.0–1.9]), right-sided obstructive lesion (OR, 1.2 [95% CI, 1.0–1.4]), and pulmonary valve stenosis (OR, 1.2 [95% CI, 1.0–1.4]). There was not a significant association between this exposure and truncus arteriosus (OR, 1.2 [95% CI, 0.7–2.1]) and Ebstein anomaly (OR, 1.1 [95% CI, 0.7–1.8]).[25] Exposure to secondhand smoke also has been implicated as a risk factor for CCDs.[23]
  - Smoking and binge drinking together may also increase risk. Mothers who smoke and report any binge drinking in the 3 months before pregnancy may be at increased risk of giving birth to a child with a CCD compared with mothers who report only any binge drinking (aOR,12.65 [95% CI, 3.5–45.2] versus 9.45 [95% CI, 2.5–35.3]).[26]
- Maternal health factors have been associated with increased risk of CCDs.[27]
  - Higher maternal BMI has been identified as a risk factor for CCDs in some but not all studies. A systematic review including 8 studies that assessed the relationship between maternal obesity and CCDs found a significant association between maternal obesity and CCDs in 5 studies, whereas 3 studies found no association between CCDs and maternal obesity.[28] A second meta-analysis (14 studies) found a dose-response effect between overweight, moderate obesity, and severe obesity and a pregnancy with a CCD (pooled ORs: OR, 1.08 [95% CI, 1.02–1.15]; OR, 1.15 [95% CI, 1.11–1.20]; and OR, 1.39 [95% CI, 1.31–1.47], respectively), an association that persisted when controlling for the presence of diabetes.[29]
  - Maternal diabetes, including type 1, type 2, and gestational diabetes, is associated with fetal CCDs (OR, 1.94 [95% CI, 1.59–2.35]).[30,31]
  - Approximately 2670 (95% UI, 1795–3795) cases of CHDs could potentially be prevented annually if all females in the United States with pregestational diabetes achieved glycemic control before pregnancy.[32]
  - By 2007, folate deficiency was considered a well-documented risk for CCDs.[33] However, a more recent systematic review did not identify a relationship between folate deficiency and CCDs.[34]
  - Maternal viral infections associated with CCDs include hepatitis B virus (OR, 2.21 [95% CI, 1.66–2.95]), coxsackievirus B (OR, 2.21 [95% 1.63–3.00]), human cytomegalovirus (OR, 3.12 [95% CI, 2.44–3.98]), and rubella (OR, 2.62 [95% CI, 1.95–3.51]).[35]
  - Maternal medications associated with CCDs include receipt of antihypertensive agents (ACE inhibitors, antiadrenergic agents, β-blockers, calcium channel blockers, diuretics) during the first trimester with variable odds, depending on the lesion type and overall greater odds of CHD (OR, 2.03 [95% CI, 1.46–2.84]).[18]
  - Additional medications associated with a greater odds of CCD if taken by females during the first trimester of pregnancy include any antibacterial agents, sulfonamides, nitrofurantoins, quinolones, urinary antiseptic, erythromycin, insulin, fertility drugs, clomiphene, chorionic gonadotropin, nonsteroidal anti-inflammatory drugs, benzodiazepines, lithium, anticonvulsants, selective serotonin reuptake inhibitors (eg, paroxetine), and tricyclic antidepressants.[18]
  - Maternal factors associated with a greater odds of CCD included maternal history of a serious health condition 6 months before or during pregnancy (OR, 1.5 [95% CI, 1.1–2.2]) and maternal history of CCD (OR, 2.4 [95% CI, 1.4–4.0]).[18]
- Paternal occupational exposures may also be associated with fetal CCDs.[36]
  - More specifically, there are attributable fractions of fetal TOF attributable to paternal anesthesia (3.6%), coarctation of the aorta to parental sympathomimetic medication exposure (5.8%), VSDs to paternal pesticide exposure (5.5%), and HLHS to paternal solvent exposure (4.6%).[37]
  - More recent data from the Japan Environment and Children's Study identified higher risks for CCDs related to paternal exposure to engine oil (OR, 1.68 [95% CI, 1.02–2.77]), lead-like solder (OR, 2.03 [95% CI, 1.06–3.88]), lead-free solder (OR, 3.45 [95% CI, 1.85–6.43]), and microbes (OR, 4.51 [95% CI, 1.63–12.49]).[38]

### *Screening*

It has been almost a decade since pulse oximetry screening for CCDs was instituted as part of the uniform US

screening panel for newborns and endorsed by the AHA and the American Academy of Pediatrics.[39,40] At present, all 50 states and the District of Columbia have laws or regulations mandating newborn screening for identification of previously unidentified CCDs,[41] and several studies have demonstrated the benefit of such screening.[42–44]

- A simulation model estimates that screening the entire United States for critical CCDs with pulse oximetry would uncover 875 infants (95% UI, 705–1060) who have nonsyndromic CCDs versus 880 (95% UI, 700–1080) false-negative screenings (no CCD).[45]
- A meta-analysis of 19 studies that included 436 758 newborns found that pulse oximetry had a sensitivity of 76.3% (95% CI, 69.5%–82.0%) and a specificity of 99.9% (95% CI, 99.7%–99.9%) for detection of critical CCDs with a false-positive rate of 0.14% (95% CI, 0.07%–0.22%).[46] On the basis of these data, among healthy-appearing late-preterm or full-term infants, pulse oximetry screening will detect 5 of 6 per 10 000 with critical CCDs and falsely identify an additional 14 per 10 000 screened.
- An observational study demonstrated that statewide implementation of mandatory policies for newborn screening for critical CCDs was associated with a significant decrease (33.4% [95% CI, 10.6%–50.3%]) in infant cardiac deaths between 2007 and 2013 compared with states without such policies.[47]
- Reports outside of the United States and other high-income settings have shown similar performance of pulse oximetry screening in identifying critical CCDs,[48] with a sensitivity and specificity of pulse oximetry screening for critical CCDs of 100% and 99.7%, respectively.
- A more recent retrospective cohort study of CCD live births between 2004 and 2018 in Massachusetts did not find a reduction in delayed diagnosis once pulse oximetry screening became mandatory.[49] However, in this same study, prenatal screening was associated with improved diagnosis rates. Between 2004 and 2018, prenatal diagnosis of CCD increased by 65% ($P_{trend}$<0.001) and delayed diagnosis decreased by 56% ($P_{trend}$=0.021).

### *Social Determinants of Health/Health Equity*

Multiple studies assessing the impact of social determinants of health on CCD incidence and prevalence, infant mortality, and postsurgical outcomes found the following:

- A 2021 scoping review showed that lower SES and poverty were associated with higher incidence and prevalence of CCDs; reported associations between lower SES and parental education attainment and prenatal diagnosis of CCDs suggest lower rates of prenatal diagnosis in association with stated risk factors, as well as increased infant mortality, adverse postsurgical outcomes, decreased health care access, and impaired neurodevelopmental outcome.[50]
- The importance of a healthy maternal-fetal environment and social deprivation on CCD incidence cannot be underemphasized. Among >2.4 million infants born in California, the odds of CCD were 31% greater among infants born in neighborhoods in the lowest compared with the highest SES quartile (OR, 1.31 [95% CI, 1.21–1.42]). The odds of CCD were 1.23 times (95% CI, 1.15–1.31; *P*<0.001) greater among infants born in neighborhoods with the greatest exposure to environmental pollutants (versus the lowest quartile exposure group; OR, 1.23 [95% CI, 1.15–1.31]). Together, the odds of CCD were the highest among infants in the highest quartile for environmental exposure and social deprivation (OR, 1.48 [95% CI, 1.32–1.66]; *P*<0.0001).[51]
- In Ontario, CCDs were more common among children of mothers who lived in neighborhoods in the lowest compared with the highest income quartile (OR, 1.29 [95% CI, 1.20–1.38]) and neighborhoods with the lowest compared with the highest percentage of individuals with university or advanced degrees (aOR, 1.34 [95% CI, 1.24–1.44]).[52] Rurality and low material wealth are risk factors for CCD. In a cohort study of 798 173 singleton births, infants living in the most socially deprived neighborhoods (SDI quintile 5) had an 18% increase in the odds of CHD (aOR, 1.18 [95% CI, 1.1-1.26]) compared with those living in quintile 1.[53] Infants living in rural areas had a 13% increase in the odds (aOR, 1.13 [95% CI, 1.06–1.21]) of CHD compared with their counterparts living in urban areas.
- Maternal exposure to air pollutants may also increase the risk of CCDs. A systematic review and meta-analysis including 26 studies showed that risk of TOF (OR, 1.21 [95% CI, 1.04–1.41]) was associated with high versus low carbon monoxide exposure, increasing risk of ASD was proportionally associated with increasing exposure to particular matter (≤10 μm) and ozone (OR, 1.04 per 10 μg/m$^3$ [95% CI, 1.00–1.09] and 1.09 per 10 μg/m$^3$ [95% CI, 1.02–1.17], respectively), and increased risk of aortic coarctation was associated with high versus low nitrogen dioxide exposure (OR, 1.14 [95% CI, 1.02–1.26]).[54]
- Among infants with HLHS living within the Metropolitan Atlanta Congenital Defects Program, survival rates were worse for those residing in high-poverty census tracts (9%) compared with those residing in low-poverty census tracts (25%; *P*<0.001).[55]
- Longer length of stay, higher unplanned readmission rates, and higher resource use were also associated with lower school functioning among parents of children who had undergone cardiac surgery.

- Neurodevelopmental outcomes and quality of life measures were lowest among children living in poverty, children of parents with low educational attainment, and children of parents with transportation barriers.[50]
- SES is a major contributor to identified differences in infant mortality among infants with critical CCDs, with greater mortality among socioeconomically deprived patients (OR, 1.7 [95% CI, 1.4–2.07).[56]
- The income status of the neighborhood in which a child lives is associated with increased risk for death after congenital heart surgery and resource use.[57] Among patients undergoing cardiac surgery, children from the lowest neighborhood income quartile versus the highest had a 1.31 times increased mortality risk (OR, 1.21 [95% CI, 1.14–1.51]) after cardiac surgery independently of age, race, insurance type, geographic region, or low versus high procedure complexity.
- Adolescent and adults with CHD residing in the most deprived neighborhoods had higher rates of inpatient admission, ED visits, and outpatient visits. Among children and adults with CCD residing within the most compared with the least deprived communities, there was a 56% greater odds of inpatient admission (OR, 1.56 [95% CI, 1.25–104]), an 86% greater odds of an ED visit (RR, 1.86 [95% CI, 1.47–2.34]), and a 23% greater odds of an outpatient clinic visit (OR, 1.23 [95% CI, 1.11–1.37]).[58]
- The relationship between neighborhood household income and mortality among children with CHD is nonlinear. Higher risk for mortality exists at lower and higher income levels. The risk of death nadirs between annual neighborhood household income of $72 000 to $80 000.[59]
- Lower maternal education is associated with higher infant mortality in the first year among infants with critical CHDs (OR, 1.32 [95% CI, 1.2–1.45]).[56]
- Lower socioeconomic quartile was associated with decreased rates of prenatal detection of HLHS and TGA, particularly among children with TGA (OR for socioeconomic quartile 1, 0.78 [95% CI, 0.64–0.85] compared with quartile 4). Hispanic ethnicity (RR, 0.85 [95% CI, 0.72–0.99]) and rural residence (RR, 0.78 [95% CI, 0.64–0.95]) were also associated with lower rates of prenatal detection of TGA.[60]

### Genetics and Family History

- Eight percent to 10% of CCDs can be attributed to chromosomal aberrations (eg, DiGeorge syndrome, Down syndrome, Turner syndrome) and 5% to 15% to single-nucleotide or pathogenic copy number variants.[61]
- CCDs can have a heritable component, and parental consanguinity is a known risk factor.[20] There is a greater concordance of CCDs in monozygotic than dizygotic twins.[62] A report from Kaiser Permanente data showed that monochorionic twins were at particularly increased risk for CCDs (RR, 11.6 [95% CI, 9.2–14.5]).[63]
- Among parents with ASD or VSD, 2.6% and 3.7%, respectively, have children who are similarly affected, 21 times the estimated population frequency.[64] However, the majority of CCDs occur in families with no other history of CCDs, which supports the possibility of de novo genetic events. In fact, a large study of next-generation sequencing in CCDs suggests that 8% of cases are attributable to de novo variation.[65]
- Large chromosomal abnormalities are found in 8% to 10% of individuals with CCDs.[65] For example, aneuploidies such as trisomy 13, 18, and 21 account for 9% to 18% of CCDs.[66] The specific genes responsible for CCDs that are disrupted by these abnormalities are difficult to identify. Studies suggest that *DSCAM* and *COL6A* contribute to Down syndrome–associated CCDs.[67]
- Copy number variants contribute to 3% to 25% of CCDs that occur as part of a syndrome and to 3% to 10% of isolated CCDs and have been shown to be overrepresented in larger cohorts of patients with specific forms of CCDs.[68] The most common copy number variant is del22q11, which encompasses the *TBX1* (T-box transcription factor) gene and presents as DiGeorge syndrome and velocardiofacial syndrome. Others include del17q11, which causes William syndrome.[69]
- De novo variants have been reported in ≈8% of patients with CCDs (≈3% in isolated CCDs and ≈28% in those with extracardiac features along with CCDs).[65] Carriers of de novo variants also have been reported to have worse transplantation-free survival and a longer extubation duration.[70]
- Point variants in single genes are found in 3% to 5% of CCDs[65] and include variants in a core group of cardiac transcription factors (*NKX2.5*, *TBX1*, *TBX2*, *TBX3*, *TBX5*, *GATA4*, and *MEF2*),[69,71,72] *ZIC3*, and the *NOTCH1* gene (dominantly inherited and found in ≈5% of cases of bicuspid aortic valve) and related *NOTCH* signaling genes.[73]
- Consortia studies have allowed analysis of specific subtypes of CCDs through aggregation across centers. For example, a genome-wide study of conotruncal heart defects identified 8 candidate genes (*ARF5*, *EIF4E*, *KPNA1*, *MAP4K3*, *MBNL1*, *NCAPG*, *NDFUS1*, and *PSMG3*), 4 of which had not previously been associated with heart development.[74] Another study of nonsyndromic TOF in 829 patients with TOF found rare variants in *NOTCH1* and *FLT4* in almost 7% of patients with TOF.[75] A GWAS in 5 cohorts including 1025 conotruncal case-parent trios, 509 LV obstructive tract defect

case-parent trios, 406 conotruncal defect cases, and 2976 controls found intronic variants in the *MGAT4C* gene associated with conotruncal defects; in meta-analyses, 1 genome-wide significant association was found in an intragenic SNP associated with LV outflow tract defect.[76] Whole-genome sequencing has identified additional genetic loci for CCDs. In a study of whole-genome sequencing in 749 CCD case-parent trios with 1611 unaffected trios, a burden of de novo noncoding variants was identified in cases compared with controls, including in established CCD genes (*PTPN11*, *NOTCH1*, *FBN1*, *FLT4*, *NR2F2*, *GATA4*), with higher representation of variants in RNA-binding-protein regulatory sites.[77] These results suggest that noncoding de novo variants play a significant role in CCDs in addition to coding de novo variants.

- Recently, in addition to 14 previously recognized genes associated with CCDs, 7 new genes (*FEZ1*, *MYO16*, *ARID1B*, *NALCN*, *WAC*, *KDM5B*, and *WHSC1*) have been identified as being associated with CCDs.[78] A recent GWAS in patients of European ancestry with CCDs has identified *MACROD2*, *GOSR2*, *WNT3*, and *MSX1* to have an essential role in embryonic and postnatal cardiac morphogenesis and to contribute to the development of structural cardiac defects.[79]
- Rare monogenic CCDs also exist, including monogenic forms of ASD, heterotaxy, severe mitral valve prolapse, and bicuspid aortic valve.[69] GWASs and mechanistic studies have supported a causal role of *WNT5A* in TGA and *MUC4* in bicuspid aortic valve disease.[80,81]
- Complications related to CCDs also may have a genetic component; whole-exome sequence study identified *SOX17* as a novel candidate gene for PAH in patients with CCDs.[82]
- Genetic variants associated with CCDs may also occur within cancer risk genes.[83]
- There is no exact consensus currently on the role, type, and utility of clinical genetic testing in people with CCDs,[69] but it should be offered to patients with multiple congenital abnormalities or congenital syndromes (including CCD lesions associated with a high prevalence of 22q11 deletion or DiGeorge syndrome), and it can be considered in patients with a family history, in those with developmental delay, and in patients with CCDs and extracardiac manifestations.[14,84]
- The diagnostic yield for CCD genetic panels in familial, nonsyndromic cases is 31% to 46% and is even lower in nonfamilial disease.[85,86] Use of whole-exome genetic testing has been shown to improve rates of detection.[87]
- A Pediatric Cardiac Genomics Consortium has been developed to provide and better understand phenotype and genotype data from large cohorts of patients with CCDs.[88]

### Mortality

### (See Table 17-2 and Charts 17-1 through 17-5)

- In 2017, CCDs were among the top 8 causes of infant mortality in all global regions.[13]
- In 2021, mortality related to CCDs was 2931 deaths (Table 17-2) in the United States, a 7.4% decrease from the number of deaths in 2011 (unpublished NHLBI tabulation using NVSS[89]).
- CCDs (*ICD-10* Q20–Q28) were the most common cause of infant deaths resulting from birth defects (*ICD-10* Q00–Q99) in 2021; 21.0% of infants who died of a birth defect had a heart defect (*ICD-10* Q20–Q24; unpublished NHLBI tabulation using NVSS[89]).
- In 2021, the age-adjusted death rate (deaths per 100 000 people) attributable to CCDs was 0.95, which is the same as it was in 2011 (unpublished NHLBI tabulation using CDC WONDER[90]).
- Death rates attributed to CCDs decrease as gestational age advances to 40 weeks.[91] In-hospital mortality of infants with a major CCD is independently associated with late PTB (OR, 2.70 [95% CI, 1.69–4.33]) compared with delivery at later gestational ages.[92,93]
- Analysis of the STS Congenital Heart Surgery Database, a voluntary registry with self-reported data from 116 centers performing CCD surgery (112 based in 40 US states, 3 in Canada, and 1 in Turkey),[94] showed that of 31 102 analyzable CCD surgeries in 2018, there were 662 mortalities among the 25 608 patients included (2.5% [95% CI, 2.3%–2.7%]). For this same time period (2018), the mortality rate was 6.9% (95% CI, 6.2%–7.8%) for neonates, 2.4% (95% CI, 2.1%–2.8%) for infants, 1.1% (95% CI, 0.9%–1.3%) for children (1–18 years of age), and 1.2% (95% CI, 0.8%–1.7%) for adults (>18 years of age).[95]
- Another analysis of mortality after CCD surgery, culled from the US-based multicenter data registry of the Pediatric Cardiac Care Consortium, demonstrated that although standardized mortality ratios continue to decrease, increased mortality in patients with CCDs remains compared with the general population. The data included 35 998 patients with a median follow-up of 18 years and an overall standardized mortality ratio of 8.3% (95% CI, 8.0%–8.7%).[96]
- In Mexico, 70 741 deaths were attributed to CCDs during the years 2000 to 2015, with the standardized mortality rates increasing from 3.3 to 4 per 100 000 individuals and mortality rates increasing in the group <1 year of age from 114.4 to 146.4 per 100 000 live births.[97]

- Analysis of the NIS database of 20 649 neonates with HLHS showed a 20% decrease in mortality for neonates with HLHS between the time periods of 1998 to 2005 and 2006 to 2014 (95% CI, 25.3%–20.6%; *P*=0.001), despite the later cohort having more comorbidities, including prematurity and chromosomal abnormalities, among others.[98]
- A meta-analysis of outcomes for 848 patients with heterotaxy who underwent a Fontan procedure before May 2018 showed survival rates at 1, 5, and 10 years to be 86% (95% CI, 79%–91%), 80% (95% CI, 71%–87%), and 74% (95% CI, 59%–85%), respectively.[99]
- Trends in overall age-adjusted death rates attributable to CCDs showed a decline from 1999 to 2017 with a relative plateau between 2017 and 2021 (Chart 17-1); this varied by race, ethnicity, and sex (Charts 17-2 and 17-3). During this time, there was an overall decline in the age-adjusted death rates attributable to CCDs in NH Black, NH White, and Hispanic people (Chart 17-2). Although there was variability by race, death rates generally declined in both males and females (Chart 17-3) and in the groups 1 to 4, 5 to 14, 15 to 24, and ≥25 years of age (Chart 17-4) in the United States, although 2017 to 2021 showed a relative plateau in trends.
- CCD-related mortality varies substantially by age, with children 1 to 4 years of age demonstrating higher mortality rates than any age group other than infants from 1999 to 2020 (Chart 17-4).
- The US 2021 age-adjusted death rate (deaths per 100 000 people) attributable to CCDs was 1.10 for NH White males, 1.11 for NH Black males, 0.90 for Hispanic males, 0.86 for NH White females, 1.16 for NH Black females, and 0.64 for Hispanic females (Chart 17-5). Infant (<1 year of age) mortality rates were 24.9 for NH White infants, 34.1 for NH Black infants, and 24.2 for Hispanic infants (unpublished NHLBI tabulation using CDC WONDER[90]).
- Prenatal diagnosis can help to reduce mortality rates associated with CCDs, but prenatal diagnosis has not been consistently demonstrated to reduce mortality rates among neonates with complex CCDs such as HLHS.[100] Even among children diagnosed prenatally, greater distance between the birth center and cardiac surgical center (>90 miles) has been associated with greater mortality. Time required to drive from the birth center to the cardiac surgical center of <10, 10 to 90, and >90 minutes has been associated with 21%, 25.2%, and 39.6% mortality, respectively.
- Multiple pregnancies versus singleton pregnancy are associated with higher mortality during the first year of life among infants with critical CHD (1.61 [95% CI, 1.042–2.5]).[56]
- Efforts have been made to link data from multiple sources for the purpose of providing risk-adjusted outcome, resource use, health expenditure, and health disparity–related data for patients <18 years of age with CCDs. The New York Congenital Heart Surgeons Collaborative for Longitudinal Outcomes and Utilization of Resources has linked locally held data from 10 of 11 New York congenital heart centers to Medicaid claims data. In total, 7.7%, 8.4%, and 10.0% of children died at 3, 5, and 10 postoperative years, respectively.[101]
- For adults with CCDs, both the number of instances of clinic nonattendance (HR, 1.08 [95% CI, 1.05–1.12 per clinic nonattendance]; *P*<0.001) and the ratio of clinic nonattendance to follow-up period (HR, 1.23 [95% CI, 1.04–1.44 per clinic nonattendance per year]; *P*=0.013) are independent predictors of mortality.[102]
- Survival and health-related quality of life among individuals with CCDs are affected by genetic, epigenetic, environment, intervention-related, and disease-related outcomes.[103]
- According to data from the National Pediatric Cardiology Quality Improvement Collaborative Phase II registry, factors such as gestational age <37 weeks, birth weight <2.5 kg, secondary cardiac lesion, extracardiac anomaly, or genetic syndrome are associated with worse survival.[104] Although the presence of a single high-risk diagnosis is not associated with decreased survival, an incremental increase in the number of high-risk diagnoses is associated with reduced survival to a first birthday (OR, 0.23 [95% CI, 0.15–0.36]). The presence of 3 to 5 high-risk diagnoses is associated with an even greater odds of mortality (OR, 0.17 [95% CI, 0.10–0.30]).
- The personality type of adults with CCDs has been associated with mortality. According to the Dutch National Congenital Corvita registry, adults with type D (distressed) personality had an increased risk for all-cause mortality. After 10 years of follow-up, adults with CCDs and type D personality had survival of 82% versus 87% (non–type D personality; *P*=0.014).[105]
- Institution of an IHM for infants with HLHS may be beneficial for reducing interstage mortality.[106] Data from the National Pediatric Cardiology Quality Improvement Collaborative have indicated a >40% reduction in interstage 1 mortality, reducing mortality to <2%, in the current era, after changes in practice such as institution of IHM.[107] According to a single-center retrospective study, institution of an IHM, compared with a historical control, was associated with an average 29% lower predicted probability of interstage death (adjusted probability, −0.29 [95% CI, −0.52 to −0.57]; *P*=0.015).[108] However, the sole benefit of IHM remains a major research gap; no RCTs have assessed the role that IHM plays in improvement in

interstage mortality and morbidity, and IHM may be only 1 component of the many factors (eg, improved discharge process, care coordination, nutrition) contributing to improved outcomes.[107,108]

### Complications

Long-term effects of CCDs include arrhythmias, IE, and HF. Adults with CCDs who survive to 50 years of age have a significant chance of experiencing physical and mental health complications.[109–112]

- Individuals with CCDs are at increased risk of AF. In an analysis in Sweden including 21 982 patients with CCDs and 219 816 control patients, the risk of developing AF was 22 times higher (HR, 22.0 [95% CI, 19.3–25.1]) in those with CCDs compared with control patients without congenital HD.[113] By 42 years of age, ≈8% of patients with CCDs had been diagnosed with AF. Macroreentrant atrial tachycardia is very frequent in adults with congenital HD.[114]
- HF rates are 40%, 25%, and 50% among TOF, coarctation, and TGA/Fontan–repaired adult survivors, respectively.[112]
- Arrhythmia is very common and occurs among 35%, 32%, and 60% of TOF, coarctation, and TGA/Fontan–repaired adult survivors, respectively.[112]
- Adults with CCDs are at risk for reoperation, congestive HF, cerebrovascular events, and subacute bacterial endocarditis. Estimated reoperation rates among adults with TOF, coarctation of the aorta, and TGA and Fontan are 40%, 50%, and 10%, respectively.[112]
- Chronic hypoxia, neurohormonal derangements, intraglomerular hemodynamic shifts, ischemia, and nephrotoxins place individuals with CCD at increased risk for CKD.[115] According to data from the Swedish National Patient Register and the Cause of Death Register, the risk of CKD is 6.4 times higher in patients with CCD than control subjects (OR, 6.4 [95% CI, 5.65–7.27]).[116]
- Growth failure, in both weight and length, are common among patients with HLHS.[117] According to a secondary analysis of data from a prospective cohort study of growth and neurodevelopment in infants with CCD, infants with single-ventricle physiology compared with healthy infants had lower weight *Z* scores at 3 months (−1.64 versus −0.22; $P<0.0001$), 6 months (−1.30 versus −0.09; $P<0.0001$), 9 months (−0.76 versus 0.06; $P=0.001$), and 12 months (−0.45 versus 0.20; $P=0.005$).[118] Analysis of length *Z* scores demonstrated infants with single-ventricle physiology to be shorter than healthy infants at 3 months (−1.21 versus 0.15; $P<0.0001$), 6 months (−1.02 versus 0.22; $P<0.0001$), 9 months (−0.71 versus 0.28; $P<0.001$), and 12 months (−0.59 versus 0.10; $P=0.013$) of age.
- Children with CCDs may be at risk for adverse neurodevelopmental outcomes, including mild to severe motor impairments among 12.3% to 68.6% (IQR, 23.4%–52.2%),[119] increased attention-deficit/hyperactivity disorder–related behaviors (mean T score, 57 for inattention and 54 for hyperactivity/impulsivity compared with a normal mean T score of 50; $P<0.0001$ using Connors-3 testing), difficulties in social interaction (mean T score, 53 compared with a normal mean T score of 50; $P=0.035$), combined attention-deficit/hyperactivity disorder–related symptoms and social interaction problems in 23% of children,[120] and depression or anxiety (OR, 5.23 [95% CI, 3.9%–7.1%]).[121,122]
- Infants with single-ventricle physiology are more likely to have poorer fine and gross motor skills at 9 and 18 months compared with infants with other CCDs. Using the Dutch version of the Bayley-III shows that infants with single-ventricle physiology compared with infants with other forms of CCD performed significantly ($P\leq0.05$) worse on both fine and gross motor skills at 9 and 18 months. Mean fine motor score for single-ventricle physiology at 9 months was 9.9±1.6 versus 10.5±1.4 for TGA, 10.9±1.7 for TOF, and 11.6±1.6 for aortic arch pathology ($P=0.046$). Mean fine motor skills score for single-ventricle physiology at 18 months was 9.9±2.5 versus 11.4±1.6 for TGA, 11.6±1.7 for TOF, and 11.9±2.4 for aortic arch pathology ($P=0.002$). Mean gross motor score for single-ventricle physiology at 9 months was 6.8±3.5 versus 9.4±3.0 for TGA, 8.6±2.9 for TOF, and 8.8±2.8 for aortic arch pathology ($P=0.001$). Last, mean gross motor score for single-ventricle physiology at 18 months was 7.5±3.7 versus 10.6±3.1 for TGA, 10.2±2.8 for TOF, and 9.6±2.6 for aortic arch pathology ($P=0.001$).[123]
- Adults also may carry a higher burden of neurocognitive dysfunction and mental health complications. In the United Kingdom, adults with mild to moderate CCDs showed significantly lower performance on neurocognitive testing compared with individuals without CCDs, even when those with prior stroke or CAD were excluded. Among 1020 individuals with adult congenital HD and 497 987 without adult congenital HD, individuals with adult congenital HD had significantly poorer performance on alpha-numeric trail making, a measure of visual attention and cognitive flexibility, spending 6.4 seconds longer on alpha-numeric trail making (95% CI, 3.0–9.9 seconds; $P=0.002$) and 2.5 seconds longer on numeric trail making (95% CI, 0.5–4.6 seconds; $P=0.034$), a measure of visual attention and processing speed.[124]
- In patients with HLHS, an older age at Fontan procedure and a history of sepsis were independent predictors of poor neurocognitive outcomes.[125] According to multivariable linear regression models,

sepsis was associated with a lower full-scale intelligence quotient of −9.9 (95% CI, −17.0 to −2.90; *P*=0.007), a lower performance intelligence quotient of −9.2 (95% CI, −17 to −2.10; *P*=0.012), and a lower verbal intelligence quotient of −9.2 (95% CI, −17.02 to −1.90; *P*=0.015). Similarly, a history of Fontan procedure was associated with a lower full-scale intelligence quotient of −6.5 (95% CI, −10.4 to −2.80; *P*<0.0001), a lower performance intelligence quotient of −6.40 (95% CI, −10.5 to −2.70; *P*<0.0001), and a lower verbal intelligence quotient of −5.10 (95% CI, −9.00 to −1.10; *P*=0.013).

- Of 121 patients with adult CCDs in Australia with moderate or complex CCDs, just more than 60% of those with TOF or CoA remained employed, and approximately half had been diagnosed with anxiety or depression.[112]
- A diagnosis of anxiety is made in ≈5% to 50% of adult CCD survivors with lowest reported rates for individuals with history of coarctation repair and highest among adult survivors after Fontan surgery.[112]
- There are inconclusive data showing an increased risk of serious adverse events from COVID-19 infection in children and adults with CCDs.[126]
- Roughly one-fourth of patients living with a Fontan circulation develop liver cirrhosis throughout adulthood. The cumulative incidence of liver cirrhosis among patients with Fontan circulation is 27.5% (95%CI, 16.9%–34.4%).[127]
- Independently of the severity of the underlying heart defect, adults with congenital heart disease have an increased risk for anxiety disorder.[128] High New York Heart Association class is associated with a greater odds of anxiety and depression (OR, 2.67 [95% CI, 1.50–4.76]).

### Health Care Use: Hospitalizations (See Table 17-2)

- In 2020, the total number of first-listed hospital discharges for CCDs for all ages was 40 150 (Table 17-2).[129]
- Hospitalization of infants with CCDs is common; one-third of patients with CCDs require hospitalization during infancy,[130,131] often in an ICU.
- Socioeconomic and sociodemographic factors affect hospitalization rates and length of stay. However, adjustments to length of hospital stay (eg, longer length of stay) may help to mitigate previously identified higher mortality risk for Black infants with CCDs.[132]
- The number of adults with CCD and HF-related admissions increased according to data from the Pediatric Health Information Systems database from 2005 to 2015. A total of 562 admissions occurred at 39 pediatric hospitals, increasing from 4.1% to 6.3% (*P*=0.015) during the study period.[133] Compared with adults with non-CCD HF-related admissions, adults with CCD and HF-related admissions also demonstrated increased length of stay ≥7 days (aOR, 2.5 [95% CI, 2.0–3.1]), incident arrhythmias (aOR, 2.8 [95% CI, 1.7–4.5]), and in-hospital mortality (aOR, 1.9 [95% CI, 1.1–3.1]).[134]
- Among adults with commercially purchased insurance, those with CCDs had more health care visits and higher expenditures than those without CCDs, even when controlling for baseline characteristics and comorbidities. Among individuals with CCDs, median ambulatory, physician, nonphysician, ED, prescription, and out-of-pocket ambulatory costs were $3598 (IQR, $1221–$9454), $1120 (IQR, $440–$2503), $839 (IQR, $90–$3413), $2005 (IQR, $993–$4035), $213 (IQR, $13–$1237), and $802 (IQR, 246–1862), and among individuals without CCDs, $1068 (IQR, $230–$3640), $375 (IQR, $69–$1083), $125 (IQR, $0–$704), $1583 (IQR, $808–$3209), $64 (IQR, $0–$527), and $261 (IQR, $33–$892), respectively (*P*<0.001 for all comparisons).[135]
- Among adolescents and adults with CCDs, residence within the census tracts with highest area deprivation index (most deprived areas) was associated with a 51% higher odds of inpatient admission, 74% higher odds of ED visit, 41% higher odds of cardiac surgeries, and 45% higher odds of major adverse cardiac events compared with residence within the census tracts with the lowest deprivation index.[135]

### Cost

- Using HCUP NIS 2013 data, 1 study noted that hospitalization costs for individuals of all ages with CCDs exceeded $6.1 billion in 2013, which represents 27% of all birth defect–associated hospital costs.[136]
- Among pediatric hospitalizations (0–20 years of age) in the HCUP 2012 Kids' Inpatient Database[137]:
  - Pediatric hospitalizations with CCDs (4.4% of total pediatric hospitalizations) accounted for $6.6 billion in hospitalization spending (23% of total pediatric hospitalization costs).
  - 26.7% of all CCD costs were attributed to critical CCDs, with the highest costs attributable to HLHS, coarctation of the aorta, and TOF.
  - Median hospital cost was $51 302 (IQR, $32 088–$100 058) in children who underwent cardiac surgery, $21 920 (IQR, $13 068–$51 609) in children who underwent cardiac catheterization, $4134 (IQR, $1771–$10 253) in children who underwent noncardiac surgery, and $23 062 (IQR, $5529–$71 887) in children admitted for medical treatments.

  - The mean cost of CCDs was higher in infancy ($36 601) than in older ages and in those with critical CCDs ($52 899).
- A Canadian study published in 2017 demonstrated increasing hospitalization costs for children and adults with CCDs, particularly those with complex lesions. Among 59 917 hospitalizations, annual CHD costs increased by 21.6% from CAD: $99.7 (95% CI, $89.4–$110.1) million in 2004 to $121.2 (95% CI, $112.8–$129.6) million in 2013 ($P<0.001$). Costs were higher for children compared with adults. The cost increase was greater in adults (4.5%/y; $P<0.001$) than in children (0.7%/y; $P=0.006$). Adults accounted for 38.2% of costs in 2004 versus 45.8% in 2013 ($P=0.002$). Costs increased most among adults with complex CHD (7.2%/y; $P=0.001$). Adult men accounted for greater increases in costs relative to women ($P<0.001$). Length of stay was unchanged over time.[138]
- A US study evaluating cost and length of stay in neonates with HLHS revealed significant regional differences in cost, length of stay, and mortality. Adjusted average length of stay was shortest in the West and longest in the South (26.1 days [95% CI, 24.0–35.1] versus 34.9 days [95% CI, 31.8–38.1]); average adjusted charges were lowest in the Northeast ($324 600 [95% CI, $271 400–$377 900]) and highest in the West ($400 500 [95% CI, $346 700–$454 300]; $P=0.05$).[139]
- A 2021 study in Queensland, Australia, of 2519 patients found that catheter-based and surgical interventions accounted for 90% of the total costs of caring for patients with CCDs.[140]
- A Pediatric Heart Network study found an overall cost reduction for TOF repair of 27% after a clinical practice guideline including early extubation was introduced. A similar cost reduction was not found for patients with aortic coarctation repair.[141]
- A cross-sectional survey from the NHIS of US households (2011–2017) found that nearly half (48.9%) of families of children with CCDs had some financial hardship attributable to medical bills. Among 17% of families who reported that they could not pay their medical bills (most severe hardship category), there were significantly higher rates of food insecurity and delays in care because of cost.[142]
- Cost of CCD care may be affected by center volume. Data from the Pediatric Health Information Systems database show that of 1024 neonates with truncus arteriosus, of whom 495 (48%) were treated at high-volume centers, costs at the 75th percentile were lower at high-volume versus low-volume centers by $28 456 ($P=0.02$). Patients at high-volume centers had lower median postoperative ventilation days (5 days versus 6 days; $P<0.001$), ICU length of stay (13 days versus 19 days; $P<0.001$), hospital length of stay (23 days versus 28 days; $P=0.02$), and inotropic agent use (3 days versus 4 days; $P=0.004$).[58,143]

### Global Burden of CCDs (See Charts 17-6 and 17-7)

- A total of 3.12 (95% UI, 2.40–4.11) million babies were born with CCDs in 2019, representing 2305.2 per 100 000 live births (95% UI, 1772.9–3039.2).[12]
- As with all-age prevalence, there is global variability in birth prevalence by sustainable development index. In 2017, prevalence was estimated to be 25.0 per 1000 in countries with low sustainable development index and 11.8 to 12.6 per 1000 in countries with high-middle or high sustainable development index.[13]
- A 2019 systematic review including 103 632 049 live births globally showed the following per 1000 births in order of prevalence: VSD, 3.071; ASD, 1.441; patent ductus arteriosus, 1.004; pulmonary stenosis, 0.546; TOF, 0.356; TGA, 0.295; atrioventricular septal defects, 0.290; aortic coarctation, 0.287; HLHS, 0.178; double-outlet RV, 0.106; and truncus arteriosus, 0.078 (among others reviewed).[144]
- CCDs were responsible for 261 247 deaths globally in 2017 (95% CI, 216 567–308 159), which is a 30% decline from 1990.[13] The majority of these deaths (69%) were in infants <1 year of age (180 624 [95% CI, 146 825–214 178]). In large part, CCD mortality tracks socioeconomic development index, with the highest mortality in low and low-middle socioeconomic development index quintiles.[13]
- Based on 204 countries and territories in 2021[145]:
  - The prevalence of congenital heart anomalies was 15.81 (95% UI, 13.87–17.23) million cases.
  - There were 0.26 (95% UI, 0.22–0.31) million deaths estimated for congenital heart anomalies worldwide.
  - Age-standardized mortality rates of congenital heart anomalies were highest in Oceania, North Africa and the Middle East, the Caribbean, and western sub-Saharan Africa. They were lowest in high-income Asia Pacific, Australasia, and Western Europe (Chart 17-6).
  - The age-standardized prevalence of congenital heart anomalies was highest in high-income Asia Pacific, Central Asia, and Western Europe (Chart 17-7).
- In a 2019 systematic review including 103 632 049 live births globally, the mean prevalence of CCDs globally was 8.2 per 1000. Prevalence of CCDs in Africa was estimated at ≈25% of that in other regions, likely attributable to sparse population-level data and low diagnostic access.[144]

- There are multiple recent estimates on the prevalence of CCDs in China.
  - According to a systematic review and meta-analysis of CCD data from China, birth prevalence of CCDs has increased from 0.2 per 1000 live births (1980–1984) to 4.9 per 1000 live births (2015–2019) with higher rates among males (4.2 per 1000 versus 3.5 per 1000), individuals living in urban compared with rural areas (2.5 per 1000 versus 4.3 per 1000), and those in higher income brackets (no data from lower-income regions but 4.0 per 1000 in high-income areas versus 1.5 per 1000 in upper-middle–income areas),[146] possibly reflecting differences in diagnostic access.
  - In another study from China (Zhengzhou, Henan), the overall prevalence of CCDs was 8.44 per 1000 live births during 2014 to 2020.[147]
  - From January to December 2019, among 51 857 newborns born in 11 cities in eastern China, the total birth prevalence of CCDs was 5.79 per 1000 births.[148] Birth prevalence was higher in low-income (6.14 per 1000 births) compared with high-income (5.58 per 1000 births; $P$=0.009) areas.
  - In the Yunnan region of China, differences in CCD prevalence among ethnic groups were found. The overall CCD prevalence was 6.04 cases per 1000 children.[149] The ethnic groups displaying the highest CCD prevalence were the Lisu (15.51 per 1000), Achang (13.18 per 1000), Jingpo (12.32 per 1000), Naxi (9.68 per 1000), and Tibetan (8.57 per 1000).
- Birth incidence is increasing in the Kingdom of Bahrain, with 9.45 per 1000 live births in 2016 compared with 6.45 per 1000 live births affected in 2000.[150]
- Between 1977 and 2015, a Danish study of 15 900 patients with simple CCDs (ASD, VSD, patent ductus arteriosus) found increasing incidence per 100 000 (ASD in adults, 8.8 [95% CI, 7.1–10.5] to 31.8 [95% CI, 29.2–34.5]; ASD in children, 26.6 [95% CI, 20.9–32.3] to 150.8 [95% CI, 126.5–175.0]; VSD in children, 72.1 [95% CI, 60.3–83.9] to 115.4 [95% CI, 109.1–121.6], and patent ductus arteriosus in children, 49.2 [95% CI, 39.8–58.5] to 102.2 [95% CI, 86.7–117.6]).[151]
- According to a population-based study from Malaysia, CCDs occurred in 1.26 of every 1000 births (2006–2015) with no significant change in incidence over time.[152]
- In Argentina, according to data provided by the national Network of Congenital Anomalies (2009–2018), the prevalence of CCDs was 11.46 (95% CI, 11.02–11.92) per 10 000 births.[153]
- Estimated (pooled) prevalence of ASD among CCDs in East Africa is 10.36% (95% CI, 8.05%–12.68%; $I^2$=89.5%; $P$<0.001).[154]
- Estimated (pooled) prevalence of VSD among CCDs in East Africa is 29.92% (95% CI, 26.12%–33.72%; $I^2$=89.2%; $P$<0.001), in Ethiopia is 36.04% (95% CI, 29.36%–42.72%), in Djibouti is 37% (95% CI, 18.79%–55.21%), and in Sudan is 32.59% (95% CI, 26.67%–38.59%).[154]
- Although gains in CCD mortality were seen over the past 3 decades, unfavorable period and cohort effects were found in many countries, raising questions about health care adequacy to care for children with CCDs.[155]
  - India, China, Pakistan, and Nigeria had the highest mortality, accounting for 39.7% of deaths resulting from CCDs globally.
  - During the past 30 years, favorable mortality reductions were generally found in most high-SDI countries like South Korea (net drift, −4.0% [95% CI, −4.8% to −3.1%] per year) and in many middle-SDI countries like Brazil (−2.7% [95% CI, −3.1% to 2.4%]) and South Africa (95% CI, −2.5% [−3.2% to −1.8%]).
  - However, 52 of 129 countries had either increasing trends (net drifts ≥0.0%) or stagnated reductions (≥−0.5%) in mortality.

## Kawasaki Disease

### *ICD-9 446.1; ICD-10 M30.3.*

KD is an acute inflammatory illness characterized by fever, rash, nonexudative limbal-sparing conjunctivitis, extremity changes, red lips and strawberry tongue, and a swollen lymph node. The most significant consequence of this vasculitis is coronary artery aneurysms, which can result in coronary ischemic events and other cardiovascular outcomes in the acute period or years later.[156] The cause of KD is unknown but may be an immune response to an acute infectious illness based in part on genetic susceptibilities.[157,158]

### *Prevalence*

- KD is the most common cause of acquired HD in children in the United States and other high-income countries.[159]

### *Incidence*

- A review of HCUP/Kids' Inpatient Database for KD hospitalizations in children <18 years of age in the United States during 2009 to 2012 revealed 10 486 hospitalizations for KD of 12 678 005 total hospitalizations. The incidence of KD was estimated at 6.35 per 100 000.[160]
- The incidence of KD was estimated at 20.8 per 100 000 US children <5 years of age in 2006.[161] This was calculated from 2 databases and limited by reliance on weighted hospitalization data from 38 states.
- Male children have a 1.5-fold higher incidence of KD than female children.[161]

- Although KD can occur into adolescence (and rarely adulthood), 76.8% of US children with KD are <5 years of age.[161]
- Race-specific incidence rates indicate that KD is most common among Americans of Asian and Pacific Islander descent (30.3 per 100 000 children <5 years of age), occurs with intermediate frequency in NH Black (17.5 per 100 000 children <5 years of age) and Hispanic (15.7 per 100 000 children <5 years of age) children, and is least common in White children (12.0 per 100 000 children <5 years of age).[161]
- Geographic variation in KD incidence exists within the United States. States with higher Asian American populations have higher rates of KD; for example, rates are 2.5-fold higher in Hawaii (50.4 per 100 000 children <5 years of age) than in the continental United States.[162] Within Hawaii, the race-specific rates of KD per 100 000 children <5 years of age in 1996 to 2006 were 210.5 for Japanese, 86.9 for Native Hawaiian, 83.2 for Chinese, 64.5 for Filipino, and 13.7 for White children.[162]
- There are seasonal variations in KD that may track other respiratory and enteric viruses[163]; KD is more common during the winter and early spring months, except in Hawaii, where no clear seasonal trend is seen.[161,162]
- Incidence of KD may have decreased during SARS-CoV-2 mitigation policies (social distancing and masks), with 1 center reporting a 67% decline ($P$=0.01) comparing April to December 2020 with the same months in the past 8 years[164] and another study in Korea reporting only 60% of predicted cases (incidence 18.8 per 100 000) after standard precautions were implemented compared with the predicted mean incidence (32.2 per 100 000) based on >50 000 cases between 2010 and 2020.[165]
- KD rarely recurs. Recurrences constitute 2% to 4% of total KD cases in both the United States and Japan,[166] and the incidence of first recurrence among children with a history of KD has been reported as 6.5 per 1000 person-years in Japan (2007–2010) and 2.6 per 1000 person-years in Canada (2004–2014).[167,168]

### Secular Trends

- Although the incidence of KD is rising worldwide, there has been no clear secular trend in the United States, but recent data are lacking. US hospitalizations for KD were 17.5 and 20.8 per 100 000 children <5 years of age in 1997 and 2006, respectively, but the test for linear trend was not significant.[161]

### Genetics/Family History/Risk Factors

- GWASs have identified loci in *FCGR2A*, *FAM167-BLK*, *CD40*, *IHGV3-66*, HLA class II region, *NAALADL2*, and *ZFHX3* to be associated with KD.[169–173] Recently, a novel loci (intergenic variant rs6017006) has been identified to be associated with coronary artery aneurysm in patients of European descent with KD.[174]
- Various genetic variants have been associated with KD susceptibility or development of coronary artery lesions in KD; however, thus far, these variants have not explained differences in incidence between ancestry groups (eg, Japanese versus European).[157,173,175]
- Advanced maternal age (≥35 years; OR, 1.18 [95% CI, 1.07–1.30]; $P$<0.001), maternal ankylosing spondylitis (OR, 2.01 [95% CI, 1.17–4.43]; $P$=0.01), and Sjögren syndrome (OR, 1.75 [95% CI, 1.03–2.95]; $P$=0.04) may be perinatal factors associated with increased risk of KD.[176]
- Certain types of air pollution, both prenatally and during early life, may contribute to the development of KD in children. The strongest risk related to carbon monoxide (parts per million) is during pregnancy (OR, 1.67 (95% CI, 1.23–2.28]; $P$=0.001) and after delivery (1.61 [95% CI, 1.16–2.22]; $P$=0.004).[177]

### Treatment and Control

- Treatment of acute KD rests on diminishing the inflammatory response with IVIG, which reduces the incidence of coronary artery aneurysms (from 25% to ≈4% for aneurysms defined by absolute dimensions).[159] Aspirin is routinely used for its anti-inflammatory and antiplatelet effects, but it does not reduce the incidence of coronary artery aneurysms.[178]
- On the basis of a Cochrane review, adding prednisolone to the standard IVIG regimen could further reduce the incidence of coronary artery abnormalities (RR, 0.29 [95% CI, 0.18–0.46]), but the applicability of these data to non-Asian patients and less severe KD cases is not certain.[179]
- Treatment of IVIG resistance is currently not standardized. A multicenter comparative-effectiveness trial including 30 US hospitals and 103 patients (4 weeks–17 years of age) showed that infliximab compared with a second dose of IVIG resulted in shorter fever duration (1.5 days [SD, 1.4 days] versus 2.5 days [SD, 2.5 days]) and shorter hospitalization (3.2 days [SD, 2.1 days] versus 4.5 days [SD, 2.5 days]). No difference was found in coronary artery outcomes.[180]
- Cyclophosphamide may arrest further coronary artery dilation in those with severe and progressive coronary artery enlargement after KD.[181]
- Management of established coronary artery aneurysms in the short and long term is centered on thromboprophylaxis. Successful coronary intervention for late coronary stenosis or thrombosis has been accomplished percutaneously and surgically (eg, CABG).[182,183]

### Complications of KD

In the acute phase (up to ≈6 weeks from fever onset), several important cardiovascular complications can occur.

- KD shock syndrome, with variable contributions from myocardial dysfunction and decreased peripheral resistance, occurs in 5% to 7% of patients with KD and is associated with higher risk of coronary arterial dilation, resistance to IVIG treatment, and, rarely, long-term myocardial dysfunction or death.[184]
- It is estimated that even with current therapy (high-dose IVIG within the first 10 days of illness), 20% of children develop transient coronary artery dilation (*Z* score >2), 5% develop coronary artery aneurysms (*Z* score ≥2.5), and 1% develop giant aneurysms (*Z* score ≥10 or >8 mm).[159] Estimates are complicated by variability in ascertainment methods (administrative codes or research measurement), size criteria, timing (because the majority of dilated segments and approximately half of aneurysms reduce to normal dimensions over time), and therapeutic regimens in the underlying studies. In US data from 2 centers in 2004 to 2008, maximal coronary artery dimensions reached *Z* scores ≥2.5 in 30% of patients with KD up to 12 weeks from fever onset, including medium (*Z* score ≥5–<10) and giant aneurysms in ≈6% and ≈3% of patients with KD, respectively.[185]
- A recent study showed that younger age (OR, 0.94 [95% CI, 0.90–0.99]), IVIG nonresponse (OR, 6.70 [95% CI, 1.80–24.50]), and noncoronary cardiac events (OR, 3.20 [95% CI, 1.10-8.70]), in particular in very young children (<6 months), may also increase risk for more severe KD with coronary artery aneurysms (OR, 2.18 [95% CI, 1.25–3.80]).[186]
- In Latin America, children <6 months of age were more likely to have delayed diagnoses (OR, 0.17 [95% CI, 0.08–0.35]) and less obvious clinical features (oral changes: OR, 0.26 [95 % CI, 0.12–0.58]; cervical lymphadenopathy: OR, 0.28 [95% CI, 0.14–0.28]; extremity changes: OR, 0.45 [95% CI, 0.23–0.88]; complete KD: OR, 0.24 [95% CI, 0.13–0.47]) and were at greater risk of developing coronary artery aneurysm (OR, 11.25 [95% CI, 3.87–36.25]), even after controlling for day of treatment initiation.[187]
- Peak KD-associated mortality occurs during the acute phase but is rare, estimated at 0% to 0.17% in older US data and 0.03% in data from Japan.[188–190] Mortality is related to thrombosis or rupture of rapidly expanding aneurysms or, less commonly, shock or macrophage activation syndrome with multiorgan failure.[190,191]
- Prognosis is predicted largely by coronary artery size 1 month from illness onset. In a Taiwanese study of 1073 patients with KD from 1980 to 2012, coronary artery aneurysms were present in 18.3% beyond 1 month, including 11.6% small, 4.1% medium, and 2.5% giant aneurysms. Among those with persistent aneurysms beyond 1 month, IHD death occurred in 2%, nonfatal AMI occurred in another 2%, and myocardial ischemia occurred in another 3%, for a total of a 7% ischemic event rate during 1 to 46 years of follow-up. Nearly all events occurred in those with giant aneurysms, for whom the ischemia event–free survival rates were 0.63 and 0.36 at 10 and 20 years, respectively, after KD onset.[192] Findings were similar in a Japanese study of 76 patients with giant aneurysms diagnosed since 1972 and followed up through 2011 and in a Canadian study of 1356 patients with KD diagnosed in 1990 to 2007 and followed up for up to 15 years.[182,193]
- A Japanese multicenter cohort study of 1006 individuals identified risk factors for 10-year incidence of coronary events (thrombosis, stenosis, obstruction, acute ischemic events, or coronary intervention).[194] Significant risk factors included giant aneurysm (HR, 8.9 [95% CI, 5.1–15.4]), male sex (HR, 2.8 [95% CI, 1.7–4.8]), and resistance to IVIG therapy (HR, 2.2 [95% CI, 1.4–3.6]).
- In 2021, US mortality attributable to KD was 11 patients for all-cause mortality, whereas data for underlying mortality are suppressed due to confidentiality constraints because there were <10 deaths (unpublished NHLBI tabulation using CDC WONDER[90]).

### Health Care Use

- In 2020, there were 3235 principal and 4680 all-listed diagnoses hospital discharges for KD (HCUP,[195] unpublished NHLBI tabulation).
- A Canadian study found that children with KD compared with control subjects had higher rates of hospitalization (adjusted rate ratio, 2.07 [95% CI, 2.00–2.15]), outpatient visits (adjusted rate ratio, 1.30 [95% CI, 1.28–1.33]), and ED visits (adjusted rate ratio, 1.22 [95% CI, 1.18–1.26]) throughout follow-up.[196] Within 1 year after discharge, 717 children with KD (15.6%) were rehospitalized, 4587 (99.8%) had ≥1 outpatient physician visits, and 1695 (45.5%) had ≥1 ED visits.
- Patients with KD also had higher composite health care costs after discharge (eg, median cost within 1 year [Canadian dollars], $2466 [KD cases] versus $234 [comparators]).[196]

### Global Burden of KD

- The annual incidence of KD is highest in Japan, at 264 per 100 000 children <5 years of age in 2014, followed by South Korea at 134.4 per 100 000 children <5 years of age in 2014 and Taiwan at 82.7 per 100 000 in children <5 years of age.[197]
- In Japan, the cumulative incidence of KD at 10 years of age has been calculated with national survey data as >1%, at 1.5 per 100 males and 1.2 per

100 females for 2007 to 2010.[198] With the use of different methodology with complete capture of cases through the national health insurance program, Taiwan recorded a cumulative incidence of 2.8% by 5 years of age in 2014.[199]

- The incidence of KD is lower in Canada, at 19.6 per 100 000 children <5 years of age for the period of 2004 to 2014, and in European countries such as Italy with 14.7 per 100 000 children <5 years of age in 2008 to 2013, Spain with 8 per 100 000 children <5 years of age in 2004 to 2014, Germany with 7.2 per 100 000 children <5 years of age in 2011 to 2012, and the United Kingdom and Ireland with 4.6 per 100 000 children <5 years of age in 2014 to 2015.[168,200–204]

## Multisystem Inflammatory Syndrome in Children

MIS-C is a clinical syndrome characterized by fever, inflammation, and multiorgan dysfunction that most commonly manifests late in the course of SARS-CoV-2 infection.[205] MIS-C has overlapping signs and symptoms of KD and toxic shock syndrome. Case definitions of MIS-C by the CDC and WHO require fever, elevated makers of inflammation, evidence of recent SARS-CoV2 infection or exposure, multisystem organ involvement, and exclusion of alternate diagnoses. The first case reports of MIS-C (which has gone by many names) came from the United States and Europe in April 2020,[206] with dozens of case series now reported from around the world.

- MIS-C most commonly occurs 4 to 6 weeks after a population peak of SARS-CoV2 infection.[207]
- Since May 2020, the CDC has been tracking reports of MIS-C. As of March 17, 2023, 9370 cases and 76 attributable deaths (0.81%) have been reported. Median age of cases was 9 years; 57% of cases have occurred in children who are Hispanic or Latino (2333 cases) or Black (2685 cases); 98% tested positive for SARS-CoV2 (reverse transcriptase–polymerase chain reaction, serology, or antigen test); and 60% of reported patients were male.[208]
- A meta-analysis of patient characteristics in MIS-C shows that more males (55.8% [95% CI, 50.3%–61.2%]) are affected, most patients (79.1% [95% CI, 70.8–85.5]) require intensive care admission, nearly one-third of patients (29.2% [95% CI, 19.9%–40.5%]) require mechanical ventilation, and a small number (7.6% [95% CI, 4.1%–13.8%]) require extracorporeal membrane oxygenation.[209]
- Risk of MIS-C may vary with ethnicity, with apparently higher risk among those of African descent.[210,211]
- A potential association has been found in 2 studies between severe vitamin D deficiency and severe disease in children presenting with MIS-C.[212,213]
- There is also a potential association of obesity with incomplete recovery from MIS-C. In Poland, among 306 children with MIS-C, obese children had a higher rate of incomplete recovery (OR, 4.2 [95% CI, 1.4–12.1]).[214]
- Some data suggest that the risks of MIS-C have changed over the course of the SARS-CoV-2 pandemic.
- In England during the Alpha wave, MIS-C occurred in 0.038% (IQR, 0.037%–0.041%) of pediatric SARS-CoV-2 infection; during the Delta wave, MISC-C occurred in 0.026% (IQR, 0.025%–0.029%).[215]
- A multicenter, international, cross-sectional study collected the MIS-C incidence from the participant regions and countries for the period of July 2020 to November 2021.[216] Over 2 subsequent 4-week periods of measure in a reference population of 17 906 432 children, a significant decrease trend ratio of MIS-C/COVID-19 cases was found globally ($P<0.001$).
- Among 903 cases of MIS-C in Brazil, the RR of death caused by MIS-C was 5.29 (95% CI, 2.83–9.87; $P<0.001$) times higher in adolescents from 15 to 19 years of age compared with children 0 to 4 years of age. In addition, residency in the North region, a region with poorer health and economic indicators, was a risk factor for death (RR, 3.72 [95% CI, 1.29–10.74]; $P=0.008$).[217]

**Table 17-1. Annual Birth Prevalence of CCDs in the United States, 1930 to 2010**

| Type of presentation | Rate per 1000 live births | Estimated number (variable with yearly birth rate) |
|---|---|---|
| Fetal loss | Unknown | Unknown |
| Invasive procedure during the first year | 2.4 | 9200 |
| Detected during the first year* | 8 | 36 000 |
| Bicuspid aortic valve | 13.7 | 54 800 |

CCD indicates congenital cardiovascular defect.

*Includes stillbirths and pregnancy termination at <20 weeks' gestation; includes some defects that resolve spontaneously or do not require treatment.

Source: Data derived from van der Linde et al[218] and Parker et al.[219]

**Table 17-2. CCDs in the United States**

| Population group | Estimated prevalence, 2010, all ages | Mortality, 2021, all ages* | Hospital discharges, 2020, all ages |
|---|---|---|---|
| Both sexes | 2.4 million | 2931 | 40 150 |
| Males | … | 1591 (54.3%)† | |
| Females | … | 1340 (45.7%)† | |
| NH White males | … | 986 | … |
| NH White females | … | 829 | … |
| NH Black males | … | 211 | … |
| NH Black females | … | 227 | … |
| Hispanic males | … | 279 | … |
| Hispanic females | … | 195 | … |
| NH Asian males | … | 50 | … |
| NH Asian females | … | 32 | … |
| NH American Indian or Alaska Native people | … | 35 | … |
| NH Native Hawaiian or Pacific Islander | | Suppressed‡ | |

CCD indicates congenital cardiovascular defect; ellipses (…), data not available; and NH, non-Hispanic.

*Mortality for Hispanic, NH American Indian or Alaska Native, and NH Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting Hispanic origin or race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native, Asian, Pacific Islander, and Hispanic decedents, as well as undercounts of these groups in censuses.

†These percentages represent the portion of total congenital cardiovascular mortality that is for males vs females.

‡Suppressed due to confidentiality constraints because there were fewer than 10 deaths.

Sources: Prevalence: Gilboa et al.[15] Mortality (for underlying cause of CCDs): unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using National Vital Statistics System.[89] These data represent underlying cause of death only. Hospital discharges (with a principal diagnosis of CCD): unpublished NHLBI tabulation using Healthcare Cost and Utilization Project, 2019.[195] Data include those inpatients discharged alive, dead, or status unknown.

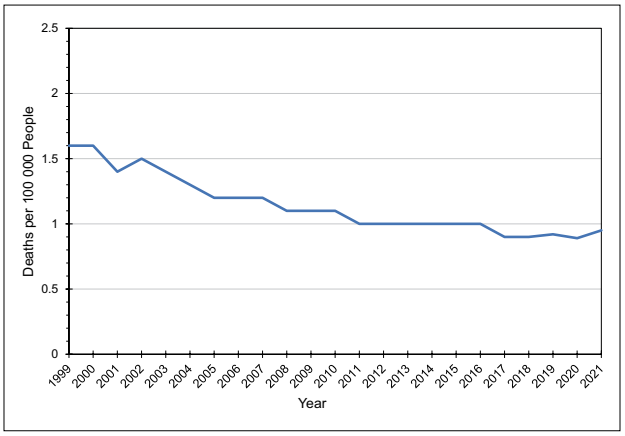



**Chart 17-1. Trends in age-adjusted death rates attributable to CCDs, United States, 1999 to 2021.**
CCD indicates congenital cardiovascular defect.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research.[90]

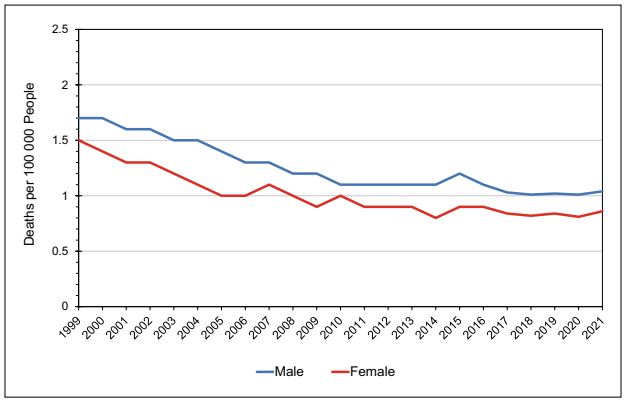



**Chart 17-3. Trends in age-adjusted death rates attributable to CCDs, by sex, United States, 1999 to 2021.**
CCD indicates congenital cardiovascular defect.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research.[90]

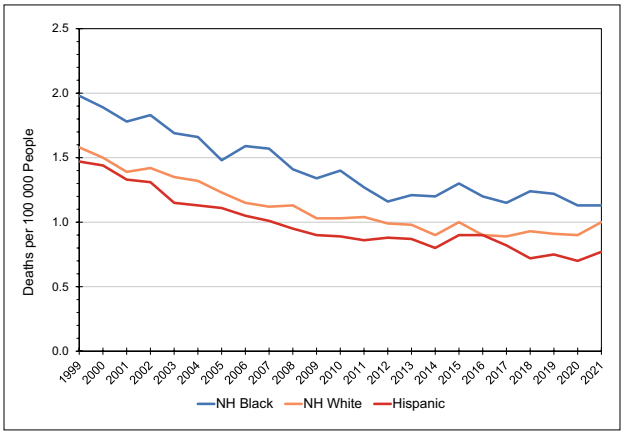



**Chart 17-2. Trends in age-adjusted death rates attributable to CCDs, by race and ethnicity, United States, 1999 to 2021.**
CCD indicates congenital cardiovascular defect; and NH, non-Hispanic.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research.[90]

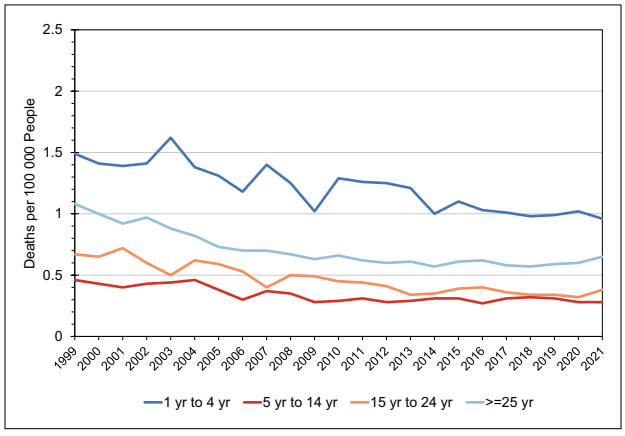



**Chart 17-4. Trends in age-specific death rates attributable to CCDs, by age at death, United States, 1999 to 2021.**
CCD indicates congenital cardiovascular defect.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research.[90]

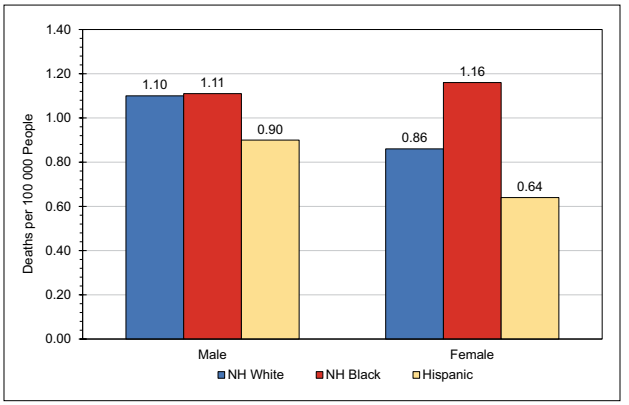



**Chart 17-5. Age-adjusted death rates attributable to CCDs, by sex, race, and ethnicity, United States, 2021.**
CCD indicates congenital cardiovascular defect; and NH, non-Hispanic.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research.[90]

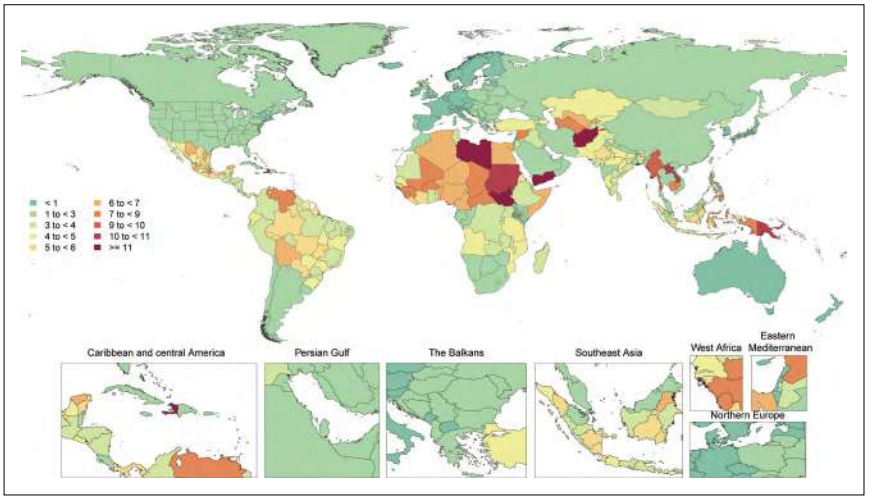



**Chart 17-6. Age-standardized global mortality rates of congenital heart anomalies per 100 000, both sexes, 2021.**
During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.
GBD indicates Global Burden of Disease.
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[145]

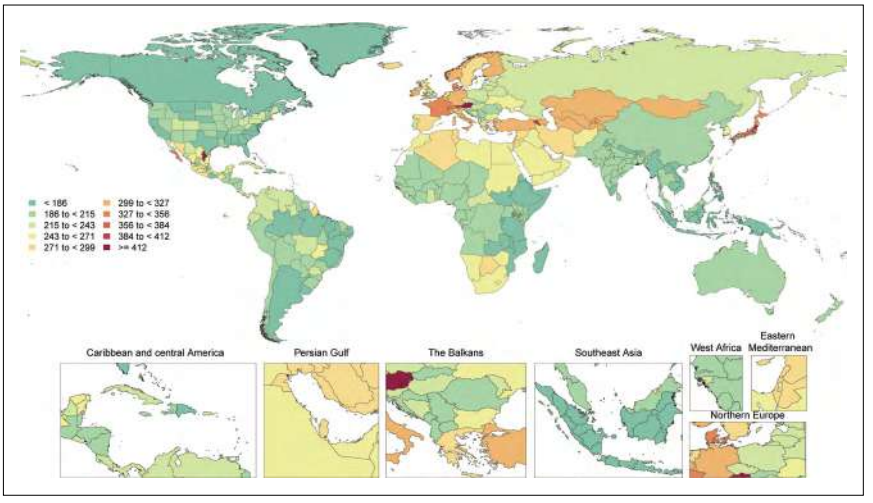



**Chart 17-7. Age-standardized global prevalence rates of congenital heart anomalies per 100 000, both sexes, 2021.**
During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.
GBD indicates Global Burden of Disease.
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[145]

## REFERENCES


1. Mamasoula C, Addor MC, Carbonell CC, Dias CM, Echevarria-Gonzalez-de-Garibay LJ, Gatt M, Khoshnood B, Klungsoyr K, Randall K, Stoianova S, et al. Prevalence of congenital heart defects in Europe, 2008-2015: a registry-based study. *Birth Defects Res*. 2022;114:1404–1416. doi: 10.1002/bdr2.2117
2. Chimah OU, Emeagui KN, Ajaegbu OC, Anazor CV, Ossai CA, Fagbemi AJ, Emeagui OD. Congenital malformations: prevalence and characteristics of newborns admitted into Federal Medical Center, Asaba. *Health Sci Rep*. 2022;5:e599. doi: 10.1002/hsr2.599
3. Bhide P, Kar A. A national estimate of the birth prevalence of congenital anomalies in India: systematic review and meta-analysis. *BMC Pediatr*. 2018;18:175. doi: 10.1186/s12887-018-1149-0
4. Cocomello L, Taylor K, Caputo M, Cornish RP, Lawlor DA. Health and well-being in surviving congenital heart disease patients: an umbrella review with synthesis of best evidence. *Front Cardiovasc Med*. 2022;9:870474. doi: 10.3389/fcvm.2022.870474
5. Fteropoulli T, Stygall J, Cullen S, Deanfield J, Newman SP. Quality of life of adult congenital heart disease patients: a systematic review of the literature. *Cardiol Young*. 2013;23:473–485. doi: 10.1017/S1047951112002351
6. Mellion K, Uzark K, Cassedy A, Drotar D, Wernovsky G, Newburger JW, Mahony L, Mussatto K, Cohen M, Limbers C, et al; Pediatric Cardiac Quality of Life Inventory Testing Study Consortium. Health-related quality of life outcomes in children and adolescents with congenital heart disease. *J Pediatr*. 2014;164:781–788.e1. doi: 10.1016/j.jpeds.2013.11.066
7. Karsdorp PA, Everaerd W, Kindt M, Mulder BJ. Psychological and cognitive functioning in children and adolescents with congenital heart disease: a meta-analysis. *J Pediatr Psychol*. 2007;32:527–541. doi: 10.1093/jpepsy/jsl047
8. Siciliano RE, Prussien KV, Lee CA, Patel NJ, Murphy LK, Compas BE, Jordan LC. Cognitive function in pediatric hypoplastic left heart syndrome: systematic review and meta-analysis. *J Pediatr Psychol*. 2019;44:937–947. doi: 10.1093/jpepsy/jsz021
9. Aleksonis HA, King TZ. Relationships among structural neuroimaging and neurocognitive outcomes in adolescents and young adults with congenital heart disease: a systematic review. *Neuropsychol Rev*. 2022;33:432–458. doi: 10.1007/s11065-022-09547-2
10. Marino BS, Lipkin PH, Newburger JW, Peacock G, Gerdes M, Gaynor JW, Mussatto KA, Uzark K, Goldberg CS, Johnson WH Jr, et al; on behalf of the American Heart Association Congenital Heart Defects Committee, Council on Cardiovascular Disease in the Young, Council on Cardiovascular Nursing, and Stroke Council. Neurodevelopmental outcomes in children with congenital heart disease: evaluation and management: a scientific statement from the American Heart Association. *Circulation*. 2012;126:1143–1172. doi: 10.1161/CIR.0b013e318265ee8a
11. Holcomb RM, Ündar A. Are outcomes in congenital cardiac surgery better than ever? *J Card Surg*. 2022;37:656–663. doi: 10.1111/jocs.16225
12. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, Barengo NC, Beaton AZ, Benjamin EJ, Benziger CP, et al; GBD-NHLBI-JACC Global Burden of Cardiovascular Diseases Writing Group. Global burden of cardiovascular diseases and risk factors, 1990-2019: update from the GBD 2019 Study. *J Am Coll Cardiol*. 2020;76:2982–3021. doi: 10.1016/j.jacc.2020.11.010
13. GBD 2017 Congenital Heart Disease Collaborators. Global, regional, and national burden of congenital heart disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Child Adolesc Health*. 2020;4:185–200. doi: 10.1016/S2352-4642(19)30402-X
14. Warnes CA, Williams RG, Bashore TM, Child JS, Connolly HM, Dearani JA, del Nido P, Fasules JW, Graham TP Jr, Hijazi ZM, et al. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines on the Management of Adults With Congenital Heart Disease). *Circulation*. 2008;118:e714–e833. doi: 10.1161/CIRCULATIONAHA.108.190690
15. Gilboa SM, Devine OJ, Kucik JE, Oster ME, Riehle-Colarusso T, Nembhard WN, Xu P, Correa A, Jenkins K, Marelli AJ. Congenital heart defects in the United States: estimating the magnitude of the affected population in 2010. *Circulation*. 2016;134:101–109. doi: 10.1161/CIRCULATIONAHA.115.019307
16. Hoffman JI, Kaplan S. The incidence of congenital heart disease. *J Am Coll Cardiol*. 2002;39:1890–1900. doi: 10.1016/s0735-1097(02)01886-7
17. Mai CT, Isenburg JL, Canfield MA, Meyer RE, Correa A, Alverson CJ, Lupo PJ, Riehle-Colarusso T, Cho SJ, Aggarwal D, et al; National Birth Defects Prevention Network. National population-based estimates for major birth defects, 2010-2014. *Birth Defects Res*. 2019;111:1420–1435. doi: 10.1002/bdr2.1589
18. Boyd R, McMullen H, Beqaj H, Kalfa D. Environmental exposures and congenital heart disease. *Pediatrics*. 2022;149:e2021052151. doi: 10.1542/peds.2021-052151
19. Auger N, Carrier FM, Arbour L, Ayoub A, Healy-Profitós J, Potter BJ. Association of first trimester anaesthesia with risk of congenital heart defects in offspring. *Int J Epidemiol*. 2022;51:737–746. doi: 10.1093/ije/dyab019
20. Ahmadi A, Gharipour M, Navabi ZS, Heydari H. Risk factors of congenital heart diseases: a hospital-based case-control study in Isfahan, Iran. *ARYA Atheroscler*. 2020;16:1–6. doi: 10.22122/arya.v16i1.1941
21. Lee LJ, Lupo PJ. Maternal smoking during pregnancy and the risk of congenital heart defects in offspring: a systematic review and metaanalysis. *Pediatr Cardiol*. 2013;34:398–407. doi: 10.1007/s00246-012-0470-x
22. Sullivan PM, Dervan LA, Reiger S, Buddhe S, Schwartz SM. Risk of congenital heart defects in the offspring of smoking mothers: a population-based study. *J Pediatr*. 2015;166:978–984.e2. doi: 10.1016/j.jpeds.2014.11.042
23. Liu Y, Zhang H, Li J, Liang C, Zhao Y, Chen F, Wang D, Pei L. Geographical variations in maternal lifestyles during pregnancy associated with congenital heart defects among live births in Shaanxi province, Northwestern China. *Sci Rep*. 2020;10:12958. doi: 10.1038/s41598-020-69788-0
24. Deng C, Pu J, Deng Y, Xie L, Yu L, Liu L, Guo X, Sandin S, Liu H, Dai L. Association between maternal smoke exposure and congenital heart defects from a case-control study in China. *Sci Rep*. 2022;12:14973. doi: 10.1038/s41598-022-18909-y
25. Bolin EH, Gokun Y, Romitti PA, Tinker SC, Summers AD, Roberson PK, Hobbs CA, Malik S, Botto LD, Nembhard WN; National Birth Defects Prevention Study. Maternal smoking and congenital heart defects, National Birth Defects Prevention Study, 1997-2011. *J Pediatr*. 2022;240:79–86.e1. doi: 10.1016/j.jpeds.2021.09.005
26. Mateja WA, Nelson DB, Kroelinger CD, Ruzek S, Segal J. The association between maternal alcohol use and smoking in early pregnancy and congenital cardiac defects. *J Womens Health (Larchmt)*. 2012;21:26–34. doi: 10.1089/jwh.2010.2582
27. Butler M. An exploratory analysis of maternal health variables increasing the severity of congenital heart disease in infants. *J Perinat Neonatal Nurs*. 2022;36:344–352. doi: 10.1097/JPN.0000000000000640
28. Hedermann G, Hedley PL, Thagaard IN, Krebs L, Ekelund CK, Sorensen TIA, Christiansen M. Maternal obesity and metabolic disorders associate with congenital heart defects in the offspring: a systematic review. *PLoS One*. 2021;16:e0252343. doi: 10.1371/journal.pone.0252343
29. Cai GJ, Sun XX, Zhang L, Hong Q. Association between maternal body mass index and congenital heart defects in offspring: a systematic review. *Am J Obstet Gynecol*. 2014;211:91–117. doi: 10.1016/j.ajog.2014.03.028
30. Nie X, Liu X, Wang C, Wu Z, Sun Z, Su J, Yan R, Peng Y, Yang Y, Wang C, et al. Assessment of evidence on reported non-genetic risk factors of congenital heart defects: the updated umbrella review. *BMC Pregnancy Childbirth*. 2022;22:371. doi: 10.1186/s12884-022-04600-7
31. Huida J, Ojala T, Ilvesvuo J, Surcel HM, Priest JR, Helle E. Maternal first trimester metabolic profile in pregnancies with transposition of the great arteries. *Birth Defects Res*. 2022;115:517–524. doi: 10.1002/bdr2.2139
32. Simeone RM, Devine OJ, Marcinkevage JA, Gilboa SM, Razzaghi H, Bardenheier BH, Sharma AJ, Honein MA. Diabetes and congenital heart defects: a systematic review, meta-analysis, and modeling project. *Am J Prev Med*. 2015;48:195–204. doi: 10.1016/j.amepre.2014.09.002
33. Jenkins KJ, Correa A, Feinstein JA, Botto L, Britt AE, Daniels SR, Elixson M, Warnes CA, Webb CL. Noninherited risk factors and congenital cardiovascular defects: current knowledge: a scientific statement from the American Heart Association Council on Cardiovascular Disease in the Young. *Circulation*. 2007;115:2995–3014. doi: 10.1161/CIRCULATIONAHA.106.183216
34. Mires S, Caputo M, Overton T, Skerritt C. Maternal micronutrient deficiency and congenital heart disease risk: a systematic review of observational studies. *Birth Defects Res*. 2022;114:1079–1091. doi: 10.1002/bdr2.2072
35. Wang T, Li Q, Chen L, Ni B, Sheng X, Huang P, Zhang S, Qin J. Maternal viral infection in early pregnancy and risk of congenital heart disease in offspring: a prospective cohort study in central China. *Clin Epidemiol*. 2022;14:71–82. doi: 10.2147/CLEP.S338870
36. Fazekas-Pongor V, Csaky-Szunyogh M, Fekete M, Meszaros A, Cseh K, Penzes M. Congenital heart diseases and parental occupational exposure in a Hungarian case-control study in 1997 to 2002. *Congenit Anom (Kyoto)*. 2021;61:55–62. doi: 10.1111/cga.12401
37. Wilson PD, Loffredo CA, Correa-Villasenor A, Ferencz C. Attributable fraction for cardiac malformations. *Am J Epidemiol*. 1998;148:414–423. doi: 10.1093/oxfordjournals.aje.a009666

38. Hayama-Terada M, Aochi Y, Ikehara S, Kimura T, Yamagishi K, Sato T, Iso H. Paternal occupational exposures and infant congenital heart defects in the Japan Environment and Children's Study. *Environ Health Prev Med*. 2023;28:12. doi: 10.1265/ehpm.22-00202
39. Mahle WT, Martin GR, Beekman RH 3rd, Morrow WR; Section on Cardiology and Cardiac Surgery Executive Committee. Endorsement of Health and Human Services recommendation for pulse oximetry screening for critical congenital heart disease. *Pediatrics*. 2012;129:190–192. doi: 10.1542/peds.2011-3211
40. Glidewell J, Grosse SD, Riehle-Colarusso T, Pinto N, Hudson J, Daskalov R, Gaviglio A, Darby E, Singh S, Sontag M. Actions in support of newborn screening for critical congenital heart disease: United States, 2011-2018. *MMWR Morb Mortal Wkly Rep*. 2019;68:107–111. doi: 10.15585/mmwr.mm6805a3
41. Glidewell J, Olney RS, Hinton C, Pawelski J, Sontag M, Wood T, Kucik JE, Daskalov R, Hudson J; Centers for Disease Control and Prevention (CDC). State legislation, regulations, and hospital guidelines for newborn screening for critical congenital heart defects: United States, 2011-2014. *MMWR Morb Mortal Wkly Rep*. 2015;64:625–630.
42. de-Wahl Granelli A, Wennergren M, Sandberg K, Mellander M, Bejlum C, Inganas L, Eriksson M, Segerdahl N, Agren A, Ekman-Joelsson BM, et al. Impact of pulse oximetry screening on the detection of duct dependent congenital heart disease: a Swedish prospective screening study in 39,821 newborns. *BMJ*. 2009;338:a3037. doi: 10.1136/bmj.a3037
43. Meberg A, Brugmann-Pieper S, Due R Jr, Eskedal L, Fagerli I, Farstad T, Froisland DH, Sannes CH, Johansen OJ, Keljalic J, et al. First day of life pulse oximetry screening to detect congenital heart defects. *J Pediatr*. 2008;152:761–765. doi: 10.1016/j.jpeds.2007.12.043
44. Riede FT, Worner C, Dahnert I, Mockel A, Kostelka M, Schneider P. Effectiveness of neonatal pulse oximetry screening for detection of critical congenital heart disease in daily clinical routine: results from a prospective multicenter study. *Eur J Pediatr*. 2010;169:975–981. doi: 10.1007/s00431-010-1160-4
45. Ailes EC, Gilboa SM, Honein MA, Oster ME. Estimated number of infants detected and missed by critical congenital heart defect screening. *Pediatrics*. 2015;135:1000–1008. doi: 10.1542/peds.2014-3662
46. Plana MN, Zamora J, Suresh G, Fernandez-Pineda L, Thangaratinam S, Ewer AK. Pulse oximetry screening for critical congenital heart defects. *Cochrane Database Syst Rev*. 2018;3:CD011912. doi: 10.1002/14651858.CD011912.pub2
47. Abouk R, Grosse SD, Ailes EC, Oster ME. Association of US state implementation of newborn screening policies for critical congenital heart disease with early infant cardiac deaths. *JAMA*. 2017;318:2111–2118. doi: 10.1001/jama.2017.17627
48. Jawin V, Ang HL, Omar A, Thong MK. Beyond critical congenital heart disease: newborn screening using pulse oximetry for neonatal sepsis and respiratory diseases in a middle-income country. *PLoS One*. 2015;10:e0137580. doi: 10.1371/journal.pone.0137580
49. Liberman RF, Heinke D, Lin AE, Nestoridi E, Jalali M, Markenson GR, Sekhavat S, Yazdy MM. Trends in delayed diagnosis of critical congenital heart defects in an era of enhanced screening, 2004-2018. *J Pediatr*. 2023;257:113366. doi: 10.1016/j.jpeds.2023.02.012
50. Davey B, Sinha R, Lee JH, Gauthier M, Flores G. Social determinants of health and outcomes for children and adults with congenital heart disease: a systematic review. *Pediatr Res*. 2021;89:275–294. doi: 10.1038/s41390-020-01196-6
51. Peyvandi S, Baer RJ, Chambers CD, Norton ME, Rajagopal S, Ryckman KK, Moon-Grady A, Jelliffe-Pawlowski LL, Steurer MA. Environmental and socioeconomic factors influence the live-born incidence of congenital heart disease: a population-based study in California. *J Am Heart Assoc*. 2020;9:e015255. doi: 10.1161/JAHA.119.015255
52. Miao Q, Dunn S, Wen SW, Lougheed J, Reszel J, Lavin Venegas C, Walker M. Neighbourhood maternal socioeconomic status indicators and risk of congenital heart disease. *BMC Pregnancy Childbirth*. 2021;21:72. doi: 10.1186/s12884-020-03512-8
53. Miao Q, Dunn S, Wen SW, Lougheed J, Sharif F, Walker M. Associations of congenital heart disease with deprivation index by rural-urban maternal residence: a population-based retrospective cohort study in Ontario, Canada. *BMC Pediatr*. 2022;22:476. doi: 10.1186/s12887-022-03498-6
54. Hu CY, Huang K, Fang Y, Yang XJ, Ding K, Jiang W, Hua XG, Huang DY, Jiang ZX, Zhang XJ. Maternal air pollution exposure and congenital heart defects in offspring: a systematic review and meta-analysis. *Chemosphere*. 2020;253:126668. doi: 10.1016/j.chemosphere.2020.126668
55. Siffel C, Riehle-Colarusso T, Oster ME, Correa A. Survival of children with hypoplastic left heart syndrome. *Pediatrics*. 2015;136:e864–e870. doi: 10.1542/peds.2014-1427
56. Tran R, Forman R, Mossialos E, Nasir K, Kulkarni A. Social determinants of disparities in mortality outcomes in congenital heart disease: a systematic review and meta-analysis. *Front Cardiovasc Med*. 2022;9:829902. doi: 10.3389/fcvm.2022.829902
57. Anderson BR, Fieldston ES, Newburger JW, Bacha EA, Glied SA. Disparities in outcomes and resource use after hospitalization for cardiac surgery by neighborhood income. *Pediatrics*. 2018;141:e20172432. doi: 10.1542/peds.2017-2432
58. Tillman AR, Colborn KL, Scott KA, Davidson AJ, Khanna A, Kao D, McKenzie L, Ong T, Rausch CM, Duca LM, et al. Associations between socioeconomic context and congenital heart disease related outcomes in adolescents and adults. *Am J Cardiol*. 2021;139:105–115. doi: 10.1016/j.amjcard.2020.10.040
59. Lopez KN, Baker-Smith C, Flores G, Gurvitz M, Karamlou T, Nunez Gallegos F, Pasquali S, Patel A, Peterson JK, Salemi JL, et al; on behalf of the American Heart Association Congenital Cardiac Defects Committee of the Council on Lifelong Congenital Heart Disease and Heart Health in the Young; Council on Epidemiology and Prevention; and Council on Lifestyle and Cardiometabolic Health. Addressing social determinants of health and mitigating health disparities across the lifespan in congenital heart disease: a scientific statement from the American Heart Association [published correction appears in *Circulation*. 2022;11:e20758]. *J Am Heart Assoc*. 2022;11:e025358. doi: 10.1161/JAHA.122.025358
60. Krishnan A, Jacobs MB, Morris SA, Peyvandi S, Bhat AH, Chelliah A, Chiu JS, Cuneo BF, Freire G, Hornberger LK, et al; Fetal Heart Society. Impact of socioeconomic status, race and ethnicity, and geography on prenatal detection of hypoplastic left heart syndrome and transposition of the great arteries. *Circulation*. 2021;143:2049–2060. doi: 10.1161/CIRCULATIONAHA.120.053062
61. Pierpont ME, Brueckner M, Chung WK, Garg V, Lacro RV, McGuire AL, Mital S, Priest JR, Pu WT, Roberts A, et al; on behalf of the American Heart Association Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; and Council on Genomic and Precision Medicine. Genetic basis for congenital heart disease: revisited: a scientific statement from the American Heart Association [published correction appears in *Circulation*. 2018;138:e713]. *Circulation*. 2018;138:e653–e711. doi: 10.1161/CIR.0000000000000606
62. Wang X, Li P, Chen S, Xi L, Guo Y, Guo A, Sun K. Influence of genes and the environment in familial congenital heart defects. *Mol Med Rep*. 2014;9:695–700. doi: 10.3892/mmr.2013.1847
63. Pettit KE, Merchant M, Machin GA, Tacy TA, Norton ME. Congenital heart defects in a large, unselected cohort of monochorionic twins. *J Perinatol*. 2013;33:457–461. doi: 10.1038/jp.2012.145
64. Nora JJ, Dodd PF, McNamara DG, Hattwick MA, Leachman RD, Cooley DA. Risk to offspring of parents with congenital heart defects. *JAMA*. 1969;209:2052–2053.
65. Jin SC, Homsy J, Zaidi S, Lu Q, Morton S, DePalma SR, Zeng X, Qi H, Chang W, Sierant MC, et al. Contribution of rare inherited and de novo variants in 2,871 congenital heart disease probands. *Nat Genet*. 2017;49:1593–1601. doi: 10.1038/ng.3970
66. Hartman RJ, Rasmussen SA, Botto LD, Riehle-Colarusso T, Martin CL, Cragan JD, Shin M, Correa A. The contribution of chromosomal abnormalities to congenital heart defects: a population-based study. *Pediatr Cardiol*. 2011;32:1147–1157. doi: 10.1007/s00246-011-0034-5
67. Korbel JO, Tirosh-Wagner T, Urban AE, Chen XN, Kasowski M, Dai L, Grubert F, Erdman C, Gao MC, Lange K, et al. The genetic architecture of Down syndrome phenotypes revealed by high-resolution analysis of human segmental trisomies. *Proc Natl Acad Sci USA*. 2009;106:12031–12036. doi: 10.1073/pnas.0813248106
68. Soemedi R, Wilson IJ, Bentham J, Darlay R, Topf A, Zelenika D, Cosgrove C, Setchfield K, Thornborough C, Granados-Riveron J, et al. Contribution of global rare copy-number variants to the risk of sporadic congenital heart disease. *Am J Hum Genet*. 2012;91:489–501. doi: 10.1016/j.ajhg.2012.08.003
69. Zaidi S, Brueckner M. Genetics and genomics of congenital heart disease. *Circ Res*. 2017;120:923–940. doi: 10.1161/CIRCRESAHA.116.309140
70. Boskovski MT, Homsy J, Nathan M, Sleeper LA, Morton S, Manheimer KB, Tai A, Gorham J, Lewis M, Swartz M, et al. De novo damaging variants, clinical phenotypes, and post-operative outcomes in congenital heart disease. *Circ Genom Precis Med*. 2020;13:e002836. doi: 10.1161/CIRCGEN.119.002836
71. Xie H, Zhang E, Hong N, Fu Q, Li F, Chen S, Yu Y, Sun K. Identification of TBX2 and TBX3 variants in patients with conotruncal heart defects by target sequencing. *Hum Genomics*. 2018;12:44. doi: 10.1186/s40246-018-0176-0

72. Garg V, Kathiriya IS, Barnes R, Schluterman MK, King IN, Butler CA, Rothrock CR, Eapen RS, Hirayama-Yamada K, Joo K, et al. GATA4 mutations cause human congenital heart defects and reveal an interaction with TBX5. *Nature*. 2003;424:443–447. doi: 10.1038/nature01827
73. Preuss C, Capredon M, Wunnemann F, Chetaille P, Prince A, Godard B, Leclerc S, Sobreira N, Ling H, Awadalla P, et al; MIBAVA Leducq Consortium. Family based whole exome sequencing reveals the multifaceted role of Notch signaling in congenital heart disease. *PLoS Genet*. 2016;12:e1006335. doi: 10.1371/journal.pgen.1006335
74. Sewda A, Agopian AJ, Goldmuntz E, Hakonarson H, Morrow BE, Taylor D, Mitchell LE; Pediatric Cardiac Genomics Consortium. Gene-based genome-wide association studies and meta-analyses of conotruncal heart defects. *PLoS One*. 2019;14:e0219926. doi: 10.1371/journal.pone.0219926
75. Page DJ, Miossec MJ, Williams SG, Monaghan RM, Fotiou E, Cordell HJ, Sutcliffe L, Topf A, Bourgey M, Bourque G, et al. Whole exome sequencing reveals the major genetic contributors to nonsyndromic tetralogy of Fallot. *Circ Res*. 2019;124:553–563. doi: 10.1161/CIRCRESAHA.118.313250
76. Agopian AJ, Goldmuntz E, Hakonarson H, Sewda A, Taylor D, Mitchell LE; Pediatric Cardiac Genomics Consortium. Genome-wide association studies and meta-analyses for congenital heart defects. *Circ Cardiovasc Genet*. 2017;10:e001449. doi: 10.1161/CIRCGENETICS.116.001449
77. Richter F, Morton SU, Kim SW, Kitaygorodsky A, Wasson LK, Chen KM, Zhou J, Qi H, Patel N, DePalma SR, et al. Genomic analyses implicate noncoding de novo variants in congenital heart disease. *Nat Genet*. 2020;52:769–777. doi: 10.1038/s41588-020-0652-z
78. Audain E, Wilsdon A, Breckpot J, Izarzugaza JMG, Fitzgerald TW, Kahlert AK, Sifrim A, Wunnemann F, Perez-Riverol Y, Abdul-Khaliq H, et al. Integrative analysis of genomic variants reveals new associations of candidate haploinsufficient genes with congenital heart disease. *PLoS Genet*. 2021;17:e1009679. doi: 10.1371/journal.pgen.1009679
79. Lahm H, Jia M, Dressen M, Wirth F, Puluca N, Gilsbach R, Keavney BD, Cleuziou J, Beck N, Bondareva O, et al. Congenital heart disease risk loci identified by genome-wide association study in European patients. *J Clin Invest*. 2021;131:141837. doi: 10.1172/JCI141837
80. Skoric-Milosavljevic D, Tadros R, Bosada FM, Tessadori F, van Weerd JH, Woudstra OI, Tjong FVY, Lahrouchi N, Bajolle F, Cordell HJ, et al. Common genetic variants contribute to risk of transposition of the great arteries. *Circ Res*. 2022;130:166–180. doi: 10.1161/CIRCRESAHA.120.317107
81. Gehlen J, Stundl A, Debiec R, Fontana F, Krane M, Sharipova D, Nelson CP, Al-Kassou B, Giel AS, Sinning JM, et al. Elucidation of the genetic causes of bicuspid aortic valve disease. *Cardiovasc Res*. 2023;119:857–866. doi: 10.1093/cvr/cvac099
82. Zhu N, Welch CL, Wang J, Allen PM, Gonzaga-Jauregui C, Ma L, King AK, Krishnan U, Rosenzweig EB, Ivy DD, et al. Rare variants in SOX17 are associated with pulmonary arterial hypertension with congenital heart disease. *Genome Med*. 2018;10:56. doi: 10.1186/s13073-018-0566-x
83. Morton SU, Shimamura A, Newburger PE, Opotowsky AR, Quiat D, Pereira AC, Jin SC, Gurvitz M, Brueckner M, Chung WK, et al. Association of damaging variants in genes with increased cancer risk among patients with congenital heart disease. *JAMA Cardiol*. 2021;6:457–462. doi: 10.1001/jamacardio.2020.4947
84. Nees SN, Chung WK. The genetics of isolated congenital heart disease. *Am J Med Genet C Semin Med Genet*. 2020;184:97–106. doi: 10.1002/ajmg.c.31763
85. Blue GM, Kirk EP, Giannoulatou E, Dunwoodie SL, Ho JW, Hilton DC, White SM, Sholler GF, Harvey RP, Winlaw DS. Targeted next-generation sequencing identifies pathogenic variants in familial congenital heart disease. *J Am Coll Cardiol*. 2014;64:2498–2506. doi: 10.1016/j.jacc.2014.09.048
86. Jia Y, Louw JJ, Breckpot J, Callewaert B, Barrea C, Sznajer Y, Gewillig M, Souche E, Dehaspe L, Vermeesch JR, et al. The diagnostic value of next generation sequencing in familial nonsyndromic congenital heart defects. *Am J Med Genet A*. 2015;167:1822–1829. doi: 10.1002/ajmg.a.37108
87. Szot JO, Cuny H, Blue GM, Humphreys DT, Ip E, Harrison K, Sholler GF, Giannoulatou E, Leo P, Duncan EL, et al. A screening approach to identify clinically actionable variants causing congenital heart disease in exome data. *Circ Genom Precis Med*. 2018;11:e001978. doi: 10.1161/CIRCGEN.117.001978
88. Hoang TT, Goldmuntz E, Roberts AE, Chung WK, Kline JK, Deanfield JE, Giardini A, Aleman A, Gelb BD, Mac Neal M, et al. The Congenital Heart Disease Genetic Network Study: cohort description. *PLoS One*. 2018;13:e0191319. doi: 10.1371/journal.pone.0191319
89. Centers for Disease Control and Prevention and National Center for Health Statistics. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death micro-data files. Accessed April 8, 2023. https://cdc.gov/nchs/nvss/mortality_public_use_data.htm
90. Centers for Disease Control and Prevention and National Center for Health Statistics. Multiple cause of death, CDC WONDER online database. Accessed April 1, 2023. https://wonder.cdc.gov/mcd-icd10.html.
91. Cnota JF, Gupta R, Michelfelder EC, Ittenbach RF. Congenital heart disease infant death rates decrease as gestational age advances from 34 to 40 weeks. *J Pediatr*. 2011;159:761–765. doi: 10.1016/j.jpeds.2011.04.020
92. Swenson AW, Dechert RE, Schumacher RE, Attar MA. The effect of late preterm birth on mortality of infants with major congenital heart defects. *J Perinatol*. 2012;32:51–54. doi: 10.1038/jp.2011.50
93. Best KE, Tennant PWG, Rankin J. Survival, by birth weight and gestational age, in individuals with congenital heart disease: a population-based study. *J Am Heart Assoc*. 2017;6:e005213. doi: 10.1161/JAHA.116.005213
94. Shahian DM, Jacobs JP, Edwards FH, Brennan JM, Dokholyan RS, Prager RL, Wright CD, Peterson ED, McDonald DE, Grover FL. The Society of Thoracic Surgeons national database. *Heart*. 2013;99:1494–1501. doi: 10.1136/heartjnl-2012-303456
95. Society of Thoracic Surgeons. The Society of Thoracic Surgeons (STS) national database: congenital heart surgery database participants, spring 2017 harvest. Accessed April 1, 2023. https://sts.org/sites/default/files/documents/CHSD_ExecutiveSummary_Neonates_Spring2017.pdf
96. Spector LG, Menk JS, Knight JH, McCracken C, Thomas AS, Vinocur JM, Oster ME, St Louis JD, Moller JH, Kochilas L. Trends in long-term mortality after congenital heart surgery. *J Am Coll Cardiol*. 2018;71:2434–2446. doi: 10.1016/j.jacc.2018.03.491
97. Sanchez-Barriga JJ. Mortality trends from congenital malformations of the heart and the great vessels in children and adults in the seven socioeconomic regions of Mexico, 2000-2015. *Congenit Heart Dis*. 2018;13:690–699. doi: 10.1111/chd.12631
98. Metcalf MK, Rychik J. Outcomes in hypoplastic left heart syndrome. *Pediatr Clin North Am*. 2020;67:945–962. doi: 10.1016/j.pcl.2020.06.008
99. Marathe SP, Cao JY, Celermajer D, Ayer J, Sholler GF, d'Udekem Y, Winlaw DS. Outcomes of the Fontan operation for patients with heterotaxy: a meta-analysis of 848 patients. *Ann Thorac Surg*. 2020;110:307–315. doi: 10.1016/j.athoracsur.2019.11.027
100. Morris SA, Ethen MK, Penny DJ, Canfield MA, Minard CG, Fixler DE, Nembhard WN. Prenatal diagnosis, birth location, surgical center, and neonatal mortality in infants with hypoplastic left heart syndrome. *Circulation*. 2014;129:285–292. doi: 10.1161/CIRCULATIONAHA.113.003711
101. Anderson BR, Dragan K, Crook S, Woo JL, Cook S, Hannan EL, Newburger JW, Jacobs M, Bacha EA, Vincent R, et al; New York State Congenital Heart Surgery Collaborative for Longitudinal Outcomes and Utilization of Resources (CHS-COLOUR). Improving longitudinal outcomes, efficiency, and equity in the care of patients with congenital heart disease. *J Am Coll Cardiol*. 2021;78:1703–1713. doi: 10.1016/j.jacc.2021.08.040
102. Kempny A, Diller GP, Dimopoulos K, Alonso-Gonzalez R, Uebing A, Li W, Babu-Narayan S, Swan L, Wort SJ, Gatzoulis MA. Determinants of outpatient clinic attendance amongst adults with congenital heart disease and outcome. *Int J Cardiol*. 2016;203:245–250. doi: 10.1016/j.ijcard.2015.10.081
103. Diller GP, Arvanitaki A, Opotowsky AR, Jenkins K, Moons P, Kempny A, Tandon A, Redington A, Khairy P, Mital S, et al. Lifespan perspective on congenital heart disease research: JACC state-of-the-art review. *J Am Coll Cardiol*. 2021;77:2219–2235. doi: 10.1016/j.jacc.2021.03.012
104. Backes ER, Afonso NS, Guffey D, Tweddell JS, Tabbutt S, Rudd NA, O'Harrow G, Molossi S, Hoffman GM, Hill G, et al. Cumulative comorbid conditions influence mortality risk after staged palliation for hypoplastic left heart syndrome and variants. *J Thorac Cardiovasc Surg*. 2023;165:287–298.e4. doi: 10.1016/j.jtcvs.2022.01.056
105. Kauw D, Schoormans D, Sieswerda GT, Van Melle JP, Vliegen HW, Van Dijk APJ, Hulsbergen-Zwarts MS, Post MC, Ansink TJ, Mulder BJM, et al. Type D personality associated with increased risk for mortality in adults with congenital heart disease. *J Cardiovasc Nurs*. 2022;37:192–196. doi: 10.1097/JCN.0000000000000747
106. Meakins LT, Knox P, Legge L, Penner M, Wiebe P, Mackie AS. Interstage mortality among infants with hypoplastic left heart syndrome: outcomes of a multicenter home monitoring program. *Prog Pediatr Cardiol*. 2023;68:101610. doi: 10.1016/j.ppedcard.2022.101610
107. Rudd NA, Ghanayem NS, Hill GD, Lambert LM, Mussatto KA, Nieves JA, Robinson S, Shirali G, Steltzer MM, Uzark K, et al; on behalf of the American Heart Association Council on Cardiovascular and Stroke Nursing; Council on Lifelong Congenital Heart Disease and Heart Health in the Young;

Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Clinical Cardiology; and Council on Lifestyle and Cardiometabolic Health. Interstage home monitoring for infants with single ventricle heart disease: education and management: a scientific statement from the American Heart Association. *J Am Heart Assoc*. 2020;9:e014548. doi: 10.1161/JAHA.119.014548

108. Gardner MM, Mercer-Rosa L, Faerber J, DiLorenzo MP, Bates KE, Stagg A, Natarajan SS, Szwast A, Fuller S, Mascio CE, et al. Association of a home monitoring program with interstage and stage 2 outcomes. *J Am Heart Assoc*. 2019;8:e010783. doi: 10.1161/JAHA.118.010783
109. Videbaek J, Laursen HB, Olsen M, Hofsten DE, Johnsen SP. Long-term nationwide follow-up study of simple congenital heart disease diagnosed in otherwise healthy children. *Circulation*. 2016;133:474–483. doi: 10.1161/CIRCULATIONAHA.115.017226
110. Cahill TJ, Jewell PD, Denne L, Franklin RC, Frigiola A, Orchard E, Prendergast BD. Contemporary epidemiology of infective endocarditis in patients with congenital heart disease: a UK prospective study. *Am Heart J*. 2019;215:70–77. doi: 10.1016/j.ahj.2019.05.014
111. Van De Bruaene A, Hickey EJ, Kovacs AH, Crean AM, Wald RM, Silversides CK, Redington AN, Ross HJ, Alba AC, Billia F, et al. Phenotype, management and predictors of outcome in a large cohort of adult congenital heart disease patients with heart failure. *Int J Cardiol*. 2018;252:80–87. doi: 10.1016/j.ijcard.2017.10.086
112. Rehan R, Kotchetkova I, Cordina R, Celermajer D. Adult congenital heart disease survivors at age 50 years: medical and psychosocial status. *Heart Lung Circ*. 2021;30:261–266. doi: 10.1016/j.hlc.2020.05.114
113. Mandalenakis Z, Rosengren A, Lappas G, Eriksson P, Gilljam T, Hansson PO, Skoglund K, Fedchenko M, Dellborg M. Atrial fibrillation burden in young patients with congenital heart disease. *Circulation*. 2018;137:928–937. doi: 10.1161/CIRCULATIONAHA.117.029590
114. Capestro A, Soura E, Compagnucci P, Casella M, Marzullo R, Dello Russo A. Atrial flutters in adults with congenital heart disease. *Card Electrophysiol Clin*. 2022;14:501–515. doi: 10.1016/j.ccep.2022.05.008
115. El Sayegh S, Ephrem G, Wish JB, Moe S, Lim K. Kidney disease and congenital heart disease: partnership for life. *Front Physiol*. 2022;13:970389. doi: 10.3389/fphys.2022.970389
116. Gillesen M, Fedchenko M, Giang KW, Dimopoulos K, Eriksson P, Dellborg M, Mandalenakis Z. Chronic kidney disease in patients with congenital heart disease: a nationwide, register-based cohort study. *Eur Heart J Open*. 2022;2:oeac055. doi: 10.1093/ehjopen/oeac055
117. Ntiloudi D, Rammos S, Giannakoulas G. Growth failure in patients with hypoplastic left heart syndrome: an ongoing challenge. *Int J Cardiol*. 2022;364:50–51. doi: 10.1016/j.ijcard.2022.06.011
118. Irving SY, Ravishankar C, Miller M, Chittams J, Stallings V, Medoff-Cooper B. Anthropometry based growth and body composition in infants with complex congenital heart disease. *Clin Nurs Res*. 2022;31:931–940. doi: 10.1177/10547738221075720
119. Bolduc M-E, Dionne E, Gagnon I, Rennick JE, Majnemer A, Brossard-Racine M. Motor impairment in children with congenital heart defects: a systematic review. *Pediatrics*. 2020;146:1–16. doi: 10.1542/peds.2020-0083
120. Werninger I, Ehrler M, Wehrle FM, Landolt MA, Polentarutti S, Valsangiacomo Buechel ER, Latal B. Social and behavioral difficulties in 10-year-old children with congenital heart disease: prevalence and risk factors. *Front Pediatr*. 2020;8:604918. doi: 10.3389/fped.2020.604918
121. Gonzalez VJ, Kimbro RT, Cutitta KE, Shabosky JC, Bilal MF, Penny DJ, Lopez KN. Mental health disorders in children with congenital heart disease. *Pediatrics*. 2021;147:e20201693. doi: 10.1542/peds.2020-1693
122. Nematollahi M, Bagherian B, Sharifi Z, Keshavarz F, Mehdipour-Rabori R. Self-care status in children with congenital heart disease: a mixed-method study. *J Child Adolesc Psychiatr Nurs*. 2020;33:77–84. doi: 10.1111/jcap.12265
123. Sprong MCA, van Brussel M, de Vries LS, van der Net J, Nijman J, Breur JMPJ, Slieker MG. Longitudinal motor-developmental outcomes in infants with a critical congenital heart defect. *Children*. 2022;9:570. doi: 10.3390/children9040570
124. Perrotta ML, Saha P, Zawadzki R, Beidelman M, Ingelsson E, Lui GK, Priest JR. Adults With mild-to-moderate congenital heart disease demonstrate measurable neurocognitive deficits. *J Am Heart Assoc*. 2020;9:e015379. doi: 10.1161/JAHA.119.015379
125. Atallah J, Garcia Guerra G, Joffe AR, Bond GY, Islam S, Ricci MF, AlAklabi M, Rebeyka IM, Robertson CMT; Western Canadian Complex Pediatric Therapies Follow-up Program. Survival, neurocognitive, and functional outcomes after completion of staged surgical palliation in a cohort of patients with hypoplastic left heart syndrome. *J Am Heart Assoc*. 2020;9:e013632. doi: 10.1161/JAHA.119.013632
126. Haiduc AA, Ogunjimi M, Shammus R, Mahmood S, Kutty R, Lotto A, Guerrero R, Harky A, Dhannapuneni R. COVID-19 and congenital heart disease: an insight of pathophysiology and associated risks. *Cardiol Young*. 2021;31:233–240. doi: 10.1017/S1047951120003741
127. Asbeutah AAA, Jefferies JL. Meta-analysis of the incidence of liver cirrhosis among patients with a Fontan circulation. *Am J Cardiol*. 2022;177:166–167. doi: 10.1016/j.amjcard.2022.05.009
128. Lebherz C, Frick M, Panse J, Wienstroer P, Brehmer K, Kerst G, Marx N, Mathiak K, Hövels-Gürich H. Anxiety and depression in adults with congenital heart disease. *Front Pediatr*. 2022;10:906385. doi: 10.3389/fped.2022.906385
129. Ahsan AK, Sangi R, Ahmed S, Sohail A, Rehman MU, Raza A, Tebha SS, Qamar MA, Ashraf MM, Ali H. Predictors of short versus prolonged PCICU stay after primary repair of tetralogy of Fallot at a tertiary care unit, Karachi: a single-center study. *Progress in Pediatric Cardiology*. 2022;66:101541. doi: 10.1016/j.ppedcard.2022.101541
130. Marino BS, Bird GL, Wernovsky G. Diagnosis and management of the newborn with suspected congenital heart disease. *Clin Perinatol*. 2001;28:91–136. doi: 10.1016/s0095-5108(05)70071-3
131. Dorfman AT, Marino BS, Wernovsky G, Tabbutt S, Ravishankar C, Godinez RI, Priestley M, Dodds KM, Rychik J, Gruber PJ, et al. Critical heart disease in the neonate: presentation and outcome at a tertiary care center. *Pediatr Crit Care Med*. 2008;9:193–202. doi: 10.1097/PCC.0b013e318166eda5
132. Karamlou T, Hawke JL, Zafar F, Kafle M, Tweddell JS, Najm HK, Frebis JR, Bryant RG 3rd. Widening our focus: characterizing socioeconomic and racial disparities in congenital heart disease. *Ann Thorac Surg*. 2022;113:157–165. doi: 10.1016/j.athoracsur.2021.04.008
133. Chan J, Collins RT 2nd, Hall M, John A. Resource utilization among adult congenital heart failure admissions in pediatric hospitals. *Am J Cardiol*. 2019;123:839–846. doi: 10.1016/j.amjcard.2018.11.033
134. Agarwal A, Dudley CW, Nah G, Hayward R, Tseng ZH. Clinical outcomes during admissions for heart failure among adults with congenital heart disease. *J Am Heart Assoc*. 2019;8:e012595. doi: 10.1161/JAHA.119.012595
135. Agarwal A, Vittinghoff E, Myers JJ, Dudley RA, Khan A, John A, Marcus GM. Ambulatory health care service use and costs among commercially insured US adults with congenital heart disease. *JAMA Network Open*. 2020;3:e2018752. doi: 10.1001/jamanetworkopen.2020.18752
136. Arth A, Tinker S, Simeone R, Ailes E, Cragan J, Grosse S. Inpatient hospitalization costs associated with birth defects among persons of all ages: United States, 2013. *MMWR Morb Mort Wkly Rep*. 2017;66:41–46. doi: 10.15585/mmwr.mm6602a1
137. Faraoni D, Nasr VG, DiNardo JA. Overall hospital cost estimates in children with congenital heart disease: analysis of the 2012 Kid's Inpatient Database. *Pediatr Cardiol*. 2016;37:37–43. doi: 10.1007/s00246-015-1235-0
138. Mackie AS, Tran DT, Marelli AJ, Kaul P. Cost of congenital heart disease hospitalizations in Canada: a population-based study. *Can J Cardiol*. 2017;33:792–798. doi: 10.1016/j.cjca.2017.01.024
139. Essaid L, Strassle PD, Jernigan EG, Nelson JS. Regional differences in cost and length of stay in neonates with hypoplastic left heart syndrome. *Pediatr Cardiol*. 2018;39:1229–1235. doi: 10.1007/s00246-018-1887-7
140. Strange GA, Veerappan S, Alphonso N, Refeld S, Simon S, Justo R. Prevalence and cost of managing paediatric cardiac disease in Queensland. *Heart Lung Circ*. 2021;30:254–260. doi: 10.1016/j.hlc.2020.06.002
141. McHugh KE, Mahle WT, Hall MA, Scheurer MA, Moga MA, Triedman J, Nicolson SC, Amula V, Cooper DS, Schamberger M, et al; Pediatric Heart Network Investigators. Hospital costs related to early extubation after infant cardiac surgery. *Ann Thorac Surg*. 2019;107:1421–1426. doi: 10.1016/j.athoracsur.2018.10.019
142. Ludomirsky AB, Bucholz EM, Newburger JW. Association of financial hardship because of medical bills with adverse outcomes among families of children with congenital heart disease. *JAMA Cardiol*. 2020;6:713. doi: 10.1001/jamacardio.2020.6449
143. Johnson JT, Scholtens DM, Kuang A, Feng XY, Eltayeb OM, Post LA, Marino BS. Does value vary by center surgical volume for neonates with truncus arteriosus? A multicenter study. *Ann Thorac Surg*. 2021;112:170–177. doi: 10.1016/j.athoracsur.2020.05.178
144. Liu Y, Chen S, Zuhlke L, Black GC, Choy MK, Li N, Keavney BD. Global birth prevalence of congenital heart defects 1970-2017: updated systematic review and meta-analysis of 260 studies. *Int J Epidemiol*. 2019;48:455–463. doi: 10.1093/ije/dyz009
145. Global Burden of Disease Study and Institute for Health Metrics and Evaluation. University of Washington. Accessed August 2, 2023. http://ghdx.healthdata.org/
146. Zhao L, Chen L, Yang T, Wang T, Zhang S, Chen L, Ye Z, Luo L, Qin J. Birth prevalence of congenital heart disease in China, 1980-2019: a systematic

review and meta-analysis of 617 studies. *Eur J Epidemiol*. 2020;35:631–642. doi: 10.1007/s10654-020-00653-0
147. Yan H, Zhai B, Feng R, Wang P, Zhang Y, Wang Y, Hou Y, Zhou Y. Prevalence of congenital heart disease in Chinese children with different birth weights and its relationship to the neonatal birth weight. *Front Pediatr*. 2022;10:828300. doi: 10.3389/fped.2022.828300
148. Pan F, Li J, Lou H, Li J, Jin Y, Wu T, Pan L, An J, Xu J, Cheng W, et al. Geographical and socioeconomic factors influence the birth prevalence of congenital heart disease: a population-based cross-sectional study in eastern China. *Curr Probl Cardiol*. 2022;47:101341. doi: 10.1016/j.cpcardiol.2022.101341
149. Cao Y, Huang R, Kong R, Li H, Zhang H, Li Y, Liang L, Xiong D, Han S, Zhou L, et al. Prevalence and risk factors for congenital heart defects among children in the multi-ethnic Yunnan region of China. *Transl Pediatr*. 2022;11:813–824. doi: 10.21037/tp-21-371
150. Agarwal A, Al Amer SR, Kalis NN. Epidemiology of congenital heart disease in the Kingdom of Bahrain. *Bahrain Med Bull*. 2020;42:192–195.
151. El-Chouli M, Mohr GH, Bang CN, Malmborg M, Ahlehoff O, Torp-Pedersen C, Gerds TA, Idorn L, Raunsø J, Gislason G. Time trends in simple congenital heart disease over 39 years: a Danish nationwide study. *J Am Heart Assoc*. 2021;10:e020375. doi: 10.1161/JAHA.120.020375
152. Bah MNM, Sapian MH, Alias EY. Birth prevalence and late diagnosis of critical congenital heart disease: a population-based study from a middle-income country. *Ann Pediatr Cardiol*. 2020;13:320–326. doi: 10.4103/apc.APC_35_20
153. Groisman B, Barbero P, Liascovich R, Brun P, Bidondo MP. Detection of critical congenital heart disease among newborns in Argentina through the National Surveillance System of Congenital Heart Disease (RENAC). *Arch Argent Pediatr*. 2022;120:6–13. doi: 10.5546/aap.2022.eng.6
154. Zikarg YT, Yirdaw CT, Aragie TG. Prevalence of congenital septal defects among congenital heart defect patients in East Africa: a systematic review and meta-analysis. *PLoS One*. 2021;16:e0250006. doi: 10.1371/journal.pone.0250006
155. Su Z, Zou Z, Hay SI, Liu Y, Li S, Chen H, Naghavi M, Zimmerman MS, Martin GR, Wilner LB, et al. Global, regional, and national time trends in mortality for congenital heart disease, 1990–2019: an age-period-cohort analysis for the Global Burden of Disease 2019 study. *eClinicalMedicine*. 2022;43:101249. doi: 10.1016/j.eclinm.2021.101249
156. Gordon JB, Daniels LB, Kahn AM, Jimenez-Fernandez S, Vejar M, Numano F, Burns JC. The spectrum of cardiovascular lesions requiring intervention in adults after Kawasaki disease. *JACC Cardiovasc Interv*. 2016;9:687–696. doi: 10.1016/j.jcin.2015.12.011
157. Xie X, Shi X, Liu M. The roles of genetic factors in kawasaki disease: a systematic review and meta-analysis of genetic association studies. *Pediatr Cardiol*. 2018;39:207–225. doi: 10.1007/s00246-017-1760-0
158. Nakamura Y. Kawasaki disease: epidemiology and the lessons from it. *Int J Rheum Dis*. 2018;21:16–19. doi: 10.1111/1756-185X.13211
159. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, Baker AL, Jackson MA, Takahashi M, Shah PB, et al; on behalf of the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Surgery and Anesthesia; and Council on Epidemiology and Prevention. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association [published correction appears in *Circulation*. 2019;140:e181–e184]. *Circulation*. 2017;135:e927–e999. doi: 10.1161/CIR.0000000000000484
160. Ghimire LV, Chou FS, Mahotra NB, Sharma SP. An update on the epidemiology, length of stay, and cost of Kawasaki disease hospitalisation in the United States. *Cardiol Young*. 2019;29:828–832. doi: 10.1017/S1047951119000982
161. Holman RC, Belay ED, Christensen KY, Folkema AM, Steiner CA, Schonberger LB. Hospitalizations for Kawasaki syndrome among children in the United States, 1997-2007. *Pediatr Infect Dis J*. 2010;29:483–488. doi: 10.1097/INF.0b013e3181cf8705
162. Holman RC, Christensen KY, Belay ED, Steiner CA, Effler PV, Miyamura J, Forbes S, Schonberger LB, Melish M. Racial/ethnic differences in the incidence of Kawasaki syndrome among children in Hawaii. *Hawaii Med J*. 2010;69:194–197.
163. Lim JH, Kim YK, Min SH, Kim SW, Lee YH, Lee JM. Seasonal trends of viral prevalence and incidence of Kawasaki disease: a Korea public health data analysis. *J Clin Med*. 2021;10:3301. doi: 10.3390/jcm10153301
164. Shulman S, Geevarghese B, Kim K-Y, Rowley A. The impact of social distancing for COVID-19 upon diagnosis of Kawasaki disease. *J Pediatric Infect Dis Soc*. 2021;10:742–744. doi: 10.1093/jpids/piab013
165. Kang JM, Kim YE, Huh K, Hong J, Kim DW, Kim MY, Jung SY, Kim JH, Jung J, Ahn JG. Reduction in Kawasaki disease after nonpharmaceutical interventions in the COVID-19 era: a nationwide observational study in Korea. *Circulation*. 2021;143:2508–2510. doi: 10.1161/CIRCULATIONAHA.121.054785
166. Maddox RA, Holman RC, Uehara R, Callinan LS, Guest JL, Schonberger LB, Nakamura Y, Yashiro M, Belay ED. Recurrent Kawasaki disease: USA and Japan. *Pediatr Int*. 2015;57:1116–1120. doi: 10.1111/ped.12733
167. Sudo D, Nakamura Y. Nationwide surveys show that the incidence of recurrent Kawasaki disease in Japan has hardly changed over the last 30 years. *Acta Paediatr*. 2017;106:796–800. doi: 10.1111/apa.13773
168. Manlhiot C, O'Shea S, Bernknopf B, LaBelle M, Chahal N, Dillenburg RF, Lai LS, Bock D, Lew B, Masood S, et al. Epidemiology of Kawasaki disease in Canada 2004 to 2014: comparison of surveillance using administrative data vs periodic medical record review. *Can J Cardiol*. 2018;34:303–309. doi: 10.1016/j.cjca.2017.12.009
169. Lee YC, Kuo HC, Chang JS, Chang LY, Huang LM, Chen MR, Liang CD, Chi H, Huang FY, Lee ML, et al. Two new susceptibility loci for Kawasaki disease identified through genome-wide association analysis. *Nat Genet*. 2012;44:522–525. doi: 10.1038/ng.2227
170. Burgner D, Davila S, Breunis WB, Ng SB, Li Y, Bonnard C, Ling L, Wright VJ, Thalamuthu A, Odam M, et al; International Kawasaki Disease Genetics Consortium. A genome-wide association study identifies novel and functionally related susceptibility loci for Kawasaki disease. *PLoS Genet*. 2009;5:e1000319. doi: 10.1371/journal.pgen.1000319
171. Khor CC, Davila S, Breunis WB, Lee YC, Shimizu C, Wright VJ, Yeung RS, Tan DE, Sim KS, Wang JJ, et al; Hong Kong–Shanghai Kawasaki Disease Genetics Consortium. Genome-wide association study identifies *FCGR2A* as a susceptibility locus for Kawasaki disease. *Nat Genet*. 2011;43:1241–1246. doi: 10.1038/ng.981
172. Onouchi Y, Ozaki K, Burns JC, Shimizu C, Terai M, Hamada H, Honda T, Suzuki H, Suenaga T, Takeuchi T, et al; Japan Kawasaki Disease Genome Consortium. A genome-wide association study identifies three new risk loci for Kawasaki disease. *Nat Genet*. 2012;44:517–521. doi: 10.1038/ng.2220
173. Johnson TA, Mashimo Y, Wu JY, Yoon D, Hata A, Kubo M, Takahashi A, Tsunoda T, Ozaki K, Tanaka T, et al; Korean Kawasaki Disease Genetics Consortium, Taiwan Kawasaki Disease Genetics Consortium, Taiwan Pediatric ID Alliance, Japan Kawasaki Disease Genome Consortium. Association of an *IGHV3-66* gene variant with Kawasaki disease. *J Hum Genet*. 2021;66:475–489. doi: 10.1038/s10038-020-00864-z
174. Hoggart C, Shimizu C, Galassini R, Wright VJ, Shailes H, Bellos E, Herberg JA, Pollard AJ, O'Connor D, Choi SW, et al; International Kawasaki Disease Genetics Consortium. Identification of novel locus associated with coronary artery aneurysms and validation of loci for susceptibility to Kawasaki disease. *Eur J Hum Genet*. 2021;29:1734–1744. doi: 10.1038/s41431-021-00838-5
175. Onouchi Y. The genetics of Kawasaki disease. *Int J Rheum Dis*. 2018;21:26–30. doi: 10.1111/1756-185X.13218
176. Chang CL, Lin MC, Lin CH, Ko TM. Maternal and perinatal factors associated with Kawasaki disease among offspring in Taiwan. *JAMA Netw Open*. 2021;4:e213233. doi: 10.1001/jamanetworkopen.2021.3233
177. Kuo NC, Lin CH, Lin MC. Prenatal and early life exposure to air pollution and the incidence of Kawasaki disease. *Sci Rep*. 2022;12:3415. doi: 10.1038/s41598-022-07081-y
178. Huang YH, Hsin YC, Wang LJ, Feng WL, Guo MMH, Chang LS, Tu YK, Kuo HC. Treatment of Kawasaki disease: a network meta-analysis of four dosage regimens of aspirin combined with recommended intravenous immunoglobulin. *Front Pharmacol*. 2021;12:725126. doi: 10.3389/fphar.2021.725126
179. Wardle AJ, Connolly GM, Seager MJ, Tulloh RM. Corticosteroids for the treatment of Kawasaki disease in children. *Cochrane Database Syst Rev*. 2017;1:CD011188. doi: 10.1002/14651858.CD011188.pub2
180. Burns JC, Roberts SC, Tremoulet AH, He F, Printz BF, Ashouri N, Jain SS, Michalik DE, Sharma K, Truong DT, et al; KIDCARE Multicenter Study Group. Infliximab versus second intravenous immunoglobulin for treatment of resistant Kawasaki disease in the USA (KIDCARE): a randomised, multicentre comparative effectiveness trial. *Lancet Child Adolesc Health*. 2021;5:852–861. doi: 10.1016/S2352-4642(21)00270-4
181. Halyabar O, Friedman KG, Sundel RP, Baker AL, Chang MH, Gould PW, Newburger JW, Son MBF. Cyclophosphamide use in treatment of refractory Kawasaki disease with coronary artery aneurysms. *Pediatr Rheumatol Online J*. 2021;19:31. doi: 10.1186/s12969-021-00526-0
182. Suda K, Iemura M, Nishiono H, Teramachi Y, Koteda Y, Kishimoto S, Kudo Y, Itoh S, Ishii H, Ueno T, et al. Long-term prognosis of patients

with Kawasaki disease complicated by giant coronary aneurysms: a single-institution experience. *Circulation*. 2011;123:1836–1842. doi: 10.1161/CIRCULATIONAHA.110.978213
183. Dionne A, Bakloul M, Manlhiot C, McCrindle BW, Hosking M, Houde C, Pepelassis D, Dahdah N. Coronary artery bypass grafting and percutaneous coronary intervention after Kawasaki disease: the pediatric Canadian series. *Pediatr Cardiol*. 2017;38:36–43. doi: 10.1007/s00246-016-1480-x
184. Taddio A, Rossi ED, Monasta L, Pastore S, Tommasini A, Lepore L, Bronzetti G, Marrani E, Mottolese BD, Simonini G, et al. Describing Kawasaki shock syndrome: results from a retrospective study and literature review. *Clin Rheumatol*. 2017;36:223–228. doi: 10.1007/s10067-016-3316-8
185. Ogata S, Tremoulet AH, Sato Y, Ueda K, Shimizu C, Sun X, Jain S, Silverstein L, Baker AL, Tanaka N, et al. Coronary artery outcomes among children with Kawasaki disease in the United States and Japan. *Int J Cardiol*. 2013;168:3825–3828. doi: 10.1016/j.ijcard.2013.06.027
186. Fabi M, Andreozzi L, Frabboni I, Dormi A, Corinaldesi E, Lami F, Cicero C, Tchana B, Francavilla R, Sprocati M, et al. Non-coronary cardiac events, younger age, and IVIG unresponsiveness increase the risk for coronary aneurysms in Italian children with Kawasaki disease. *Clin Rheumatol*. 2021;40:1507–1514. doi: 10.1007/s10067-020-05331-w
187. Moreno E, Garcia SD, Bainto E, Salgado AP, Parish A, Rosellini BD, Ulloa-Gutierrez R, Garrido-Garcia LM, Dueñas L, Estripeaut D, et al; REKAMLATINA-2 Study Group Investigators. Presentation and outcomes of Kawasaki disease in Latin American infants younger than 6 months of age: a multinational multicenter study of the REKAMLATINA Network. *Front Pediatr*. 2020;8:384. doi: 10.3389/fped.2020.00384
188. Holman RC, Curns AT, Belay ED, Steiner CA, Schonberger LB. Kawasaki syndrome hospitalizations in the United States, 1997 and 2000. *Pediatrics*. 2003;112:495–501. doi: 10.1542/peds.112.3.495
189. Chang RK. Hospitalizations for Kawasaki disease among children in the United States, 1988-1997. *Pediatrics*. 2002;109:e87. doi: 10.1542/peds.109.6.e87
190. Makino N, Nakamura Y, Yashiro M, Sano T, Ae R, Kosami K, Kojo T, Aoyama Y, Kotani K, Yanagawa H. Epidemiological observations of Kawasaki disease in Japan, 2013–2014. *Pediatr Int*. 2018;60:581–587. doi: 10.1111/ped.13544
191. Garcia-Pavon S, Yamazaki-Nakashimada MA, Baez M, Borjas-Aguilar KL, Murata C. Kawasaki disease complicated with macrophage activation syndrome: a systematic review. *J Pediatr Hematol Oncol*. 2017;39:445–451. doi: 10.1097/MPH.0000000000000872
192. Lin MT, Sun LC, Wu ET, Wang JK, Lue HC, Wu MH. Acute and late coronary outcomes in 1073 patients with Kawasaki disease with and without intravenous gamma-immunoglobulin therapy. *Arch Dis Child*. 2015;100:542–547. doi: 10.1136/archdischild-2014-306427
193. Manlhiot C, Millar K, Golding F, McCrindle BW. Improved classification of coronary artery abnormalities based only on coronary artery z-scores after Kawasaki disease. *Pediatr Cardiol*. 2010;31:242–249. doi: 10.1007/s00246-009-9599-7
194. Miura M, Kobayashi T, Kaneko T, Ayusawa M, Fukazawa R, Fukushima N, Fuse S, Hamaoka K, Hirono K, Kato T, et al; Z-Score Project 2nd Stage Study Group. Association of severity of coronary artery aneurysms in patients with Kawasaki disease and risk of later coronary events. *JAMA Pediatrics*. 2018;172:e180030. doi: 10.1001/jamapediatrics.2018.0030
195. Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project (HCUP). Accessed April 1, 2023. http://hcupnet.ahrq.gov/
196. Robinson C, Chanchlani R, Gayowsky A, Darling E, Seow H, Batthish M. Health care utilization and costs following Kawasaki disease. *Paediatr Child Health*. 2022;27:160–168. doi: 10.1093/pch/pxab092
197. Elakabawi K, Lin J, Jiao F, Guo N, Yuan Z. Kawasaki disease: global burden and genetic background. *Cardiol Res*. 2020;11:9–14. doi: 10.14740/cr993
198. Nakamura Y, Yashiro M, Yamashita M, Aoyama N, Otaki U, Ozeki Y, Sano T, Kojo T, Ae R, Aoyama Y, et al. Cumulative incidence of Kawasaki disease in Japan. *Pediatr Int*. 2018;60:19–22. doi: 10.1111/ped.13450
199. Wu MH, Lin MT, Chen HC, Kao FY, Huang SK. Postnatal risk of acquiring Kawasaki disease: a nationwide birth cohort database study. *J Pediatr*. 2017;180:80–86.e2. doi: 10.1016/j.jpeds.2016.09.052
200. Singh S, Vignesh P, Burgner D. The epidemiology of Kawasaki disease: a global update. *Arch Dis Child*. 2015;100:1084–1088. doi: 10.1136/archdischild-2014-307536
201. Cimaz R, Fanti E, Mauro A, Voller F, Rusconi F. Epidemiology of Kawasaki disease in Italy: surveillance from national hospitalization records. *Eur J Pediatr*. 2017;176:1061–1065. doi: 10.1007/s00431-017-2947-3
202. Sanchez-Manubens J, Anton J, Bou R, Iglesias E, Calzada-Hernandez J, Rodo X, Morgui JA; el Grupo de Trabajo en Enfermedad de Kawasaki en Cataluña. Kawasaki disease is more prevalent in rural areas of Catalonia (Spain) [in Spanish]. *An Pediatr (Barc)*. 2017;87:226–231. doi: 10.1016/j.anpedi.2016.12.009
203. Jakob A, Whelan J, Kordecki M, Berner R, Stiller B, Arnold R, von Kries R, Neumann E, Roubinis N, Robert M, et al. Kawasaki disease in Germany: a prospective, population-based study adjusted for underreporting. *Pediatr Infect Dis J*. 2016;35:129–134. doi: 10.1097/INF.0000000000000953
204. Tulloh RMR, Mayon-White R, Harnden A, Ramanan AV, Tizard EJ, Shingadia D, Michie CA, Lynn RM, Levin M, Franklin OD, et al. Kawasaki disease: a prospective population survey in the UK and Ireland from 2013 to 2015. *Arch Dis Child*. 2018;104:640–646. doi: 10.1136/archdischild-2018-315087
205. Dionne A, Son MBF, Randolph AG. An update on multisystem inflammatory syndrome in children related to SARS-CoV-2. *Pediatr Infect Dis J*. 2022;41:e6–e9. doi: 10.1097/INF.0000000000003393
206. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet*. 2020;395:1607–1608. doi: 10.1016/S0140-6736(20)31094-1
207. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, Newburger JW, Kleinman LC, Heidemann SM, Martin AA, et al; Overcoming COVID-19 Investigators. Multisystem inflammatory syndrome in U.S. children and adolescents. *N Engl J Med*. 2020;383:334–346. doi: 10.1056/NEJMoa2021680
208. Centers for Disease Control and Prevention. Health department-reported cases of multisystem inflammatory syndrome in children (MIS-C) in the United States. 2023. Accessed May 23, 2023. https://covid.cdc.gov/covid-data-tracker/#mis-national-surveillance
209. Jiang L, Tang K, Levin M, Irfan O, Morris SK, Wilson K, Klein JD, Bhutta ZA. COVID-19 and multisystem inflammatory syndrome in children and adolescents. *Lancet Infect Dis*. 2020;20:e276–e288. doi: 10.1016/S1473-3099(20)30651-4
210. Toubiana J, Poirault C, Corsia A, Bajolle F, Fourgeaud J, Angoulvant F, Debray A, Basmaci R, Salvador E, Biscardi S, et al. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. *BMJ*. 2020;369:m2094. doi: 10.1136/bmj.m2094
211. Toubiana J, Cohen JF, Brice J, Poirault C, Bajolle F, Curtis W, Moulin F, Matczak S, Leruez M, Casanova JL, et al. Distinctive features of Kawasaki disease following SARS-CoV-2 infection: a controlled study in Paris, France. *J Clin Immunol*. 2021;41:526–535. doi: 10.1007/s10875-020-00941-0
212. Torpoco Rivera D, Misra A, Sanil Y, Sabzghabaei N, Safa R, Garcia RU. Vitamin D and morbidity in children with multisystem inflammatory syndrome related to Covid-19. *Prog Pediatr Cardiol*. 2022;66:101507. doi: 10.1016/j.ppedcard.2022.101507
213. Hadžić-Kečalović A, Ćosićkić A, Pašić A, Selimović A, Sabitović D, Kardašević M, Mršić D. Vitamin D assessment in patients with multisystem inflammatory syndrome and SARS-CoV-2 infection. *Central Eur J Paediatr*. 2022;18:91–99. doi: 10.5457/p2005-114.321
214. Gawlik AM, Berdej-Szczot E, Chmiel I, Lorek M, Antosz A, Firek-Pędras M, Szydłowski L, Ludwikowska KM, Okarska-Napierała M, Dudek N, et al. A tendency to worse course of multisystem inflammatory syndrome in children with obesity: MultiOrgan Inflammatory Syndromes COVID-19 related study. *Front Endocrinol (Lausanne)*. 2022;13:934373. doi: 10.3389/fendo.2022.934373
215. Ptak K, Szymonska I, Olchawa-Czech A, Kukla K, Cisowska M, Kwinta P. Comparison of the course of multisystem inflammatory syndrome in children during different pandemic waves. *Eur J Pediatr*. 2023;182:1647–1656. doi: 10.1007/s00431-022-04790-4
216. Buonsenso D, Perramon A, Català M, Torres JP, Camacho-Moreno G, Rojas-Solano M, Ulloa-Gutierrez R, Camacho-Badilla K, Pérez-Corrales C, Cotugno N, et al; COPP-Consortium. Multisystem inflammatory syndrome in children in Western countries? Decreasing incidence as the pandemic progresses? An observational multicenter international cross-sectional study. *Pediatr Infect Dis J*. 2022;41:989–993. doi: 10.1097/INF.0000000000003713
217. Barros LAF, Oliveira VDS, Morais WJ, Dias LA, Almeida JP, Soares MB, Aquino EC, Pinto RM. Pediatric inflammatory multisystemic syndrome in Brazil: sociodemographic characteristics and risk factors to death. *J Pediatr (Rio J)*. 2023;99:31–37. doi: 10.1016/j.jped.2022.04.003
218. van der Linde D, Konings EE, Slager MA, Witsenburg M, Helbing WA, Takkenberg JJ, Roos-Hesselink JW. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2011;58:2241–2247. doi: 10.1016/j.jacc.2011.08.025
219. Parker SE, Mai CT, Canfield MA, Rickard R, Wang Y, Meyer RE, Anderson P, Mason CA, Collins JS, Kirby RS, et al; National Birth Defects Prevention Network. Updated national birth prevalence estimates for selected birth defects in the United States, 2004-2006. *Birth Defects Res A Clin Mol Teratol*. 2010;88:1008–1016. doi: 10.1002/bdra.20735

# 18. DISORDERS OF HEART RHYTHM

*See Charts 18-1 through 18-12*

Click here to return to the Table of Contents
Click here to return to the Abbreviations

## Arrhythmias (Disorders of Heart Rhythm)

2021, United States: Underlying cause mortality—57 801. Any-mention mortality—687 696.

2020, United States: Hospital discharges—552 115.

## Bradyarrhythmias

### *ICD-9* 426.0, 426.1, 427.81; *ICD-10* I44.0 to I44.3, I49.5.

2021, United States: Underlying cause mortality—1552. Any-mention mortality—10 087.

2020, United States: Hospital discharges—90 975.

## Disorders of Atrioventricular Conduction

### *Prevalence and Incidence*

#### *Prolonged PR Interval*

- The prevalence of PR-interval prolongation ranged between 1.9% (sex-pooled 95% CI, 1.3%–3.0%) and 3.7% (95% CI, 3.1%–4.3%) in studies (N=1081–10 785) conducted in different European countries.[1–3]

#### *Second-Degree Atrioventricular Block*

- Mobitz II second-degree atrioventricular block is rare in healthy individuals (<0.003%),[4] whereas Mobitz I (Wenckebach) is observed in 1% to 2% of healthy individuals <20 years of age, especially during sleep.[5] In a population-based sample of Chinese adults (N=15 181 402), the age- and sex-standardized prevalence of second-degree atrioventricular block was reported as 0.18% (95% CI, 0.17%–0.18%) but was not further classified as Mobitz I or II.[6]

#### *Third-Degree or Complete Heart Block*

- The prevalence of complete (third-degree) atrioventricular block in the general adult population is low. The prevalence was 0.6% in a large sample of people (N=552 623) with hypertension and without diabetes enrolled with Veterans Health Administration hospitals.[7] The age- and sex-standardized prevalence of third-degree heart block in a population-based sample of Chinese adults (N=15 181 402) was 0.04% (95% CI, 0.03%–0.04%).[6]
- In an analysis of standard 12-lead ECGs from 264 324 Brazilian primary care patients, prevalence of complete atrioventricular block was 0.05%, ranging from 0.02% in individuals 20 to <40 years of age to 0.3% in people ≥80 years of age.[8] In a larger Brazilian cohort (N=1 536 363), the prevalence of complete atrioventricular block was far less (0.04%).[4]
- In 122 815 recordings from 122 454 unique patients prescribed 14-day continuous single-lead electrocardiographic monitoring with the Zio patch device between 2011 and 2013, prevalence of high-grade atrioventricular block (defined as either Mobitz II or complete atrioventricular block) was 1.2% (1486 of all tracings).[9] In a post hoc analysis of the LOOP randomized trial, high-grade atrioventricular block was identified in 115 of 6004 trial participants, all of whom were ≥70 years of age and had hypertension, diabetes, HF, or prior stroke.[10]
- Atrioventricular block of varying degrees is reported in 8.6% of patients hospitalized with acute COVID-19 infection.[11] The prevalence appears higher in Asia (22.7%) than in Europe (8.1%) and North America (7.0%).

### *Risk Factors*

- Sex and race and ethnicity may impart varying risk. In individuals from MESA (N=1252) without recognized CVD or CVD risk factors, PR-interval reference ranges in individuals ≥65 years of age were reported as 176 milliseconds (32 milliseconds) in males and 162 milliseconds (22 milliseconds) in females of White race; 178 milliseconds (31 milliseconds) in males and 160 milliseconds (19 milliseconds) in females of Black race; and 162 milliseconds (17 milliseconds) in males and 163 milliseconds (18 milliseconds) in females of Hispanic ethnicity.[12]
- Although a prolonged PR interval and Mobitz type I second-degree atrioventricular block can occur in healthy people, especially during sleep, presence of Mobitz II second- or third-degree atrioventricular block may indicate underlying HD, including CHD, and HF.[5]
- Long sinus pauses and atrioventricular block can occur during sleep apnea, which may be reversible

The 2024 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2024. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

with treatment of the condition.[13,13a] In a meta-analysis of 10 studies (N=1077) the estimated prevalence of daytime atrioventricular nodal disease in individuals with sleep apnea was 6.01% (95% CI, 2.53%–13.87%) and nighttime prevalence (11 studies, N=2177) was 16.46% (95% CI, 3.96%–22.82%).[13]

### Complications

- In the FHS, PR-interval prolongation (>200 milliseconds) was associated with increased risk of AF (HR, 2.06 [95% CI, 1.36–3.12]), pacemaker implantation (HR, 2.89 [95% CI, 1.83–4.57]), and all-cause mortality (HR, 1.44 [95% CI, 1.09–1.91]).[14] Compared with FHS participants with a PR interval ≤200 milliseconds, those with a PR interval >200 milliseconds had an absolute increased risk per year of 1.0% for AF, 0.5% for pacemaker implantation, and 2.1% for death. In the LOOP study, which enrolled individuals 70 to 90 years of age without AF, a PR interval with a duration <120 or >200 milliseconds was associated with an HR of 1.46 (95% CI, 1.14–1.86) for the development of AF.[15]
- In a large, prospective, regional French registry of 6662 patients with STEMI presenting from 2006 to 2013, high-degree atrioventricular block was noted in 3.5% of individuals. In 64% of those with high-grade atrioventricular block, this level of conduction disease was present on admission. After multivariable adjustment, high-degree atrioventricular block on admission or occurring during the first 24 hours of hospitalization was not associated with in-hospital mortality (OR, 0.99 [95% CI, 0.60–1.66]).[16]

## Sinus Node Dysfunction

### Prevalence and Incidence

- In a post hoc analysis of the LOOP randomized trial, SND was identified in 270 of 6004 trial participants, all of whom were ≥70 years of age and had hypertension, diabetes, HF, or prior stroke.[10]
- Bradycardia (including SND) has been reported in 12.8% of patients hospitalized with acute COVID-19 infection. The occurrence of bradycardia appears to be higher in Asia (20.5%) than in Europe 10.7%) and North or South America (13.6% and 8.0%, respectively).[11]
- A survey of 3846 patients hospitalized with acute COVID-19 infection at 2 London institutions revealed only 6 patients requiring permanent pacemaker implantation (4 implantations were indicated for Mobitz 2 or complete heart block, and 2 were for SND). All implantations were in males, whose mean age was 82.7 years.[17]

### Risk Factors

- The causes of SND can be classified as intrinsic (secondary to pathological conditions involving the sinus node) or extrinsic (caused by depression of sinus node function by external factors such as drugs or autonomic influences).[18]
- In the CHS and ARIC studies, factors associated with incident SND included White versus Black race (Black participants: HR, 0.59 [95% CI, 0.37–0.98]), higher mean BMI, height, prevalent hypertension, lower heart rate, right bundle-branch block, NT-proBNP, cystatin C, and history of a major cardiovascular event.[19]

### Family History and Genetics

- Bradycardia and atrioventricular block have a heritable component. Monogenic cardiomyopathies are associated with bradycardia. For example, *LMNA* cardiomyopathy is associated with atrioventricular block. Rare coding variants in genes affecting ion channels (eg, *HCN4*,[20] *SCN5A*,[21] *RYR2*,[22] *KCNJ3*,[23] and *KCNJ5*[24]) and variants in *ANK2*[25] and *TRPM4*[26] have been associated with SND in families and sporadic cases with severe forms of disease. In a genome sequencing study of 792 Icelandic individuals with sick sinus syndrome, a missense variant in *MYH6* was found to be associated with SND (OR, 12.5 [95% CI, 8.1–19.4]; $P=1.5\times10^{-29}$).[27]

### Complications

- A large (N=1 692 157) observational study in France demonstrated a higher incidence of stroke in individuals with SND compared with those with other cardiac conditions (HR, 1.27 [95% CI, 1.19–1.35]). In contrast, the study observed that individuals with SND had a lower incidence of stroke compared with those with AF (HR, 0.77 [95% CI, 0.73–0.82]).[28]

Clinical trials and professional consensus have established that individuals with SND receiving atrial and ventricular pacing modes have decreased risk of AF compared with those receiving solely ventricular pacing.[29]

## SVT (Excluding AF and Atrial Flutter)

## *ICD-9* 427.0; *ICD-10* I47.1.

2021, United States: Underlying cause mortality—231. Any-mention mortality—2527.

2020, United States: Hospital discharges—35 110.

### Prevalence, Incidence, and Risk Factors

- Analysis of health claims data (IBM MarketScan Commercial Research database) from 2008 to 2016 identified the prevalence of documented SVT (including AF/atrial flutter) as 428.9 (95% CI, 418.0–440.1) per 100 000 individuals in females and 227.2 (95% CI, 218.9–235.8) in males.[30] An analysis conducted in an integrated health care delivery system from 2010 to 2015 reported the prevalence of SVT as 140.2 (95% CI, 100.1–179.2) per

100 000 individuals and the incidence as 72.7 (95% CI, 52.5–91.8) per 100 000 individuals.[31] SVT in both studies was more common in females than males.

- An analysis of the nationally representative Nationwide Emergency Department Sample from 2016 to2018 (N=20.6 million) identified that SVT (excluding AF/atrial flutter) accounted for 2.4% of ED visits in females and 1.5% in males.[32]
- A global registry of acute COVID-19 infections reported that 9.7% of patients hospitalized with acute COVID-19 infection had SVTs other than AF or flutter.[11] The prevalence of SVT was reported as higher in Asia (18.2%) than in Europe (10.3%) and North and South America (8.4% and 12.0%, respectively).

### Family History and Genetics

- Although general SVT does not appear to have a strong heritable component, atrioventricular nodal reentry tachycardia has shown familial clustering.[33] A study of candidate gene sequencing in 298 patients with atrioventricular nodal reentry tachycardia and 10 family members with atrioventricular nodal reentry tachycardia identified 229 coding variants, of which 65 were novel, with a large proportion of variants identified in the *HCN1* through *HCN4* genes.[34]
- Patients with ARVC can often present with ventricular arrhythmias. The Clinical Genome Resource Gene Curation Expert Panel appraised the 26 genes reportedly associated with ARVC and found that only 6 genes (*PKP2*, *DSP*, *DSG2*, *DSC2*, *JUP*, and *TMEM43*) had strong evidence and 2 genes (*DES* and *PLN*) had moderate evidence of association with ARVC.[35]

### Complications

- Among 2 350 328 pregnancies included in Taiwan's national insurance database between 2001 and 2012, 769 females experienced paroxysmal SVT during pregnancy. Compared with no paroxysmal SVT during pregnancy, paroxysmal SVT during pregnancy was associated with a higher risk for poor maternal outcomes (severe morbidity and cesarean delivery) and poor fetal outcomes (LBW, preterm labor, fetal stress, and obvious fetal abnormalities).[36]
- In a Swedish study of 214 patients (51% females) with paroxysmal SVT undergoing ablation, females had a longer history of symptomatic arrhythmia (16.2±14.6 years versus 9.9±13.1 years), were more likely to report not being taken seriously when consulting for their symptoms (17% versus 7%), and were more symptomatic after 6 months of ablation than males.[37]

### Types of SVT

- Individuals with SVT (N=2260) in a registry in Singapore from 2010 to 2018 had a mean age 45±18 years. The most common SVT was atrioventricular nodal reentry (57%) followed by atrioventricular reentry (37%) and atrial tachycardia (6%). Generalizability may be limited because all individuals included in the registry underwent catheter ablation.[38]
- In children, atrioventricular reentrant tachycardia has been identified as the most common SVT mechanism (66%–68% of SVT cases), and the remainder of the patients had predominantly atrioventricular nodal reentrant tachycardia (24%–32%).[39,40]

## WPW Syndrome

### Prevalence

- WPW syndrome refers to the presence of ventricular pre-excitation on the ECG combined with a related arrhythmia (SVT). A WPW electrocardiographic pattern (ventricular pre-excitation) was observed in 44 of 34 965 adults in a population-based Chinese cohort. In males, the prevalence was 0.14% in those 20 to 44 years of age, 0.04% in those 45 to 59 years of age, and 0.02% in those ≥60 years of age. In females, the prevalence was 0.12%, 0.04%, and 0.05% in these age groups, respectively.[41] In an electrocardiographic study of 32 837 Japanese students, ventricular pre-excitation was reported in 0.07%, 0.07%, and 0.17% of elementary, junior high, and high school students, respectively.[42]

### Complications

- WPW syndrome deserves special attention because of the associated risk of sudden death. Sudden death is generally attributed to rapid heart rates in AF conducting down an accessory pathway and leading to VF.[43]
- A cohort study from Intermountain Healthcare with ≈8 years of follow-up reported that rates of cardiac arrest were low and similar between patients with WPW and control subjects without WPW. In follow-up, WPW was associated with a significantly higher risk of AF (HR, 1.55 [95% CI, 1.29–1.87]); 7.0% of the patients with WPW developed AF compared with 3.8% of those without WPW.[44]
- Asymptomatic adults with ventricular pre-excitation appear to be at no increased risk of sudden death compared with the general population.[43] Although there are rare exceptions, the majority of patients who experience cardiac arrest in association with WPW have had symptomatic SVT.
- In a single-center prospective registry study of 2169 patients who agreed to undergo an electrophysiology study for WPW syndrome from 2005 to 2010, 1168 patients (206 asymptomatic) underwent radiofrequency ablation, none of whom had malignant arrhythmias or VF in up to 8 years of follow-up. Of those who did not receive radiofrequency

ablation (n=1001; 550 asymptomatic) in follow-up, 1.5% had VF, most of whom (13 of 15) were children. The authors noted that poor prognosis was related to accessory pathway electrophysiological properties rather than patient symptoms.[45]
- A multicenter international survey of 1589 subjects ≤21 years of age (mean, 13 years of age) with pre-excitation identified that 15% had nonpersistent (intermittent) pre-excitation.[46] Two percent of the study population experienced SCA. Patients with nonpersistent pre-excitation were significantly less likely to exhibit high-risk conduction properties of the accessory pathway at electrophysiological study. A total of 29 patients (2%) experienced SCA, and 3 of these individuals had nonpersistent pre-excitation. Thus, 1.2% of 244 pediatric patients with nonpersistent pre-excitation experienced SCA.

## AF and Atrial Flutter

### *ICD-9 427.3; ICD-10 I48.*

2021, United States: Underlying cause mortality—28 037. Any-mention mortality—232 030.

2020, United States: Hospital discharges—401 055.

### *Prevalence*

### *(See Chart 18-1)*

- Prevalence of AF in the United States is estimated to increase from ≈5.2 million in 2010 to 12.1 million in 2030.[47] An analysis of 5 medical claims data sets used data from 2012 to 2017 to estimate the prevalence of AF in 2015 in the United States as 6.6 million individuals.[48]
- From the Rotterdam Study, the prevalence of AF in adults >55 years of age in the European Union was estimated to be 8.8 (95% CI, 6.5–12.3) million in 2010 and is projected to increase to 17.9 (95% CI, 13.6–23.7) million in 2060.[49]
- The prevalence of AF in Greenland in 2022 was estimated from EHR and prescription-based data and determined as 1.8% (95% CI, 1.6%–1.9%) in males and 1.0% (95% CI, 1.3%–1.5%) in females. In those age ≥70 years, the prevalence increased to 11.9% (95% CI, 10.3%–13.6%) and 10.1% (95% CI, 8.6%-11.8%), respectively.[50]
- In an integrated regional health care system, the incidence of AF increased from 4.74 (95% CI, 4.58–4.90) per 1000 person-years in 2006 to 6.82 (95% CI, 6.65–7.00) in 2018. Increases in incidence were observed in all subgroups by sex and age. The study did not report data on AF incidence by race or ethnicity.[51]
- Investigators from MESA identified clinically detected AF after 14.4 years of follow-up as 11.3% in NH White people, 7.8% in Hispanic people, 6.6% in NH Black people, and 9.9% in those of Chinese origin. In contrast, in these same individuals, the proportion with AF detected with 14-day electrocardiographic monitoring was 7.1% in NH White people, 6.9% in Hispanic people, 6.4% in NH Black people, and 5.2% in those of Chinese origin (Chart 18-1).[52]
- In a population-based analysis conducted in South Korea, the prevalence of AF increased from 0.73% in 2006 to 1.53% in 2015 and is estimated to reach 5.35% in 2050 and 5.81% in 2060.[53]

### *Incidence*

- Comparison of AF incidence across studies is challenged by differing methods with regard to population studied, restriction by age or comorbidity, and statistical approaches to population-based standardization.
- A secondary analysis of a trial conducting screening for AF in at-risk older adults determined that the incidence of AF among 14 960 individuals was 23.7 per 1000 person-years (95% CI, 21.0–26.7).[54] AF incidence increased with age (14.2 per 1000 person-years at 65–69 years of age to 50.8 per 1000 person-years at ≥85 years of age).
- In a population-based analysis conducted in South Korea, the incidence of AF between 2006 and 2015 remained flat at 1.77 new cases per 1000 person-years during this 10-year observation period.[53]
- A population-based study in England determined that incident AF increased from 247 per 100 000 person-years in 1998 to 322 per 100 000 person-years in 2017 in age- and sex-standardized models, yielding an aIRR of 1.30 (95% CI, 1.27–1.33).[55] An analysis of the California State HCUP Databases reported that the incidence of AF in American Indian people in the state of California was similar to that in White people and higher than in Black, Asian, and Hispanic people.[56]

### *Lifetime Risk and Cumulative Risk*

### *(See Chart 18-2)*

- In the ARIC study, the lifetime risk of AF was estimated as 36% (95% CI, 32%–38%) in White males, 30% (95% CI, 26%–32%) in White females, 21% (95% CI, 13%–24%) in Black males, and 22% (95% CI, 16%–25%) in Black females.[57]
- In a population-based study conducted in Taiwan, the lifetime risk of AF was estimated to be 16.9% (95% CI, 16.7%–14.2%) in males and 14.6% (95% CI, 14.4%–14.9%) in females.[58]
- The lifetime risk for AF in individuals of European ancestry has been estimated as ≈1 in 3.
  - In the BiomarCaRE Consortium including 4 community-based European studies, the incidence of AF began to increase after 50 years of age in males and 60 years of age in females with a cumulative incidence of ≈30% by 90 years of age.[59]

– In an FHS report based on participants with DNA collected after 1980, the lifetime risk of AF after 55 years of age was 37.1% when accounting for both clinical and genetic risk.[60] A subsequent analysis conducted in the FHS reported that individuals with optimal cardiovascular risk profiles had a lifetime AF risk of 23.4% (95% CI, 12.8%–34.5%), those with a borderline risk profile had a lifetime AF risk of 33.4% (95% CI, 27.9%–38.9%), and those with an elevated risk profile had a lifetime AF risk of 38.4% (95% CI, 35.5%–41.4%; Chart 18-2).[61]

### Secular Trends

- Over 50 years of observation in the FHS (1958–1967 to 1998–2007), the age-adjusted prevalence and incidence of AF approximately quadrupled (prevalence: from 2% to 10% in males, from 1% to 5% in females; incidence: from 4 to 13 per 1000 person-years in males, from 3 to 9 per 1000 person-years in females). However, when only AF that was ascertained on ECGs collected in the FHS was considered, the prevalence increased from 1.3% to 2.6% in males and from 0.8% to 1.2% in females, but the incidence did not increase (remaining at ≈2 per 1000 person-years in males and females), suggesting that enhanced surveillance may contribute to AF identification. Although the prevalence of risk factors changed over time, the hazards associated with specific risk factors did not change. Hence, the PAR associated with BMI, hypertension treatment, and diabetes increased (consistent with increasing prevalence of these conditions).[62]
- In an integrated health care system, standardized AF incidence rates increased from 4.74 (95% CI, 4.58–4.90) cases per 1000 person-years in 2006 to 6.82 (95% CI, 6.65–7.00) cases per 1000 person-years in 2018. The foremost increase in incidence was in those ≥85 years of age.[51] From 2006 to 2018, individuals with AF were more likely to have high BMI (1351/3389 [39.9%] in 2006–2008 versus 4504/9214 [48.9%] in 2015–2018), hypertension (2764 [81.6%] in 2006–2008 versus 7937 [86.1%] in 2015–2018), and ischemic stroke (328 [9.7%] in 2006–2008 versus 1455 [15.8%] in 2015–2018) but less likely to have CAD (1533 [45.2%] in 2006–2008 versus 3810 [41.4%] in 2015–2018). Incidence rates of AF increased in all diagnostic settings and priority pairings.
- Analysis of a national health insurance database in Korea from 2006 to 2015 reported that the prevalence of AF increased 2.10-fold and the incidence remained flat (1.8 per 1000 person-years). Concurrently, the 2-year risks of all-cause mortality (HR, 0.70 [95% CI, 0.68–0.93]) and ischemic stroke (HR, 0.91 [95% CI, 0.88–0.93]) after AF declined.[53]
- COVID-19 and AF: A nationwide study in Denmark reported a 47% reduction in the total number of AF diagnoses during the period of March 12 to April 1, 2020, compared with the same period in 2019 (562 versus 1053).[63] An analysis of IQVIA longitudinal prescription claims, medical claims, and institutional claims data from January 2019 to July 2020 of individuals receiving anticoagulation for AF (N=1 439 145) identified significant reductions in ED visits, inpatient admissions, and hospital admissions for ischemic stroke or bleeding at the onset of the declaration of the COVID pandemic.[64]

### Risk Factors (See Chart 18-3)

- The highest PAF for AF was for hypertension, followed by BMI, smoking, cardiac disease, and diabetes in ARIC (Chart 18-3). A large health claims analysis conducted in Japan of individuals 20 to 75 years of age (N=2 597 441, spanning 2005–2020) compared the effect of age on AF risk over 3.3±2.5 years of follow-up. In younger individuals (20–49 years of age), the modifiable risk factors of obesity, WC, hypertension, and diabetes were associated with greater risk than in those 50 to 59 or 60 to 75 years of age. For example, in multivariable-adjusted analysis, diabetes in individuals 20 to 49 years was associated with an HR of 1.35 (95% CI, 1.18–1.55) for incident AF compared with 1.10 (95% CI, 1.01–1.21) and 0.93 (95% CI, 0.84–1.03) in those 50 to 59 and 60 to 75 years of age, respectively.[65]

### BP and Hypertension

- In a single-center study (N=47 772), SBP >140 mm Hg was associated with increased risk of AF in Black individuals (HR, 1.14 [95% CI, 1.03–1.27]) and Hispanic individuals (HR, 1.18 [95% CI, 1.06–1.31]) but not NH White individuals (HR, 0.92 [95% CI, 0.83–1.02]) over 3.3 mean years of follow-up.[66] The PAR (percent) for SBP >140 mm Hg and the development of AF was 4.9 (95% CI, 1.3–8.2), 4.6 (95% CI, 1.8–7.2), and −3.0 (95% CI, −7.0 to 0.5), respectively.
- Among 9 797 418 individuals enrolled in the Korean National Health Insurance Service and followed up from 2009 to 2017, a graded association between hypertension and AF was identified. In reference to nonhypertension, the HR was 1.15 for prehypertension, 1.39 for hypertension without medication, 1.85 for hypertension treated <5 years, and 2.34 for hypertension treated ≥5 years. Each 5–mm Hg increase in SBP and DBP was associated with an increased risk of 4.3% and 4.6%, respectively, of incident AF.[67]

### BMI and Obesity

- In a meta-analysis of 16 studies involving >580 000 individuals, of whom ≈91 000 had obesity, AF developed in 6.3% of those who had obesity and 3.1% of those without obesity. Individuals with obesity had an RR of 1.51 for developing AF (95% CI, 1.35–1.68) compared with those without obesity.[68]
- A meta-analysis of 29 studies related anthropometric components to incident AF. A 5–kg/m$^2$ increment in BMI was associated with an RR of 1.28 (95% CI, 1.20–1.38) in relation to AF. The risk was nonlinear ($P$<0.0001) with stronger associations observed at higher BMIs, but a BMI of 22 to 24 kg/m$^2$ was still associated with excess risk compared with a BMI of 20 kg/m$^2$. WC, waist-hip ratio, fat mass, and weight gain also were associated with increased risk of AF.[69]
- In a meta-analysis of 10 studies (N=108 996), weight gain was associated with increased risk of AF (HR, 1.13 [95% CI, 1.04–1.23] per 5% weight gain). Nonsurgical loss of 5% body weight was not significantly related to AF risk (HR, 1.04 [95% CI, 0.94–1.16]).[70]
- A genetic mendelian randomization study conducted in a consortium of 7 cohorts of European ancestry identified significant associations between both a genotype associated with obesity and a BMI GRS comprising 39 SNPs with increased risk of incident AF.[71]

### Smoking

- A meta-analysis of 29 studies identified that current smoking was associated with an RR of 1.32 (95% CI, 1.12–1.56) for AF, former smoking with an RR of 1.09 (95% CI, 1.00–1.18), and ever-smoking with an RR of 1.21 (95% CI, 1.12–1.31) compared with the referent of never having smoked. There appeared to be a dose-response relationship such that the RR per 10 cigarettes/d was 1.14 (95% CI, 1.10–1.20) and the RR per 10 pack-years was 1.16 (95% CI, 1.09–1.25).[72]

### Diabetes and HbA1c

- In a meta-analysis of 8 prospective studies (N=102 006), elevated HbA1c was associated with an increased risk of AF when analyzed continuously (RR, 1.11 [95% CI, 1.06–1.16]) or categorically (RR, 1.09 [95% CI, 1.00–1.18]).[73]
- In a meta-analysis of observational studies (excluding a large outlier study), the RR of diabetes for incident AF was 1.28 (31 cohort studies [95% CI, 1.22–1.35]) and for prediabetes was 1.20 (4 studies [95% CI, 1.03–1.39]).[74]
- A machine-learning meta-analysis of 29 studies (N=8 037 756) reported similar risks of incident AF in individuals with type 1 and type 2 diabetes. In a meta-analysis, diabetes was associated with an RR of 1.11 (95% CI, 1.01–1.22) for incident AF in males and an RR of 1.38 (95% CI, 1.19–1.60) in females.[75]

### Activity and Exercise (See Chart 18-4)

- A meta-analysis of 15 studies (N=1 821 422) identified an inverse nonlinear relation between weekly PA and AF risk.[76] Results were most robust describing the decreased risk of AF in individuals exercising up to 50 METs of task-hours per week; data are limited for higher levels of PA.
- An analysis in the Korea National Health Insurance Service (N=66 692) classified individuals by exercise status before and after AF diagnosis. Compared with those who continued not to exercise, those who maintained exercise were significantly less likely to have ischemic stroke (HR, 0.86 [95% CI, 0.77–0.96]), HF (HR, 0.92 [95% CI, 0.88–0.96]), or mortality (HR, 0.61 [95% CI, 0.55–0.67]; Chart 18-4).[77]
- A meta-analysis of 9 observational studies concluded that endurance athletes had an increased risk of AF compared with referents not engaging in comparable exertional activity (OR, 2.34 [95% CI, 1.04–5.28]). The investigators reported substantial heterogeneity in the data and identified the highest risks observed among males and individuals <60 years of age.[78] A second meta-analysis of 11 studies (N=1 901 833) concluded that cross-country skiing was not associated with increased risk of AF (RR, 0.93 [95% CI, 0.80–1.07]), noting significant heterogeneity across studies ($I^2$=94.0%).[79]
- A meta-analysis of 23 observational studies included 1 930 725 individuals, in whom there were 45 839 cases of AF. The most physically active had an RR of 0.99 (95% CI, 0.93–1.05) compared with the least active. This association was modified by sex: The most physically active males had an increased risk (RR, 1.20 [95% CI, 1.02–1.42]) and the most physically active females had a decreased risk (RR, 0.91 [95% CI, 0.84–0.99]) for AF.[80]

### HD as a Risk Factor

- Among participants in the FHS, type of HF (HFrEF or HFpEF) was not differentially associated with the incidence of AF, but prevalent AF was marginally more strongly associated ($P$=0.06) with multivariable-adjusted incidence of HFpEF (HR, 2.34 [95% CI, 1.48–3.70]) than with HFrEF (HR, 1.32 [95% CI, 0.83–2.10]).[81]
- Individuals with congenital HD are at increased risk of AF. In an analysis in Sweden including 21 982 individuals with congenital HD and 219 816 without congenital HD, risk of developing AF was 22 times higher (HR, 22.0 [95% CI, 19.3–25.1]) in those with congenital HD compared with referents

without congenital HD.[82] By 42 years of age, ≈8% of patients with congenital HD had been diagnosed with AF.

### *Miscellaneous Risk Factors*

- Other consistently reported risk factors for AF include clinical and subclinical hyperthyroidism,[83] CKD,[84] and moderate or heavy alcohol consumption.[85] Concerning heavy alcohol consumption, a small study (N=100) correlated alcohol ingestion with AF as identified by mobile rhythm monitor and concluded that ingestion of a single alcoholic beverage was associated with an OR of 2.02 (95% CI, 1.38–3.17) and ingestion of ≥2 drinks with an OR of 3.58 (95% CI, 1.63–7.89) relative to the absence of alcohol use.[86]
- Sleep disorders:
  - In a meta-analysis of 8 studies, the sleep apnea–hypopnea syndrome was associated with an increased risk of AF after adjustment for confounders (RR, 1.40 [95% CI, 1.12–1.74]; $P<0.001$).[87]
  - A meta-analysis of sleep quality reported associations between insomnia (N=3 studies) and increased odds of AF (OR, 1.30 [95% CI, 1.26–1.35]) and frequent awakening (N=2 studies) and AF (OR, 1.36 [95% CI, 1.13–1.63]).[88]
  - In a prospective, urban-dwelling Japanese cohort (N=6898), short sleep (≤6 hours) and irregular sleep (eg, night-shift work) were associated with increased risks of AF (HR, 1.34 [95% CI, 1.01–1.77] and HR, 1.63 [95% CI, 1.16–2.30], respectively) compared with moderate sleep (7 hours) in multivariable-adjusted analyses over a median of 14.5 years of follow-up.[89]
- Air pollution:
  - A systematic review and meta-analysis of 18 studies reported short-term and long-term associations of air pollution with AF.[90] For every 10–μg/m$^3$ increase in PM2.5 and PM10 (particles with aerodynamic diameter <10 μm) concentration, the ORs for AF were 1.01 (95% CI, 1.00–1.02) and 1.03 (95% CI, 1.01–1.05), respectively. The corresponding ORs for long-term exposure were 1.07 (95% CI, 1.04–1.10) for PM2.5 and 1.03 (95% CI, 1.03–1.04) for PM10. $SO_2$ and $NO_2$ also were associated with AF in the short term: ORs for 10-ppb increments were 1.05 (95% CI, 1.01–1.09) and 1.03 (95% CI, 1.01–1.04), respectively.
- The association of caffeine ingestion and AF has been variable. In the Spanish PREDIMED study, ingestion of 1 to 7 cups of coffee weekly was associated with decreased AF risk (HR, 0.53 [95% CI, 0.36–0.79]) compared with no or rare coffee ingestion.[91] However, a higher level of caffeine ingestion (>1 cup of coffee per day) was not associated with AF risk (HR, 0.79 [95% CI, 0.49–1.28]) compared with no or rare coffee ingestion.
- Psychosocial factors:
  - Among close to 1 million individuals seeking care through the Veterans Health Administration between 2001 and 2014, a diagnosis of posttraumatic stress disorder was associated with a 13% increased risk of AF after multivariable adjustment (HR, 1.13 [95% CI, 1.02–1.24]).[92]
  - In the MESA study, higher burden of depressive symptoms was associated with higher risk of AF (HR, 1.34 [95% CI, 1.04–1.74]) when participants with a score ≥16 on the Center for Epidemiological Studies Depression Scale were compared with those with a score <2. Anger, anxiety, and chronic stress were not associated with AF risk.[93]
  - Similarly, in the ARIC study, higher levels of vital exhaustion were associated with increased AF risk (HR, 1.20 [95% CI, 1.06–1.35]). Neither anger nor social isolation was associated with the risk of AF.[94]
  - A meta-analysis of 3 prospective studies evaluating the association between job strain (defined as high demands and low control in the occupational setting) and AF risk reported an HR of 1.37 (95% CI, 1.13–1.67) for those with job strain compared with those without job strain.[95]
- AF frequently occurs secondary to other comorbidities.
  - Among 11 239 patients undergoing isolated CABG at 5 sites in the United States between 2002 and 2010, the risk-adjusted incidence of AF was 33.1%, which did not vary significantly over the observation period.[96]
  - A secondary analysis of the PARAGON-HF trial (N=4776) identified that 1552 had AF at trial enrollment. Those with AF at enrollment had 1.3-fold increased risk (RR, 1.31 [95% CI, 1.11–1.54]) of HF hospitalization, the primary outcome of the trial, compared with those without AF.[97]
  - A meta-analysis of 13 studies (N=52 959) reported that new-onset AF has been observed in 10.9% (95% CI, 7.2%–15.3%) of patients undergoing noncardiac general surgery.[98]
  - A meta-analysis of 13 studies (N=225 841) determined that new-onset AF during sepsis was associated with ≈2-fold increase in in-hospital mortality (OR, 2.09 [95% CI, 1.53–2.86]), postdischarge mortality (OR, 2.44 [95% CI, 1.81–3.29]), and stroke (OR, 1.88 [95% CI, 1.13–3.14]). The incidence of AF varied with severity of sepsis, from 1.9% in mild sepsis to 46% in septic shock.[99]
  - AF is a common occurrence in hospitalized patients with acute COVID-19 infection. A

meta-analysis of 14 studies (N=17 435) reported an incident atrial arrhythmia (AF, atrial flutter, or atrial tachycardia) in 8.2% (95% CI, 5.5%–11.3%) of patients hospitalized with COVID-19.[100] An international registry of patients hospitalized with COVID-19 reported that AF was the most common arrhythmia in COVID cases, occurring in 509 of 827 events (61.5%).[11] A meta-analysis of 12 studies (N=13 124) identified that new-onset AF during COVID-related hospitalization was associated with increased in-hospital mortality (RR, 1.86 [95% CI, 1.54–2.24]),[101] albeit limited by significant heterogeneity ($I^2$=72%).

- Reports suggest that cancer and cancer medications are associated with increased risk of AF. For example, a meta-analysis of 8 studies (N=2580) reported that ibrutinib was associated with AF (RR, 4.69 [95% CI, 2.17–7.64]).[102] A meta-analysis of 6 studies (N=533 514) evaluating the association between new-onset AF and risk of cancer reported a pooled RR of 1.24 (95% CI, 1.10–1.39).[103] The association was restricted to the first 90 days after AF diagnosis (RR, 3.44 [95% CI, 2.29–5.57]) with no association after that time.

## Social Determinants of AF and Health Equity

- Study of social determinants and AF remains limited.[104]
- In an analysis of a large regional health care system, individuals (N=28 858) living in intermediate-poverty neighborhoods (as defined by census tract–level variables) had higher adjusted odds of 5-year incident AF (OR, 1.23 [95% CI, 1.01–1.48]) compared with those residing in lower-poverty neighborhoods.[105]
- An administrative data analysis of individuals with AF in Ontario, Canada, determined that residence in the fifth quintile of neighborhood-based material deprivation was associated with increased 1-year risk of death (HR, 1.16 [95% CI, 1.13–1.20]), stroke (HR, 1.16 [95% CI, 1.07–1.27]), bleeding (HR, 1.16 [95% CI, 1.13–1.25]), and HF (HR, 1.14 [95% CI, 1.11–1.18]) compared with the first quartile.[106]
- An analysis of an administrative claims study of individuals with prevalent AF (N=336 736) identified that those with household income <$40 000/y had increased risks for HF (HR 1.17, [95% CI, 1.05–1.30]) and MI (HR, 1.18 [95% CI, 0.98–1.41]) compared with those with household income ≥$100 000/y.[107]
- In an analysis in the community-based ARIC study, AF incidence decreased with progressively increased categories of income and education.[57] The risk of AF in White males with annual income ≥$50 000 was an RR of 0.76 (95% CI, 0.65–0.88) and in White females of 0.70 (95% CI, 0.59–0.83) compared with those with annual income <$25 000. Income was not associated with AF risk in Black males; in Black females with annual income ≥$25 000, the risk was an RR of 0.73 (95% CI, 0.56–0.96) compared with those with annual income <$25 000. Similar estimates were observed with educational attainment.
- In a limited-sized cohort (N=339) followed up for a median of 2.6 years (range, 0–3.4 years), individuals in the lowest income category (≤$19 999/y) had 2.0-fold greater hospitalization risk (OR, 2.11 [95% CI, 1.08–4.09]) compared with those in the highest income category (≥$100 000/y).[108]

### *Risk Prediction of AF*

- Life's Simple 7:
  - In the REGARDS study, better CVH, as classified by Life's Simple 7, was associated with decreased risk of AF similarly between sexes and in White and Black people. Individuals with optimal CVH (score, 10–14 points) had an adjusted 32% lower risk of AF (OR, 0.68 [95% CI, 0.47–0.99]).[109]
  - The ARIC study observed that cohort participants with average (HR, 0.59 [95% CI, 0.51–0.67]) and optimal (HR, 0.38 [95% CI, 0.32–0.44]) CVH had a lower risk of incident AF. For every 1-point higher Life's Simple 7 score, the risk of AF was 12% lower (HR, 0.88 [95% CI, 0.86–0.89]).[110]
  - In 2363 participants of the ARIC study who underwent continuous electrocardiographic monitoring for 14 days, Life's Simple 7 score was associated with reduced risk of continuous AF (HR, 0.87 [95% CI, 0.79–0.95] per 1-point increase in Life's Simple 7 score) but not with risk of intermittent AF (HR, 0.92 [95% CI, 0.83–1.02]).[111]
  - A similar analysis in the MESA cohort reported a 27% lower risk of AF over a median follow-up of 11.2 years (IQR, 10.6–11.7 years) in participants with optimal CVH (HR, 0.73 [95% CI, 0.59–0.91]) compared with those with inadequate scores without substantive differences by race and ethnicity.[112]
- ARIC,[113] FHS,[114] and WHS[115] have developed risk prediction models in individual cohorts to predict new-onset AF. Predictors of increased risk of new-onset AF include advancing age, European ancestry, body size (greater height and BMI), electrocardiographic features (LVH, left atrial enlargement), diabetes, BP (SBP and hypertension treatment), and presence of CVD (CHD, HF, valvular HD). In contrast, the $HARMS_2$-AF score had an AUC of 0.782 (95% CI, 0.775–0.789) in the UK Biobank for 5-year risk prediction of AF and validation in FHS with AUC 0.757 (95% CI, 0.735–0.779).[116]
- A CHARGE-AF risk prediction model for AF has been validated in a US multiethnic patient cohort,[117]

in MESA,[118] in a UK cohort (EPIC Norfolk),[119] in a post-CABG cohort,[120] and in a large nationwide primary care database in the Netherlands.[121]
- A study evaluating electronic health records in a uniform health care system (N=2 252 219) used machine-learning models to predict 6-month incident AF.[122] The resulting model had a similar C statistic (0.800) compared with a model using basic regression and established clinical risk factors for AF (C statistic, 0.794).

### Borderline Risk Factors

- Data from the FHS examining lifetime risk of AF identified that the prevalence of AF risk factors increased gradually with age. At an index age of 55 years, lifetime AF risk was 37.0% (95% CI, 34.3%–39.6%).[61] Lifetime AF risk was 23.4% (95% CI, 12.8%–34.5%) for those with an optimal risk profile, 33.4% (95% CI, 27.9%–38.9%) in those with a borderline risk profile, and 38.4% (95% CI, 35.5%–41.4%) in those with an elevated risk profile. At index ages 65 and 75 years, the gradient of AF lifetime risk was similar.

### Subclinical Atrial Tachyarrhythmias, Unrecognized AF, and Screening for AF

#### Device-Detected AF

- Cardiac implantable electronic devices (eg, pacemakers and defibrillators) have increased clinician awareness of the frequency of subclinical AF and atrial high-rate episodes in people without a documented history of AF.
- In a meta-analysis of 28 studies including patients with pacemakers or defibrillators followed up for a mean of 22 months, new-onset device-detected atrial tachyarrhythmias were observed in 23% of patients. In 9 studies, device-detected atrial tachyarrhythmias were associated with an RR of 2.88 (95% CI, 1.79–4.64; $P<0.001$) for thromboembolism, which was higher with longer duration (≥5 minutes: RR, 3.86; <1 minute: RR, 1.77).[123]
- A meta-analysis reported that atrial high-rate episodes detected by implanted cardiac devices were associated with ≈2-fold increased thromboembolic stroke risk (RR, 2.13 [95% CI, 1.53–2.95]) in studies excluding patients with prior AF or atrial tachyarrhythmias (n=7 studies including 4961 participants) and across all studies (N=10 including 37 266 participants; RR, 1.92 [95% CI, 1.44–2.55]).[124]
- A meta-analysis of 9 studies (N=42 958) determined that individuals with low atrial high-rate episode burden as detected by an implanted device had an HR of 1.20 (95% CI, 1.03–1.41) for stroke or systemic embolism compared with those without atrial high-rate episodes.[125] In contrast, those with a high burden of atrial high-rate episodes had an HR of 2.52 (95% CI, 1.46–4.37) relative to those without atrial high-rate episodes.

### Community Screening for Undiagnosed AF (See Charts 18-5 and 18-6)

- The incidence of detecting previously undiagnosed AF by screening depends on the underlying risk of AF in the population studied, the intensity and duration of screening, and the method used to detect AF.[126] Methods vary in their sensitivity and specificity in the detection of undiagnosed AF, increasing from pulse palpation to devices such as handheld single-lead ECGs, modified BP devices, and plethysmographs.[127]
- The prevalence of undiagnosed AF in the community is unknown. Using Medicare and commercial claims data, investigators have estimated that in 2009, ≈0.7 million (13.1%) of the ≈5.3 million AF cases in the United States were undiagnosed. Of the undiagnosed AF cases, investigators estimated that 698 900 were undiagnosed, including 535 400 (95% CI, 331 900–804 400) in individuals ≥65 years of age and 163 500 (95% CI, 17 700–400 000) in individuals 18 to 64 years of age.[128]
- A single-center study examined duration of monitoring for AF detection after ischemic stroke or TIA in 379 individuals at a median of 63 years of age (IQR, 55–73 years).[129] There were 10 cases of AF detected, with 7 in the first 48 hours of monitoring (IR, 1.85% [95% CI, 0.74%–3.81%]; number needed to screen, 54) and 3 additional cases with duration of monitoring from 48 hours to 14 days (IR, 0.83% [95% CI, 0.17%–2.42%]; number needed to screen, 121).
- A multicenter, open-label, randomized trial of individuals ≥75 years of age with hypertension compared a 2-week continuous electrocardiographic patch coupled with an automated home BP machine with oscillometric AF screening capability and usual care over a 6-month period.[130] AF was detected in 23 of 434 (5.3%) in the screening group compared with 2 of 422 (0.5%) in the control group (risk difference, 4.8% [95% CI, 2.6%–7.0%]; number needed to screen, 21). By 6 months, anticoagulation was more frequently prescribed in the intervention group (18/434 [4.1%] versus 4/422 [0.9%]; risk difference, 3.2% [95% CI, 1.1%–5.3%]).[130]
- A multicenter clinical trial randomized individuals with at least 1 stroke risk factor and without prevalent AF in a 1:3 ratio to receive long-term rhythm monitoring with an implanted loop recorder (n=1501) or usual care (n=4503).[131] Over a median follow-up of 64.5 months (IQR, 59.3–69.8 months), those randomized to monitoring were 3-fold more likely to be diagnosed with AF (HR, 3.17 [95% CI, 2.81–3.59]).
- A multicenter, parallel-group RCT conducted in Sweden evaluated the effect of intermittent ECGs for 14 days as an intervention for AF detection on

a composite outcome of stroke, systemic embolism, bleeding, and mortality compared with usual care. After a median follow-up of 6.9 years (IQR, 6.5–7.2 years), there were significantly fewer primary endpoint events in the intervention group (n=13 979; 5.45 events per 100 years [95% CI, 5.52–5.61]) than in the control group (n=13 996; 5.68 events per 100 years [95% CI, 5.52–5.85]). The intervention was associated with an ≈4% reduced risk for the composite outcome (HR, 0.96 [95% CI, 0.92–1.00]).[132] Post hoc analysis concluded that this screening approach was cost-effective; screening of 1000 older adults resulted in 10.6 (95% CI, −22.5 to 1.4) fewer strokes.[133]

- A cluster randomized trial examined point-of-care screening with a single-lead ECG in 16 primary care clinics.[134] Of 30 715 individuals enrolled, 1.72% of 15 393 individuals randomized to screening were diagnosed with AF compared with 1.59% of 15 322 individuals randomized to the control arm at 1-year follow-up (risk difference, 0.13% [95% CI, −0.16% to 0.42%]; Chart 18-5).
- Systematic reviews of screening:
  - A systematic review by the US Preventive Services Task Force of asymptomatic adults at least 65 years of age included 17 studies (135 300 individuals). Compared with no screening, systematic screening with ECG detected more new cases of AF (over 1 year, absolute increase from 0.6% [95% CI, 0.1%–0.9%] to 2.8% [95% CI, 0.9%–4.7%]). However, the systematic ECGs did not detect more cases than pulse palpation. Furthermore, none of the studies compared systematic screening and usual care, and none examined health outcomes.[135]
  - The US Preventive Services Task Force has concluded that evidence for screening for AF in individuals ≥50 years of age remains lacking.[136]
  - A systematic review of 19 studies from 2007 to 2018 identified 24 single-time-point screening studies; 141 220 participants were included, of whom 1539 had newly detected AF. The detection rate adjusted for age and sex was 1.44% (95% CI, 1.13%–1.82%) in those ≥65 years of age and 0.41% in individuals <65 years of age. The study included low-, middle-, and high-income countries but did not identify geographic region variation in detection rates. The authors estimated that the number needed to screen to identify 1 treatable new AF case varied by age: 83 for ≥65 years of age, 926 for 60 to 64 years of age, and 1089 for <60 years of age.[137]
  - Another systematic review included 25 published studies from 2000 to 2015 involving 88 786 participants. The investigators reported that the incidence of newly detected AF was 1.5% (95% CI, 1.1%–1.8%) and was higher with systematic screening compared with opportunistic screening (1.8% [95% CI, 1.4%–2.3%] versus 1.1% [95% CI, 0.6%–1.6%]) and with multiple (2.1% [95% CI, 1.5%–2.8%]) versus single-time-point (1.2% [95% CI, 0.8%–1.6%]) rhythm assessments.[138]
  - A meta-analysis of 9 RCTs (N=85 209) examining systematic screening, opportunistic screening, and no screening determined that any AF screening (systematic or opportunistic) was associated with higher detection of AF (1.8% versus 1.3%; RR, 2.10 [95% CI, 1.20–3.65]) than no screening.[139]
- Wearable, commercially available technology:
  - In the largest study to date, investigators recruited 419 297 Apple Watch owners to participate in a monitoring study to detect possible AF. The median follow-up was 117 days, during which 0.52% (n=2161) received irregular pulse warnings; 450 participants returned an electrocardiographic patch (on average 13 days after notification) that detected AF in 34%.[140]
  - To date, no studies have demonstrated that AF screening reduces mortality or incidence of thromboembolic complications. The minimum duration of AF episodes required to increase risk for stroke is unknown. However, longer episode duration is associated with increased thromboembolic risk (Chart 18-6); the threshold varies depending on the presence of other stroke risk factors.[141]

### *Family History and Genetics*

- AF is found to be a common presentation in certain monogenic genetic cardiomyopathies, for examples, in individuals with *PRKAG2*- or *TTN*-related cardiomyopathy.[142,143]
- A recent prospective observational cohort study has noted that among individuals with early-onset AF (<66 years of age), the prevalence of disease-associated pathogenic/likely pathogenic variants in cardiomyopathy and arrhythmia-associated genes was 10.1%.[144] The prevalence of the pathogenic/likely pathogenic variants was highest among patients with an AF diagnosed before 30 years of age (≈17%) and was lowest among those diagnosed with AF after 60 years of age (≈7%).[144]
- A prospectively enrolled AF registry revealed that individuals with early-onset AF in the absence of structural HD had a 3-fold adjusted odds of having a first-degree relative with AF (aOR, 3.02 [95% CI, 1.82–4.95]; $P<0.001$) compared with individuals with AF without early-onset AF. Higher odds of having a proband with AF in the setting of early-onset AF were observed in individuals of African (OR, 2.69 [95% CI, 1.06–6.91]), Hispanic (OR, 9.25 [95% CI,

2.37–36.34]), and European (OR, 2.51 [95% CI, 1.29–4.87) descent.[145]

- A Taiwanese population–based study (>23 million people) reported that a history of a first-degree relative with AF was associated with a 1.92-fold (95% CI, 1.84–1.99) increased risk of newly diagnosed AF. Those investigators estimated that 19.9% of the increased risk was attributable to genetic (heritability) factors, with the remaining risk related to shared (3.5%) and nonshared (76.6%) environmental factors.[146]
- Many common genetic variants have been identified as associated with AF. A GWAS that included >65 000 patients with AF reported 97 AF-associated loci, including the most consistent genetic locus *PITX2*, 67 of which were novel in combined-ancestry analyses.[147] Another GWAS of >1 000 000 individuals identified 111 independent genes associated with AF, many of which are near deleterious mutations that cause more serious heart defects or near genes important for striated muscle function and integrity.[148]
- Whole-exome/genome sequencing studies have identified rare mutations in additional genes associated with AF, including *MYL4*,[149] and loss-of-function mutations in *SCN4B* and *KCNA5*, a conserved gene that encodes the voltage-gated Kv1.5 potassium channel.[150,151] Loss-of-function variants in the titin gene have been associated with early-onset AF.[152,153]
- Combinations of these genetic variants for AF are predictive of lifetime risk of AF. Investigators in the FHS examined the lifetime risk of AF at 55 years of age using both clinical risk score and GRS (derived from thousands of variants associated with AF in the UK Biobank). Individuals within the lowest tertile of clinical risk score and GRS had a lifetime risk of AF of 22.3% (95% CI, 15.4%–29.1%), whereas those in the highest tertile of clinical risk score and GRS had a lifetime risk of 48.2% (95% CI, 41.3%–55.1%).[60]
- Proteomic studies have identified proteins identified with incident AF. For example, in the ARIC study, 4668 participants were followed up for 5.7±1.7 years, during which 585 developed AF. After adjustment for clinical factors, NT-proBNP was associated with the risk of incident AF (HR, 1.82 [95% CI, 1.68–1.98]; $P=2.91\times10^{-45}$ per doubling of NT-proBNP). After further adjustment for medication use and GFR, the study identified 17 proteins significantly associated with incident AF. The study implicated matrix metalloprotease inhibition as the foremost canonical pathway in AF pathogenesis.[154]
- It is unclear whether genetic markers of AF could improve risk prediction for AF over models that include only clinical factors.[115] A study of 229 incident AF cases and >10 000 controls found that the net classification index for an AF GRS for incident AF was 10.0% (95% CI, 4.2%–15.7%) with slightly higher classification ability in early-onset AF cases (net reclassification index, 14.8% [95% CI, 3.8%–25.7%]) and in late-onset cases (net reclassification index, 10.4% [95% CI, 4.1%–16.7%]).[155] In contrast, a study of 5 cohorts with 18 191 individuals found that a GRS associated with incident AF added only marginally to clinical risk prediction (maximum change in C statistic from clinical score alone, 0.009–0.017).[156]
- A multi-ancestry meta-analysis of GWASs for AF including >1 000 000 individuals led to the discovery of 35 new loci. *IL6R* has been identified as a putative casual gene for AF based on transcriptome-wide association analysis indicating the role of the immune response in the pathogenesis of AF. A GRS developed from the multiancestry GWAS meta-analysis predicted the risk of cardiovascular and stroke mortality. A 1-SD increase in GRS was associated with increased odds of cardioembolic stroke [OR, 1.36 (1.13–1.63)] in individuals without diagnosed AF.[157]
- GWASs also have been conducted with variation in electrocardiographic traits used as a phenotype (ie, QRS duration and area) and have identified novel genetic variants associated with these traits that also are associated with cardiac conduction, arrhythmias, and other cardiovascular end points.[158] A GWAS meta-analysis of PR interval in 293 051 multiancestry individuals found 202 genomic loci associated with PR interval, with enrichment of cardiac muscle development/contractile and cytoskeletal genes.[159] A GRS of PR interval–associated variants was found to be associated with a higher risk of atrioventricular block (OR per SE of GRS, 1.11; $P=7\times10^{-8}$) and pacemaker implantation (OR, 1.06; $P=1.5\times10^{-4}$) and reduced risk of AF (OR, 0.95; $P=4.3\times10^{-8}$).
- In a study of 19 709 participants from ARIC, MESA, and CHS, mitochondrial DNA copy number, a marker of mitochondrial dysfunction, was associated with incident AF with participants with the lowest quintile of mitochondrial DNA copy number having an overall 13% increased risk (95% CI, 1%–27%) of AF compared with those in the highest quintile in adjusted models.[160]

## Prevention: Observational Data

### Primary Prevention of AF: Observational Data

- An observational prospective Swedish study revealed that individuals having bariatric surgery had a 29% lower (HR, 0.71 [95% CI, 0.60–0.83]; $P<0.001$) risk of developing AF in a median 19-year follow-up than matched referents.[161] A registry-based study

that matched individuals with obesity and diabetes undergoing bariatric surgery to those not having surgery reported a 41% reduced risk of AF (HR, 0.59 [95% CI, 0.44–0.78]) and concomitant HF and AF (HR, 0.23 [95% CI, 0.12–0.46]) after bariatric surgery during a mean 4.5-year follow-up.[162]

### *Secondary Prevention of AF: Observational Data*

- Data support the importance of risk factor modification for secondary prevention of AF recurrence and improved symptoms.
  - Overweight and obese individuals with symptomatic AF who opted to participate in weight loss and aggressive risk factor management interventions (n=208; mean follow-up, 47 months) had fewer hospitalizations (0.74±1.3 versus 1.05±1.60), cardioversions (0.89±1.50 versus 1.51±2.30), and ablation procedures (0.60±0.69 versus 0.72±0.86) than their counterparts who declined enrollment (n=147; mean follow-up, 49 months). Participation in risk factor management was associated with a predicted 10-year cost savings of $12 094 per patient.[163]
- Randomized data supporting the role of CPAP in primary prevention of AF in individuals with SDB are limited, and most attention has focused on secondary prevention.[164,165] In a small, parallel-arm randomized clinical trial (n=109), there was no difference in percent time in AF between intervention participants randomized to CPAP use and those receiving usual care (difference in time in AF between intervention and control, −0.6% [95% CI, −2.1 to 0.9]).[165]
- A study of 2 national Canadian primary care audits observed that of 11 264 individuals with AF, 84.3% were eligible for at least 1 evidence-based cardiovascular therapy. The proportions receiving evidence-based therapy varied by diagnosis: 40.8% of those with CAD, 48.9% of those with diabetes, 40.2% of those with HF, and 96.7% of those with hypertension.[167]

## *Prevention: Randomized Data*

### *Primary Prevention of AF: Randomized Data*

- In the ACCORD study (N=10 082), intensive glycemic control was not associated with reduced occurrence of incident AF (*P*=0.52).[168]
- Meta-analyses have suggested that BP lowering might be useful in the prevention of AF in trials of hypertension, after MI, in HF, and after cardioversion.[169] An analysis of SPRINT participants without AF at trial initiation (n=8022) determined that those randomized to the intensive BP lowering arm (SBP <120 mm Hg) had decreased AF risk (HR, 0.74 [95% CI, 0.56–0.98]) over a median 3.8-year follow-up compared with those randomized to the standard BP lowering arm (SBP <140 mm Hg).[170]
- In a large, prospective Norwegian cohort (N=43 602), individuals with BMI 25.0 to 29.9 kg/m$^2$ or ≥30 kg/m had increased risk of AF over a mean 8.1-year follow-up (HR, 1.18 [95% CI, 1.03–1.35] and HR, 1.59 [95% CI, 1.37–1.84], respectively) than those with BMI <25.0 kg/m$^2$.[171] High levels of physical activity slightly attenuated the association of obesity and AF.
- A follow-up examination of the REGARDS study (n=8977) did not identify an association between Mediterranean diet score (OR, 1.03 [95% CI, 0.95–1.11] per SD) or plant-based dietary pattern (OR, 1.03 [95% CI, 0.94–1.12] per SD) and AF.[172] In addition, less healthy eating was not associated with incident AF during an average 9.4-year follow-up.
- A meta-analysis of 14 studies (N=2883) observed that pretreatment with statins reduced the risk of postoperative AF (OR, 0.71 [95% CI, 0.60–0.85]) after cardiothoracic surgery.[173] However, sensitivity analysis excluding studies identified as having bias did not demonstrate that initiation of statins before cardiothoracic surgery was associated with reduced likelihood of postoperative AF (OR, 0.87 [95% CI, 0.71–1.07]).

### *Secondary Prevention of AF: Randomized Data*

- An Australian multisite, open-label, controlled trial randomized 140 adults who consumed ≥10 drinks of alcohol per week with a history of AF and in sinus rhythm at baseline either to abstain from alcohol or to continue their usual alcohol consumption.[174] AF recurred in 53% of the abstinence group and 73% of the control group. Compared with the control group, the abstinence group had a significantly longer duration without AF recurrence (HR, 0.55 [95% CI, 0.36–0.84]; *P*=0.005) and significantly lower AF burden (median percent time in AF, 0.5% versus 1.2%; *P*=0.01).
- An open-label, parallel-group RCT randomized individuals with PAF and AHI ≥15 to 5 months of treatment with CPAP (n=55) or control (n=54).[165] The adjusted between-group difference in AF burden as measured by loop recorder was −0.63 (95% CI, −2.55 to 1.30).
- A multicenter, randomized, open-label trial randomized individuals with AF after cardioversion to intensified pharmacological therapies and cardiac rehabilitation (n=119) or conventional therapy (n=126).[175] At the 1-year follow-up, 75% of intervention participants were in sinus rhythm (determined by 7-day Holter monitoring) compared with 63% of conventional therapy participants (OR, 1.77 [95% CI, 1.02–3.05]).

## *Awareness*

- An analysis in REGARDS reported that individuals not aware of their AF diagnosis (n=150) had a 94%

higher risk of mortality in follow-up compared with individuals who were aware (n=2058).[176]
- A study from Kaiser Permanente in California examined the relationship between AF diagnosis (2006–2009) and self-report questionnaire data (2010). Of the >12 000 individuals with diagnosed AF, 14.5% were unaware of their diagnosis, and 20.4% had limited health literacy. In adjusted analyses, limited health literacy was associated with a lack of awareness of AF diagnosis (literacy PR, 0.96 [95% CI, 0.94–0.98]).[177]

### Treatment and Control

#### Anticoagulation Undertreatment

- The GWTG–Stroke program conducted a retrospective analysis consisting of 1622 hospitals and 94 474 patients with AIS in the setting of known AF from 2012 to 2015. In that analysis, 79 008 patients (83.6%) were not receiving therapeutic anticoagulation: 13.5% had a subtherapeutic international normalized ratio; 39.9% were receiving antiplatelet treatment only; and 30.3% were not receiving any antithrombotic therapy. In adjusted analyses, compared with patients receiving no antithrombotic medications, patients receiving antecedent therapeutic warfarin, non–vitamin K antagonist oral anticoagulant drugs, or antiplatelet therapy had lower odds of moderate or severe stroke (aOR, 0.56 [95% CI, 0.51–0.60], 0.65 [95% CI, 0.61–0.71], and 0.88 [95% CI, 0.84–0.92], respectively) and lower in-hospital mortality.[178]
- In the NCDR PINNACLE registry of outpatients with AF:
  - Fewer than half of high-risk patients, defined as those with a $CHA_2DS_2$-VASc score ≥4, received an oral anticoagulant prescription.[179]
  - Between 2008 and 2014, in individuals with a $CHA_2DS_2$-VASc score >1, direct anticoagulant use increased from 0% to 24.8%, and use of warfarin decreased from 52.4% to 34.8%. Although the prevalence of oral anticoagulation treatment increased from 52.4% to 60.7% over the time period, there are substantive opportunities to improve oral anticoagulation for stroke prevention in individuals with AF.[180]
  - In the PINNACLE registry, females were significantly less likely to receive oral anticoagulation at all levels of $CHA_2DS_2$-VASc scores (56.7% versus 61.3%; $P<0.001$).[181]
  - An analysis in the PINNACLE registry also reported that receipt of warfarin compared with a DOAC varied significantly by type of insurance: Patients with military, private, and Medicare insurance were more likely to receive newer anticoagulants than individuals with Medicaid or other insurance.[182]
- The GLORIA-AF Registry reported North American anticoagulation patterns in 3320 patients with AF between 2011 and 2014, observing that factors associated with increased likelihood of receiving indicated oral anticoagulant prescription included nonparoxysmal AF (OR, 2.02), prior stroke/TIA (OR, 2.00), specialist care (OR, 1.50), more concomitant medications (OR, 1.47), commercial insurance (OR, 1.41), and HF (OR, 1.44), whereas factors inversely related were antiplatelet drugs (OR, 0.18), prior falls (OR, 0.41), and prior bleeding (OR, 0.50).[183]

#### Disparities in Treatment

#### (See Chart 18-7)

- Racial differences in access to oral anticoagulation have been identified.
  - In a 5% sample of Medicare beneficiaries, NH Black individuals were significantly less likely to receive oral anticoagulation (OR, 0.84 [95% CI, 0.78–0.91]) than NH White individuals. There was no difference between Hispanic individuals (OR, 0.92 [95% CI, 0.83–1.01]) and NH White individuals. Among initiators of oral anticoagulation, DOAC use was low (35.8% NH White individuals, 29.3% NH Black individuals, 40.0% Hispanic individuals). NH Black individuals were less likely to initiate DOACs than NH White individuals (OR, 0.75 [95% CI, 0.66–0.85]); in contrast, the odds of DOAC initiation did not differ between Hispanic and NH White individuals (OR, 1.02 [95% CI, 0.88–1.18]).[184]
  - An analysis of the ORBIT-AF II population (N=12 417), of whom 646 (5.2%) were of Black race and 671 (5.4%) of Hispanic ethnicity, determined in multivariable-adjusted analysis that Black individuals (OR, 0.75 [95% CI, 0.56–0.99) were significantly less likely to receive oral anticoagulation than White individuals.[185] This difference was attenuated by adjustment for social and economic factors (OR, 0.78 [95% CI, 0.59–1.04]). The difference between Hispanic and White individuals was not significant.
  - An analysis of the GWTG–AFIB registry (N=69 553) determined that Black individuals were less likely than White individuals to be discharged on oral anticoagulation (OR, 0.75 [95% CI, 0.68–0.84]).[186] In 16 307 individuals with 1-year follow-up data, the risks of bleeding (HR, 2.08 [95% CI, 1.53–2.83]), stroke (HR, 2.07 [95% CI, 1.34–3.20]), and mortality (HR, 1.22 [95% CI, 1.02–1.47]) were higher in Black individuals compared with White individuals.
  - In the Florida Puerto Rico AF Stroke Study, a registry of individuals with ischemic stroke and AF (N=24 040), Black individuals were more likely to receive warfarin at hospital discharge after stroke

(OR, 1.22 [95% CI, 1.07–1.40]) compared with references of White race.[187] In contrast, Black race was not associated with likelihood of receipt of a DOAC compared with White race. Likewise, Hispanic ethnicity was not associated with likelihood of receipt of warfarin or DOAC compared with White race.

- An administrative data analysis of individuals in Ontario, Canada, determined that residence in the fifth quintile of neighborhood-based material deprivation was associated with decreased 1-year likelihood of cardiology visits (HR, 0.84 [95% CI, 0.82–0.86]), anticoagulation (HR, 0.97 [95% CI, 0.95–0.98]), receipt of an echocardiogram (HR, 0.97 [95% CI, 0.96–0.99]), cardioversion (HR, 0.80 [95% CI, 0.76–0.84]), or ablation (HR, 0.45 [95% CI, 0.30–0.67]; Chart 18-7).[106]

### *Role of Coordinated Care*

- A systematic review and meta-analysis identified 3 studies of coordinated systems of care that included 1383 patients.[188] The investigators reported that AF integrated care approaches were associated with reduced all-cause mortality (OR, 0.51 [95% CI, 0.32–0.80]; *P*=0.003) and cardiovascular hospitalizations (OR, 0.58 [95% CI, 0.44–0.77]; *P*=0.0002) but not with cerebrovascular events or hospitalizations related to AF.

## Mortality

### *2016 ICD-9 427.3; ICD-10 I48.*

*(See Charts 18-8 and 18-9)*

- In 2021, AF was the underlying cause of death in 28 037 people and was listed on 232 030 US death certificates (any-mention mortality; unpublished NHLBI tabulation using NVSS[189]).
- The AAMR attributable to AF was 7.1 per 100 000 people in 2021 (unpublished NHLBI tabulation using CDC WONDER[190]).
- Although there was significant between-study heterogeneity (*P*<0.001), a meta-analysis of 30 studies (N=4 371 714) identified that the adjusted risk of death was significantly higher in females with AF than in males (RR, 1.12 [95% CI, 1.07–1.17]).[191]
- The GBD Study indicates increases in sex-specific, age-standardized mortality estimates across US states between 1990 and 2017.[192] The greatest percentage increases were as follows: for males, Mississippi (+26.4%), Oklahoma (+24.9%), Idaho (+24.8%), and New Hampshire (+22.4%); and for females, Oregon (+54.6%), Montana (+46.7%), Utah (+42.5%), and Nebraska (+40.5%; Chart 18-8).
- An observational study of Olmsted County, Minnesota, residents with first diagnosis of AF or atrial flutter between 2000 and 2010 had a high early mortality compared with individuals of similar age and sex; the standardized mortality ratio was 19.4 (95% CI, 17.3–21.7) in the first 30 days and 4.2 (95% CI, 3.5–5.0) for days 31 to 90. Survival within the first 90 days did not change over time (aHR, 0.96 [95% CI, 0.85–1.31] for 2010 versus 2000).[193]
- The association of AF with mortality in the FHS has remained stable over time. In the FHS, the HR for the association of AF with all-cause mortality was 1.9 (95% CI, 1.7–2.2) between 1972 and 1985, 1.4 (95% CI, 1.3–1.6) between 1986 and 2000, and 1.7 (95% CI, 1.5–2.0) between 2001 and 2015 ($P_{trend}$=0.70).[194]
- From 2006 to 2015, all-cause mortality events decreased in individuals diagnosed with AF (N=679 416) in the Korean National Insurance Service (Chart 18-9).[53] The 2-year risk of all-cause mortality decreased by 30% for individuals diagnosed in 2013 relative to those diagnosed in 2006 (HR, 0.70 [95% CI, 0.68–0.72]).
- AF is also associated with increased mortality in subgroups of individuals, including the following:
  - Individuals with other cardiovascular conditions and procedures, including HCM,[195,196] MI,[197] pre-CABG,[198] post-CABG[199,200] (both short term[199] and long term[199,200]), aortic valve replacement (transcatheter or surgical),[201,202] PAD,[203,204] and stroke.[205]
  - Individuals with AF have increased mortality with concomitant HF, including HFpEF[206] and HFrEF.[206] In a meta-analysis that examined the timing of AF in relation to HF onset with regard to mortality, the risk of death associated with incident AF was higher (RR, 2.21 [95% CI, 1.96–2.49]) than that associated with prevalent AF (RR, 1.19 [95% CI, 1.03–1.38]; $P_{interaction}$<0.001).[207] A population-based analysis of administrative data (N=52 447) determined that individuals with AF had 3.3-fold increased 3-year mortality risk after incident HF (95% CI, 3.08–3.43).[208]
  - AF is also associated with an increased risk of death in individuals with other conditions, including diabetes,[168,209] sepsis,[210] and critical illness in the ICU[211]; in individuals after primary PCI[212]; and in individuals ≥80 years of age with hypertension.[213]
- In the ARIC study, the rate difference for all-cause mortality for individuals with versus without AF per 1000 person-years was 106.0 (95% CI, 86.0–125.9) in Black participants, which was higher than the 55.9 (95% CI, 48.1–63.7) rate difference in mortality observed for White participants.[214]
- There was substantial variation in mortality with AF in US counties from 1980 to 2014.[215] Investigators estimated that there were ≈22 700 (95% UI, 19 300–26 300) deaths attributable to AF in

2014 and 191 500 (95% UI, 168 000–215 300) YLL. In an examination of county-level data, the age-standardized AF mortality rates were 5.6 per 100 000 for the 10th percentile and 9.7 per 100 000 for the 90th percentile. The counties with age-standardized death rates >90th percentile were clustered in Oregon; California; Utah; Idaho; northeastern Montana; areas east of Kansas City, MO; and southwest West Virginia.[215]

- In a study using the NIS for the period of 2010 to 2015 (N=3 264 258), adjusted in-hospital mortality in the setting of AF was higher (4.8% versus 4.3%; *P*=0.02) among Medicaid beneficiaries than among individuals with private insurance. Medicaid recipients were significantly less likely to be discharged to home (55.3%) than those with private insurance (61.3%) and were noted to have longer median length of stay (5 days [IQR, 3–9 days]) compared with those with private insurance (4 days [IQR, 2–8 days]).[216]
- Serial cross-sectional analyses of annual US death certificate data for cardiovascular mortality identified an increase in AAMR per 100 000 population in those diagnosed with AF from 18.0 (95% CI, 17.8–18.2) in 2011 to 22.3 (95% CI, 22.0–22.4) in 2018.[217]
- Investigators conducted multivariable cross-sectional analyses of the NIS between 2012 and 2014 (N=248 731) and observed that patients admitted to rural hospitals (n=29 785) had a 17% higher risk of death than those admitted to urban hospitals (OR, 1.17 [95% CI, 1.04–1.32]).[218]
- AF has been associated with increased mortality in patients with COVID-19. A meta-analysis of studies published in 2020 including 23 studies and 108 745 patients with COVID-19 showed that AF was associated with increased mortality (pooled effect size, 1.14 [95% CI, 1.03–1.26]).[219]
- In a Swedish study based on 75 primary care centers, an adjusted analysis of patients diagnosed with AF revealed that males living in low-SES neighborhoods were 49% (HR, 1.49 [95% CI, 1.13–1.96]) more likely to die than their counterparts living in middle-income neighborhoods over a median follow-up of 3.5 years (IQR, 1.5–5.5 years). The results were similar in models that additionally adjusted for anticoagulant and statin treatment (HR, 1.39 [95% CI, 1.05–1.83]).[220] In another study from the same group, unmarried and divorced males and males with lower educational attainment with AF had a higher risk of mortality than their married and better-educated male counterparts.[221]

## Complications

### Extracranial Systemic Embolic Events

- Among 14 941 participants in the ARIC study, incident AF was associated with an increased risk of extracranial systemic embolic events (HR, 3.58 [95% CI, 2.57–5.00]) after adjustment for covariates.[222] This association was stronger in females (HR, 5.26 [95% CI, 3.28–8.44]) than in males (HR, 2.68 [95% CI, 1.66–4.32]).
- In the ARIC study (N=14 941), incident AF was associated with adjusted increased risk of extracranial systemic emboli (HR, 3.58 [95% CI, 3.28–8.44]) compared with those without AF.[222] Risk of embolism increased with higher CHADS-VASc score (HR per 1-point increase, 1.24 [95% CI, 1.05-1.47]).

### Stroke

- A systematic review of prospective studies found wide variability in stroke risk between studies and between patients with AF, ranging from 0.5%/y to 9.3%/y.[223]
- Before the widespread use of anticoagulant drugs, after accounting for standard stroke risk factors, AF was associated with a 4- to 5-fold increased risk of ischemic stroke. Although the RR of stroke associated with AF (≈3- to 5-fold increased risk) has not varied substantively with advancing age, the proportion of strokes attributable to AF has increased significantly. In the FHS, AF accounted for ≈1.5% of strokes in individuals 50 to 59 years of age and ≈23.5% in those 80 to 89 years of age.[224]
- In Medicare analyses that were adjusted for comorbidities, Black (HR, 1.46 [95% CI, 1.38–1.55]; *P*<0.001) and Hispanic (HR, 1.11 [95% CI, 1.03–1.18]; *P*<0.001) people had a higher risk of stroke than White people with AF.[225] The increased risk persisted in analyses adjusted for anticoagulant therapy status. Additional analyses from the Medicare registry demonstrated that the addition of Black race to the $CHA_2DS_2$-VASc scoring system significantly improved the prediction of stroke events among patients with newly diagnosed AF who were ≥65 years of age.[226]
- In an analysis of individuals with AF receiving care in a multihospital health system, Black individuals with AF were more likely to be younger and female and to have more cardiovascular risk factors than White individuals with AF. In addition, in adjusted analyses, compared with White participants with AF, Black participants with new-onset AF were more likely to have an ischemic stroke precede (OR, 1.37 [95% CI, 1.03–1.81]) or follow (HR, 1.67 [95% CI, 1.30–2.14]) the diagnosis of AF. The rate of ischemic stroke per year after AF diagnosis was 1.5% (95% CI, 1.3%–1.8%) in White participants and 2.5% (95% CI, 2.1%–2.9%) in Black participants.[227]
- In patients with COVID-19 in a global database, risk of ischemic stroke and other thromboembolic complications was higher in those with AF compared

with those without AF (9.9% versus 7.0%; RR, 1.41 [95% CI, 1.26–1.59]).[228]

- A meta-analysis that examined stroke risk by sex and presence of AF reported that AF conferred a multivariable-adjusted 2-fold stroke risk in females compared with males (RR, 1.99 [95% CI, 1.46–2.71]); however, the studies were noted to have significant heterogeneity.[191]

### *Cognition and Dementia*

- A meta-analysis of 11 prospective studies including 112 876 participants with normal baseline cognition and without acute stroke reported an adjusted 34% (HR, 1.34 [95% CI, 1.24–1.44]) higher incidence of dementia in individuals with AF compared with those without AF.[229] Another meta-analysis included >2 million participants in 14 observational studies and 2 randomized studies and observed a similar increased risk of incident dementia (HR, 1.36 [95% CI, 1.23–1.51]; $P<0.0001$).[230] A third meta-analysis of 6 studies including ≈1.6 million individuals determined that the association of AF varied by age (RR, 1.06 [95% CI, 0.55–2.06] in those <65 years of age and RR, 1.50 [95% CI, 1.00–2.26] in those <70 years of age).[231]
- In a multicenter study of individuals with diagnosed AF (mean, 73 years of age) from Switzerland, among 1390 patients without a history of stroke or TIA, clinically silent infarcts were observed in 245 patients (18%) with small noncortical infarcts and 201 (15%) with large noncortical or cortical infarcts according to brain MRIs.[232] Furthermore, in adjusted analyses of all the vascular brain features, large noncortical or cortical infarcts had the strongest association with reduced Montreal Cognitive Assessment score (β=−0.26 [95% CI, −0.40 to −0.13]; $P<0.001$), even when restricted to individuals with clinically silent infarcts.
- In the REGARDS study, participants with self-reported or ECG-ascertained AF had significantly lower scores on cognitive testing compared with those without (eg, Montreal Cognitive Assessment, Word List Learning, and Delayed Recall tasks). Over 8.1 mean years of follow-up, declines in Word List Learning scores were steeper in those with AF compared with those without AF.[233] None of the other cognitive measures showed a significant decline in those with and without AF.
- An administrative study in the United Kingdom examined oral anticoagulation and risk of dementia and cognitive impairment in individuals with AF. DOAC users were significantly less likely to receive a diagnosis of dementia (HR, 0.84 [95% CI, 0.73–0.98]) or MCI (HR, 0.74 [95% CI, 0.65–0.84]) than those treated with a vitamin K antagonist over 501 days (IQR, 199–978 days) of follow-up observation.[234]

### *Physical Disability and Subjective Health*

- In systematic reviews of published studies (including prospective and cross-sectional studies), AF has been associated with physical disability, poor subjective health,[235] and diminished quality of life.[236]
- Females with AF have consistently been demonstrated to have lower quality of life with AF than males. In the ORBIT-AF Registry, females had significantly lower AF-specific quality of life scores (mean, 80; IQR, 62–92) compared with males (mean, 83; IQR, 69–94).[237] A smaller, single-center study (N=339) identified that females with AF reported worse physical and social function than males with the condition.[238]

### *Falls*

- AF has been associated with increased risk of falls. A meta-analysis of 7 studies (N=36 444) concluded that individuals with AF have 1.2-fold increased risk of falls (OR, 1.20 [95% CI, 1.07–1.33]) relative to those without AF. Heterogeneity of studies was limited ($I^2$=37%).[239]

### *Heart Failure (See Chart 18-10)*

- AF and HF share many antecedent risk factors, and ≈40% of people with either AF or HF will develop the other condition.[81,240]
- In the community, estimates of the incidence of HF in individuals with AF ranged from 3.3[240] to 5.8[241] per 100 person-years of follow-up. In Olmsted County, Minnesota, in individuals with AF, the incidence of HFpEF was 3.3 per 100 person-years of follow-up (95% CI, 3.0–3.7), which was more common than HFrEF (2.1 [95% CI, 1.9–2.4]).[241]
- A study of Medicare beneficiaries (N=39 710) examined the relationship between AF burden and new-onset HF, HF hospitalization, and mortality in those with newly implanted cardiac devices and prevalent AF. A 10% increase in burden of AF at 1 year after device implantation was associated with new HF (HR, 1.09 [95% CI, 1.06–1.12]) and mortality (HR, 1.05 [95% CI, 1.01–1.10]). Among those with prevalent HF, a 10% increased AF burden was associated with HF hospitalization (HR, 1.05 [95% CI, 1.04–1.06]) and mortality (HR, 1.06 [95% CI, 1.05–1.08]).[242]
- An analysis in the REGARDS study (N=25 787) determined that cohort participants with AF (n=1896) had multivariable-adjusted increased risk of HFrEF (HR, 1.87 [95% CI, 1.38–2.54]) and HFpEF (HR, 1.65 [95% CI, 1.20–2.28]) over a 14-year follow-up (Chart 18-10).[243]
- A meta-analysis of 9 studies reported that individuals with AF have a 5-fold increased risk of HF (RR, 4.62 [95% CI, 3.13–6.83]).[244]

### *Myocardial Infarction*

- A meta-analysis of 16 cohort studies reported that AF was associated with a 1.54 (95% CI, 1.26–1.85) increased risk of MI in follow-up.[244]
- Both REGARDS[245] and ARIC[246] observed that the risk of MI after AF was higher in females than in males.
- For individuals with AF in REGARDS,[245] CHS,[247] and ARIC,[214] a higher risk of MI was observed in Black than White people.
- In ARIC, AF as a time-varying independent variable was associated with a 63% increased risk of MI (HR, 1.63 [95% CI, 1.32–2.02]). In further analysis, AF was associated with an adjusted increased risk of NSTEMI (HR, 1.80 [95% CI, 1.39–2.31]) but not STEMI (HR, 0.49 [95% CI, 0.18–1.34]; *P* for comparison of HR=0.004).[246]

### *Chronic Kidney Disease*

- In a health plan registry of people with CKD (N=206 229), new-onset AF (n=16 463) was associated with an adjusted 1.67-fold (95% CI, 1.46–1.91) increased risk of developing ESRD compared with no AF (74 versus 64 per 1000 person-years of follow-up).[248]
- A multinational consortium of 81 cohorts (N=24 353 175) determined that in those with CKD (n=605 596), AF was associated with increased risk of requiring renal replacement therapy (n=93 600; HR, 1.37 [95% CI, 1.05–1.77]).[249]

### *SCD and VF*

- In a meta-analysis of 27 studies including 8401 individuals with AF and 67 608 controls without AF, AF was associated with a doubling in risk of sudden death (pooled RR, 2.04 [95% CI, 1.77–2.35]; *P*<0.01). When the meta-analysis was restricted to 7 studies that conducted multivariable analyses, AF remained associated with an increased risk of sudden death (pooled RR, 2.22 [95% CI, 1.59–3.09]; *P*<0.01).[250]
- An analysis of a French national database (N=3 381 472) determined that over a 5.4-year median follow-up (IQR, 5.0–5.8 years), individuals with AF had a greater multivariable-adjusted risk (HR, 1.17 [95% CI, 1.11–1.23]) for ventricular arrhythmias than those without AF.[251] A mediation analysis identified the odds of cardiac arrest mediated by AF-associated ventricular arrhythmias as an OR of 1.04 (95% CI, 1.04–1.04).

### *AF Type and Complications*

- A meta-analysis of 12 studies (N=99 996) reported that compared with paroxysmal AF, nonparoxysmal AF was associated with a multivariable-adjusted increased risk of thromboembolism (HR, 1.38 [95% CI, 1.19–1.61]; *P*<0.001) and death (HR, 1.22 [95% CI, 1.09–1.37]; *P*<0.001).[252]
- In the Canadian Registry of Atrial Fibrillation, 755 patients with paroxysmal AF were followed up for a median of 6.35 years. At 1, 5, and 10 years, 8.6%, 24.3%, and 36.3%, respectively, had progressed to persistent AF. Within 10 years, >50% of the patients had progressed to persistent AF or had died.[253]

### *Atrial Flutter Versus AF*

- Using a 5% sample of Medicare beneficiaries from 2008 to 2014, investigators identified 18 900 ischemic strokes among 318 138 individuals with AF and 14 953 with atrial flutter. The study reported the annual stroke rate to be 2.02% (95% CI, 1.99%–2.05%) in individuals with AF and 1.38% (95% CI, 1.22%–1.57%) in those with atrial flutter. After adjustment for demographics and vascular risk factors, the risk of stroke was significantly lower in individuals with atrial flutter than in those with AF (HR, 0.69 [95% CI, 0.61–0.79]).[254]
- A national Taiwanese study compared the prognoses of 175 420 individuals with AF and 6239 individuals with atrial flutter. Using propensity scoring, the study observed that compared with individuals with atrial flutter, those with AF had significantly higher incidences of ischemic stroke (1.63-fold [95% CI, 1.42–1.87]), HF hospitalization (1.70-fold [95% CI, 1.46–1.97]), and all-cause mortality (1.08-fold [95% CI, 1.03–1.13]).[255]

## ***Hospitalizations and Ambulatory Care Visits***

- According to HCUP data,[256] in 2020, there were 401 055 hospital discharges with AF and atrial flutter as the principal diagnosis (unpublished NHLBI tabulation).
- There were 8 365 000 physician office visits (NAMCS, unpublished NHLBI tabulation)[257] in 2019 and 664 947 ED visits in 2020 for AF and atrial flutter (HCUP,[256] unpublished NHLBI tabulation).
- Using cross-sectional data (2006–2014) from the HCUP's Nationwide ED Sample, the NIS, and the NVSS, investigators estimated that in 2014 AF listed as a primary diagnosis accounted for ≈599 790 ED visits and 453 060 hospitalizations, with a mean length of stay of 3.5 days (SE, 0.02 day). When AF listed as a comorbid condition was included, there were ≈4 million (3.6% of total) ED visits and 3.5 million (12.0% of total) hospitalizations.[258]
- A meta-analysis of 35 prospective studies including 311 314 patients with AF reported an all-cause hospital admission rate of 43.7 (95% CI, 38.5–48.9) per 100 person-years. In studies (n=24) that reported admission causes (n=234 028 patients with AF), cardiovascular hospitalizations were more frequent than noncardiovascular hospitalizations (26.3 [95% CI, 22.7–29.9] versus 15.7 [95% CI, 12.5–18.9], respectively).[259]

- A retrospective analysis of administrative data using MarketScan Research Databases (N=3 398 490) identified that individuals with AF (n=156 732) had 9 (95% CI, 8.96–9.12) ambulatory visits, 0.3 (95% CI, 0.33–0.34) inpatient admissions, and 2.7 (95% CI, 2.71–2.77) prescribed medications more than those without AF.[260] Among those with AF, patients living in rural areas had 1.99 fewer (95% CI, −2.26 to −1.71) and 0.05 more (95% CI, 0.02–0.8) emergency room visits than patients with AF living in metropolitan areas.

## Cost

- A study examining public and private health insurer records from 1996 to 2016 reported that AF was 33rd in spending for health conditions with an estimated $28.4 billion (95% CI, $24.6–$33.8 billion) in 2016 dollars.[261] The annualized rate of change standardized to the population for 2016 was 3.4%. The estimates varied by the following features:
  - Age group: <20 years, 0%; 20 to 64 years, 25.0%; and ≥65 years, 75.0%.
  - Type of payer: public insurance, 56.4%; private insurance, 36.9%; and out of pocket, 6.7%.
  - Type of care: ambulatory, 29.4%; inpatient, 29.8%; prescribed pharmaceuticals, 10.5%; nursing care facility, 15.3%; and ED, 5.1%.
- A systematic review that examined costs of ischemic stroke in individuals with AF included 16 studies from 9 countries. In international dollars adjusted to 2015 values, the analysis estimated that stroke-related health care costs were $8184, $12 895, and $41 420 for lower-middle–, middle-, and high-income economies, respectively.[262]
- Costs of AF have been estimated for higher-income countries. In Denmark, for example, investigators estimated that the 3-year societal costs of AF were approximately €20 403 to €26 544 per person and €219 to €295 million total.[263]

## Global Burden of AF

## (See Charts 18-11 and 18-12)

- Based on 204 countries and territories in 2021[264]:
  - The total number of global deaths estimated for AF/atrial flutter in 2021 was 0.35 (95% UI, 0.30–0.38) million, with 0.14 (95% UI, 0.13–0.15) million among males and 0.21 (95% UI, 0.17–0.24) million among females.
  - Age-standardized mortality estimated for AF was highest in Australasia followed by Western Europe. Mortality was lowest in high-income Asia Pacific (Chart 18-11).
  - Globally, 52.55 (95% UI, 43.49–63.74) million individuals had prevalent AF/atrial flutter in 2021, with 27.90 (95% UI, 22.90–33.83) million among males and 24.65 (95% UI, 20.28–29.94) million among females.
  - Age-standardized prevalence of AF was highest in high-income North America, Australasia, and Western Europe in 2021. North Africa and the Middle East had the lowest age-standardized prevalence rates (Chart 18-12).
- Investigators conducted a prospective registry of 15 400 patients with AF presenting to EDs in 47 countries. They observed substantial regional variability in annual AF mortality: South America (17%) and Africa (20%) had double the mortality rate of North America, Western Europe, and Australia (10%; $P<0.001$). In this cohort, HF deaths (30%) exceeded deaths attributable to stroke (8%).[265]

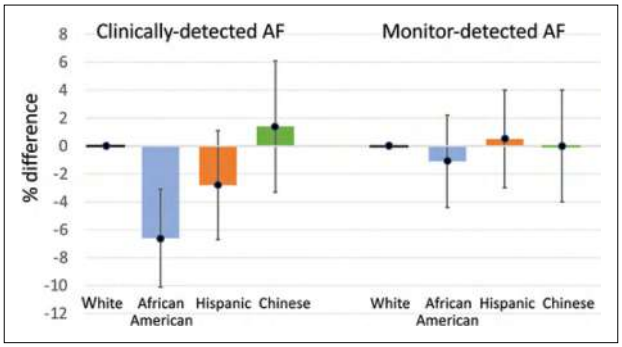



**Chart 18-1. Adjusted percent difference in AF prevalence compared with White individuals for clinically detected AF (2000–2018) and monitor-detected AF (2016–2018) in the MESA Study.**

Adjusted for age, sex, height, weight, treated hypertension, current smoking, diabetes, SBP, history of HF, and history of MI; estimates for monitor-detected AF are also adjusted for monitoring duration. Vertical lines indicate 95% CI.

AF indicates atrial fibrillation; HF, heart failure; MESA, Multi-Ethnic Study of Atherosclerosis; MI, myocardial infarction; and SBP, systolic blood pressure.

Source: Reprinted with permission from Heckbert et al.[52]



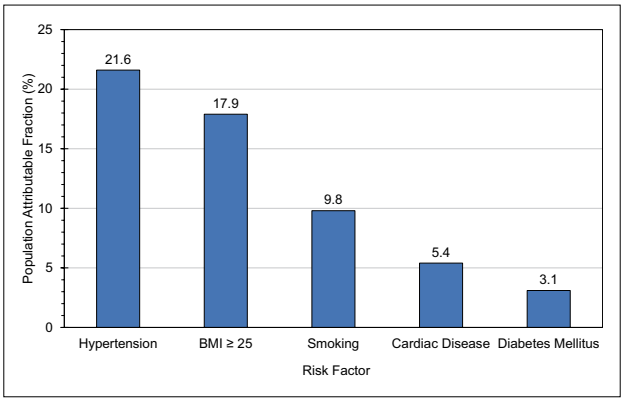



**Chart 18-3. PAF of major risk factors for AF in the ARIC study, 1987 to 2007.**

Cardiac disease includes a history of CAD or HF; smoking refers to current smoker.

AF indicates atrial fibrillation; ARIC, Atherosclerosis Risk in Communities; BMI, body mass index; CAD, coronary artery disease; HF, heart failure; and PAF, population attributable fraction.

Source: Data derived from Huxley et al.[266]

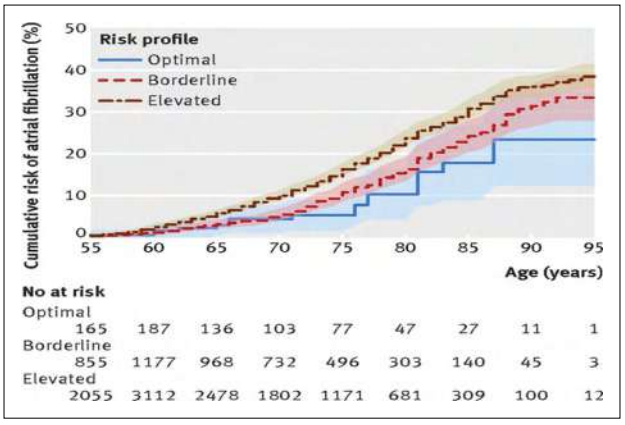



**Chart 18-2. Lifetime risk (cumulative incidence at 95 years of age) for AF at different ages (through 94 years of age), by sex in the FHS, 1968 to 2014.**

AF indicates atrial fibrillation; and FHS, Framingham Heart Study.

Source: Reprinted from Staerk et al.[61] Copyright © 2018, The Authors. Published on behalf of the Authors by the British Medical Group. This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build on this work noncommercially, and license their derivative works on different terms, provided the original work is properly cited and the use is noncommercial. See http://creativecommons.org/licenses/by-nc/4.0/.

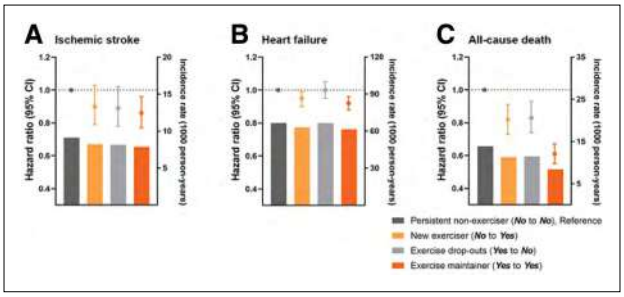



**Chart 18-4. Retrospective analysis conducted in the Korean National Health Insurance Service of individuals (N=66 692) with newly diagnosed AF who underwent self-reported exercise assessment 2 years before and after AF diagnosis, 2010 to 2016.**

**A**, Ischemic stroke. **B**, HF. **C**, All-cause death. HRs with 95% CIs for ischemic stroke, HF, and all-cause death according to the change in exercise status.[77] Bars denote weighted incidence rates; dots, HRs; and whiskers, 95% CIs computed by weighted Cox proportional hazards models with inverse probability of treatment weighting.

AF indicates atrial fibrillation; HF, heart failure; and HR, hazard ratio.

Source: Adapted from Ahn et al.[77] Copyright © 2021, The Authors. This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits noncommercial reuse, distribution, and reproduction in any medium, provided the original work is properly cited.

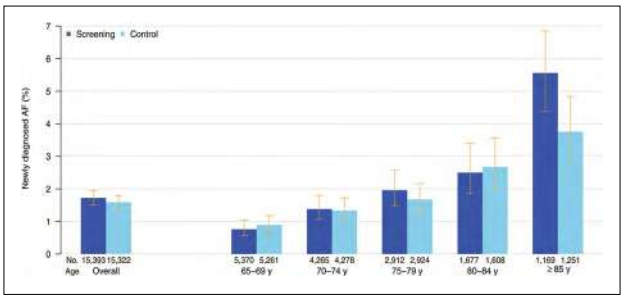



**Chart 18-5. Proportion of adults by age category with newly diagnosed AF by screening (n=15 393) at a primary care visit compared with controls (n=15 322) who were not screened in a single US health care system: VITAL-AF RCT.**
Error bars indicate 95% CI.
AF indicates atrial fibrillation; RCT, randomized controlled trial; and VITAL-AF, Screening for Atrial Fibrillation Among Older Patients in Primary Care Clinics.
Source: Reprinted with permission from Lubitz et al.[134]

| Maximum Daily AF Duration | CHA$_2$DS$_2$-VASc Score 0 (n=2922, 13.4%) | 1 (n=2151, 9.9%) | 2 (n=4554, 20.9%) | 3-4 (n=7164, 32.9%) | ≥5 (n=4977, 22.9%) |
|---|---|---|---|---|---|
| No AF (n=16815 (77.2%)) | 0.33% (40 events) | 0.62% (46 events) | 0.70% (95 events) | 0.83% (139 events) | 1.79% (157 events) |
| AF 6 min–23.5 h (n=3381 (15.5%)) | 0.52% (11 events) | 0.32% (4 events) | 0.62% (17 events) | 1.28% (42 events) | 2.21% (36 events) |
| AF >23.5h (n=1572 (7.2%)) | 0.86% (4 events) | 0.50% (3 events) | 1.52% (19 events) | 1.77% (28 events) | 1.68% (13 events) |

**Chart 18-6. Risk of stroke and systemic embolism in nonanticoagulated patients (N=21 768) by AF duration and CHA$_2$DS$_2$-VASc score from the Optum electronic health record deidentified database, 2007 to 2017.**
Stroke and systemic embolism rates over the 1% threshold are shaded red; those under the 1% threshold are shaded green.
AF indicates atrial fibrillation.
Source: Reprinted with permission from Kaplan et al.[141] Copyright © 2019 American Heart Association, Inc.

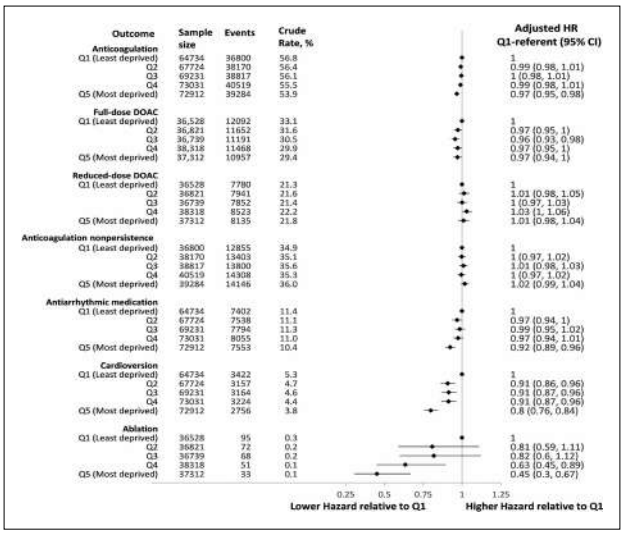



**Chart 18-7. Treatment and interventions related to AF within 1 year of incident diagnosis by quintile of material deprivation in the Canadian province of Ontario.**
HRs with 95% CIs for therapies and treatment relevant for AF. Material deprivation derived from Ontario, Canada, census tract-level indices (mean population, 400–700 people) with analysis conducted at the individual level.
AF indicates atrial fibrillation; DOAC, direct oral anticoagulant; HR, hazard ratio; and Q, quintile.
Source: Reprinted with permission from Abdel-Qadir et al.[106]

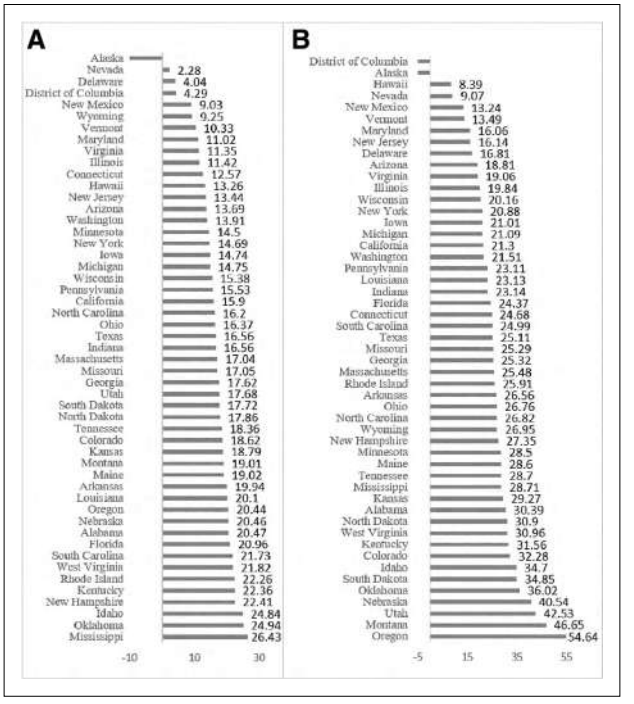



**Chart 18-8. Change in the age-standardized mortality rate per 100 000 population from 1990 to 2017, by US state in (A) males and (B) females.**
Data derived from the Global Burden of Disease Study, which identifies a single underlying cause of death.
Source: Reprinted from DeLago et al.[192] Copyright 2017, with permission from American College of Cardiology.

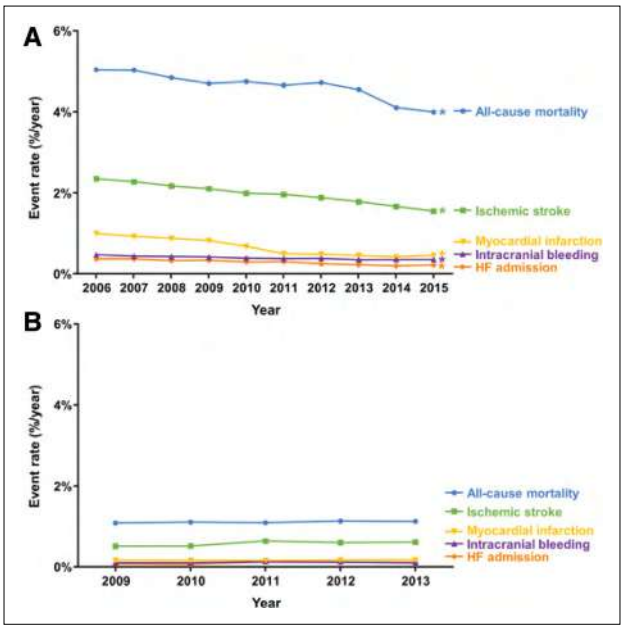



**Chart 18-9. Temporal trends of the 1-year adverse event rates from 2006 to 2015 in (A) 679 416 adults with newly diagnosed AF and (B) those without AF in the Korean National Health Insurance Service database.**

The 1-year adverse event rates (percent per year) were calculated by dividing the number of the first lifetime event that occurred in each year by the total number of patients at the start of the year who had not experienced that event previously. $P_{trends}$<0.001.

AF indicates atrial fibrillation; and HF, heart failure.

Source: Reprinted from Kim et al[53] with permission. Copyright © 2018 Elsevier.

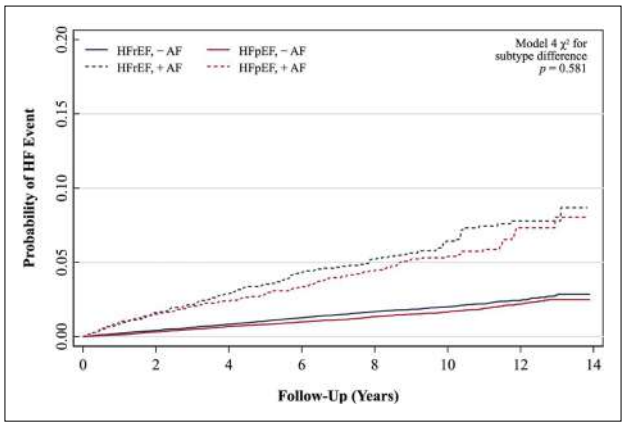



**Chart 18-10. Kaplan-Meier estimates for incident HFpEF or HFrEF by concomitant atrial fibrillation status in the REGARDS Study (N=25 787).**

Prevalent AF ascertained by baseline ECG or participant self-report of diagnosis. Analysis of heart failure subtype difference adjusted for age, sex, race, income, education, geographic region, smoking history, systolic blood pressure, diabetes, BMI, LDL, LVH by ECG, estimated GFR, baseline CHD status and CHD as a time-varying covariate, and medications.

AF indicates atrial fibrillation; BMI, body mass index; CHD, coronary heart disease; GFR, glomerular filtration rate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LDL, low-density lipoprotein; and LVH, left ventricular hypertrophy.

Source: Reproduced from Nicoli et al.[243] Copyright 2022 with permission from BMJ Publishing Group Ltd.

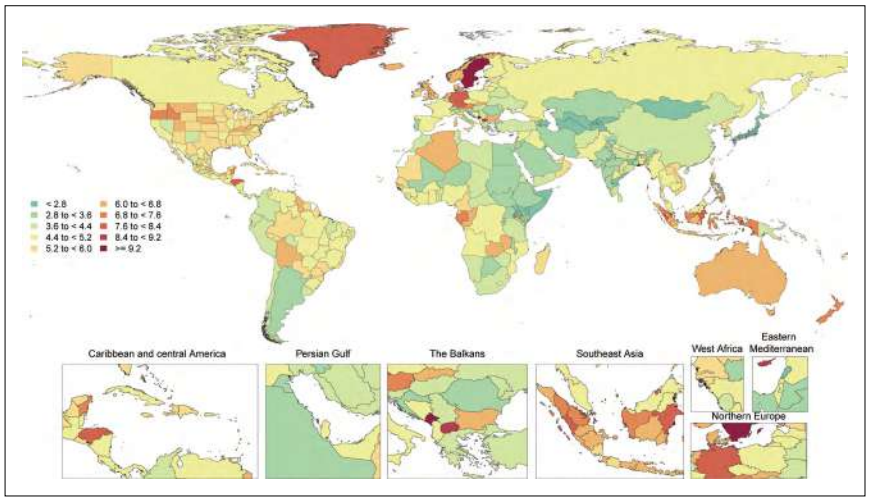



**Chart 18-11. Age-standardized global mortality rates of AF and atrial flutter per 100 000, both sexes, 2021.**

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

AF indicates atrial fibrillation; and GBD, Global Burden of Disease.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[264]

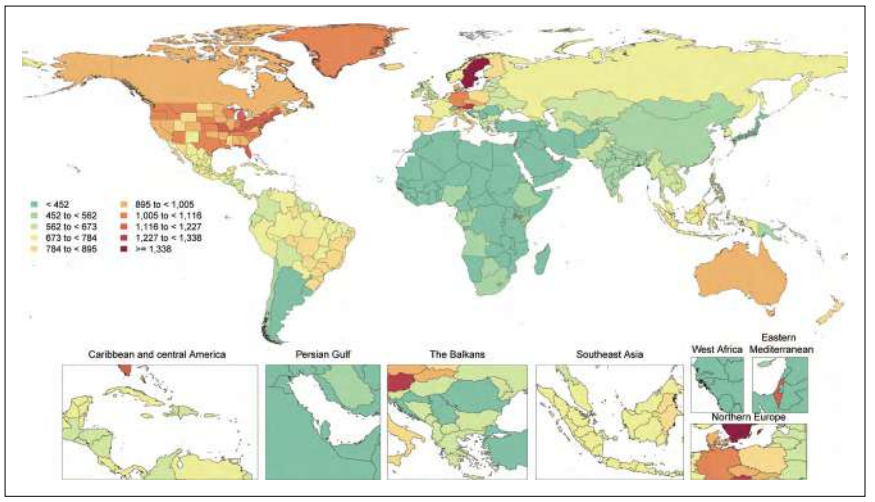



**Chart 18-12. Age-standardized global prevalence rates of AF and atrial flutter per 100 000, both sexes, 2021.**
During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.
AF indicates atrial fibrillation; and GBD, Global Burden of Disease.
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[264]

## REFERENCES


1. Aro AL, Anttonen O, Kerola T, Junttila MJ, Tikkanen JT, Rissanen HA, Reunanen A, Huikuri HV. Prognostic significance of prolonged PR interval in the general population. *Eur Heart J*. 2014;35:123–129. doi: 10.1093/eurheartj/eht176
2. Awamleh Garcia P, Alonso Martin JJ, Graupner Abad C, Jimenez Hernandez RM, Curcio Ruigomez A, Talavera Calle P, Cristobal Varela C, Serrano Antolin J, Muniz J, Gomez Doblas JJ, et al; Investigators of the OFRECE Study. Prevalence of electrocardiographic patterns associated with sudden cardiac death in the Spanish population aged 40 years or older: results of the OFRECE Study. *Rev Esp Cardiol (Engl Ed)*. 2017;70:801–807. doi: 10.1016/j.rec.2016.11.039
3. Piwonska A, Piwonski J, Szczesniewska D, Drygas W. Population prevalence of electrocardiographic abnormalities: results of the Polish WAWKARD study. *Kardiol Pol*. 2019;77:859–867. doi: 10.33963/KP.14911
4. Paixão GMM, Lima EM, Quadros AB, Cabral DPR, Coelho RR, Oliveira DM, Nascimento JS, Gomes PR, Ribeiro AL. Association between atrioventricular block and mortality in primary care patients: the CODE study. *Arq Bras Cardiol*. 2022;119:564–571. doi: 10.36660/abc.20210763
5. Wolbrette DL, Naccarelli GV. Bradycardias: sinus nodal dysfunction and atrioventricular conduction disturbances. In: Topol EJ, Califf RM, Prystowsky EN, Thomas JD, Thompson PD, eds. *Textbook of Cardiovascular Medicine*. 3rd ed. Lippicott Williams & Wilkins; 2007:1038–1049.
6. Shan R, Ning Y, Ma Y, Liu S, Wu J, Fan X, Lv J, Wang B, Li S, Li L. Prevalence and risk factors of atrioventricular block among 15 million Chinese health examination participants in 2018: a nation-wide cross-sectional study. *BMC Cardiovasc Disord*. 2021;21:289. doi: 10.1186/s12872-021-02105-3
7. Movahed MR, Hashemzadeh M, Jamal MM. Increased prevalence of third-degree atrioventricular block in patients with type II diabetes mellitus. *Chest*. 2005;128:2611–2614. doi: 10.1378/chest.128.4.2611
8. Santos J, Ribeiro ALP, Andrade-Junior D, Marcolino MS. Prevalence of electrocardiographic abnormalities in primary care patients according to sex and age group: a retrospective observational study. *Sao Paulo Med J*. 2018;136:20–28. doi: 10.1590/1516-3180.2017.0222290817
9. Solomon MD, Yang J, Sung SH, Livingston ML, Sarlas G, Lenane JC, Go AS. Incidence and timing of potentially high-risk arrhythmias detected through long term continuous ambulatory electrocardiographic monitoring. *BMC Cardiovasc Disord*. 2016;16:35. doi: 10.1186/s12872-016-0210-x
10. Diederichsen SZ, Xing LY, Frodi DM, Kongebro EK, Haugan KJ, Graff C, Hojberg S, Krieger D, Brandes A, Kober L, et al. Prevalence and prognostic significance of bradyarrhythmias in patients screened for atrial fibrillation vs usual care: post hoc analysis of the LOOP randomized clinical trial. *JAMA Cardiol*. 2023;8:326–334. doi: 10.1001/jamacardio.2022.5526
11. Coromilas EJ, Kochav S, Goldenthal I, Biviano A, Garan H, Goldbarg S, Kim JH, Yeo I, Tracy C, Ayanian S, et al. Worldwide survey of COVID-19-associated arrhythmias. *Circ Arrhythm Electrophysiol*. 2021;14:e009458. doi: 10.1161/CIRCEP.120.009458
12. Soliman EZ, Alonso A, Misialek JR, Jain A, Watson KE, Lloyd-Jones DM, Lima J, Shea S, Burke GL, Heckbert SR. Reference ranges of PR duration and P-wave indices in individuals free of cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis (MESA). *J Electrocardiol*. 2013;46:702–706. doi: 10.1016/j.jelectrocard.2013.05.006
13. Teo YH, Han R, Leong S, Teo YN, Syn NL, Wee CF, Tan BKJ, Wong RC, Chai P, Kojodjojo P, et al. Prevalence, types and treatment of bradycardia in obstructive sleep apnea: a systematic review and meta-analysis. *Sleep Med*. 2022;89:104–113. doi: 10.1016/j.sleep.2021.12.003

13a. Kusumoto FM, Schoenfeld MH, Barrett C, Edgerton JR, Ellenbogen KA, Gold MR, Goldschlager NF, Hamilton RM, Joglar JA, Kim RJ, et al. 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society [published correction appears in *Circulation*. 2019;140:e506–e508]. *Circulation*. 2019;140:e382–e482. doi: 10.1161/CIR.0000000000000628

14. Cheng S, Keyes MJ, Larson MG, McCabe EL, Newton-Cheh C, Levy D, Benjamin EJ, Vasan RS, Wang TJ. Long-term outcomes in individuals with prolonged PR interval or first-degree atrioventricular block. *JAMA*. 2009;301:2571–2577. doi: 10.1001/jama.2009.888
15. Xing LY, Diederichsen SZ, Hojberg S, Krieger DW, Graff C, Olesen MS, Nielsen JB, Brandes A, Kober L, Haugan KJ, et al. Electrocardiographic markers of subclinical atrial fibrillation detected by implantable loop recorder: insights from the LOOP Study. *Europace*. 2023;25:euad014. doi: 10.1093/europace/euad014
16. Auffret V, Loirat A, Leurent G, Martins RP, Filippi E, Coudert I, Hacot JP, Gilard M, Castellant P, Rialan A, et al. High-degree atrioventricular block complicating ST segment elevation myocardial infarction in the contemporary era. *Heart*. 2016;102:40–49. doi: 10.1136/heartjnl-2015-308260
17. Akhtar Z, Leung LWM, Kontogiannis C, Zuberi Z, Bajpai A, Sharma S, Chen Z, Beeton I, Sohal M, Gallagher MM. Prevalence of bradyarrhythmias needing pacing in COVID-19. *Pacing Clin Electrophysiol*. 2021;44:1340–1346. doi: 10.1111/pace.14313
18. Issa Z, Miller J, Zipes D. *Clinical Arrhythmology and Electrophysiology: A Companion to Braunwald's Heart Disease*. Saunders Elsevier; 2008.
19. Jensen PN, Gronroos NN, Chen LY, Folsom AR, deFilippi C, Heckbert SR, Alonso A. Incidence of and risk factors for sick sinus syndrome in the general population. *J Am Coll Cardiol*. 2014;64:531–538. doi: 10.1016/j.jacc.2014.03.056
20. Milanesi R, Baruscotti M, Gnecchi-Ruscone T, DiFrancesco D. Familial sinus bradycardia associated with a mutation in the cardiac pacemaker channel. *N Engl J Med*. 2006;354:151–157. doi: 10.1056/NEJMoa052475
21. Makiyama T, Akao M, Tsuji K, Doi T, Ohno S, Takenaka K, Kobori A, Ninomiya T, Yoshida H, Takano M, et al. High risk for bradyarrhythmic complications in patients with Brugada syndrome caused by *SCN5A* gene mutations. *J Am Coll Cardiol*. 2005;46:2100–2106. doi: 10.1016/j.jacc.2005.08.043
22. Postma AV, Denjoy I, Kamblock J, Alders M, Lupoglazoff JM, Vaksmann G, Dubosq-Bidot L, Sebillon P, Mannens MM, Guicheney P, et al. Catecholaminergic polymorphic ventricular tachycardia: RYR2 mutations, bradycardia, and follow up of the patients. *J Med Genet*. 2005;42:863–870. doi: 10.1136/jmg.2004.028993
23. Yamada N, Asano Y, Fujita M, Yamazaki S, Inanobe A, Matsuura N, Kobayashi H, Ohno S, Ebana Y, Tsukamoto O, et al. Mutant *KCNJ3*

and *KCNJ5* potassium channels as novel molecular targets in bradyarrhythmias and atrial fibrillation. *Circulation*. 2019;139:2157–2169. doi: 10.1161/CIRCULATIONAHA.118.036761
24. Kuss J, Stallmeyer B, Goldstein M, Rinne S, Pees C, Zumhagen S, Seebohm G, Decher N, Pott L, Kienitz MC, et al. Familial sinus node disease caused by a gain of GIRK (G-protein activated inwardly rectifying K(+) channel) channel function. *Circ Genom Precis Med*. 2019;12:e002238. doi: 10.1161/CIRCGEN.118.002238
25. Le Scouarnec S, Bhasin N, Vieyres C, Hund TJ, Cunha SR, Koval O, Marionneau C, Chen B, Wu Y, Demolombe S, et al. Dysfunction in ankyrin-B-dependent ion channel and transporter targeting causes human sinus node disease. *Proc Natl Acad Sci USA*. 2008;105:15617–15622. doi: 10.1073/pnas.0805500105
26. Liu H, El Zein L, Kruse M, Guinamard R, Beckmann A, Bozio A, Kurtbay G, Megarbane A, Ohmert I, Blaysat G, et al. Gain-of-function mutations in *TRPM4* cause autosomal dominant isolated cardiac conduction disease. *Circ Cardiovasc Genet*. 2010;3:374–385. doi: 10.1161/CIRCGENETICS.109.930867
27. Holm H, Gudbjartsson DF, Sulem P, Masson G, Helgadottir HT, Zanon C, Magnusson OT, Helgason A, Saemundsdottir J, Gylfason A, et al. A rare variant in *MYH6* is associated with high risk of sick sinus syndrome. *Nat Genet*. 2011;43:316–320. doi: 10.1038/ng.781
28. Bodin A, Bisson A, Gaborit C, Herbert J, Clementy N, Babuty D, Lip GYH, Fauchier L. Ischemic stroke in patients with sinus node disease, atrial fibrillation, and other cardiac conditions. *Stroke*. 2020;51:1674–1681. doi: 10.1161/STROKEAHA.120.029048
29. Deleted in proof.
30. Rehorn M, Sacks NC, Emden MR, Healey B, Preib MT, Cyr PL, Pokorney SD. Prevalence and incidence of patients with paroxysmal supraventricular tachycardia in the United States. *J Cardiovasc Electrophysiol*. 2021;32:2199–2206. doi: 10.1111/jce.15109
31. Go AS, Hlatky MA, Liu TI, Fan D, Garcia EA, Sung SH, Solomon MD. Contemporary burden and correlates of symptomatic paroxysmal supraventricular tachycardia. *J Am Heart Assoc*. 2018;7:e008759. doi: 10.1161/JAHA.118.008759
32. Raisi-Estabragh Z, Kobo O, Elbadawi A, Velagapudi P, Sharma G, Bullock-Palmer RP, Petersen SE, Mehta LS, Ullah W, Roguin A, et al. Differential patterns and outcomes of 206 million cardiovascular emergency department encounters for men and women in the United States. *J Am Heart Assoc*. 2022;11:e026432. doi: 10.1161/JAHA.122.026432
33. Michowitz Y, Anis-Heusler A, Reinstein E, Tovia-Brodie O, Glick A, Belhassen B. Familial occurrence of atrioventricular nodal reentrant tachycardia. *Circ Arrhythm Electrophysiol*. 2017;10:e004680. doi: 10.1161/CIRCEP.116.004680
34. Andreasen L, Ahlberg G, Tang C, Andreasen C, Hartmann JP, Tfelt-Hansen J, Behr ER, Pehrson S, Haunso S, LuCamp, et al. Next-generation sequencing of AV nodal reentrant tachycardia patients identifies broad spectrum of variants in ion channel genes. *Eur J Hum Genet*. 2018;26:660–668. doi: 10.1038/s41431-017-0092-0
35. James CA, Jongbloed JDH, Hershberger RE, Morales A, Judge DP, Syrris P, Pilichou K, Domingo AM, Murray B, Cadrin-Tourigny J, et al. International evidence based reappraisal of genes associated with arrhythmogenic right ventricular cardiomyopathy using the Clinical Genome Resource framework. *Circ Genom Precis Med*. 2021;14:e003273. doi: 10.1161/CIRCGEN.120.003273
36. Chang SH, Kuo CF, Chou IJ, See LC, Yu KH, Luo SF, Chiou MJ, Zhang W, Doherty M, Wen MS, et al. Outcomes associated with paroxysmal supraventricular tachycardia during pregnancy. *Circulation*. 2017;135:616–618. doi: 10.1161/CIRCULATIONAHA.116.025064
37. Carnlof C, Iwarzon M, Jensen-Urstad M, Gadler F, Insulander P. Women with PSVT are often misdiagnosed, referred later than men, and have more symptoms after ablation. *Scand Cardiovasc J*. 2017;51:299–307. doi: 10.1080/14017431.2017.1385837
38. Tan ESJ, Chan SP, Seow SC, Teo WS, Ching CK, Chong DTT, Tan VH, Chia PL, Foo DCG, Kojodjojo P; HRAS Investigators. Outcomes of supraventricular tachycardia ablation: results from the Singapore ablation and cardiac devices registry. *Pacing Clin Electrophysiol*. 2022;45:50–58. doi: 10.1111/pace.14410
39. Anand RG, Rosenthal GL, Van Hare GF, Snyder CS. Is the mechanism of supraventricular tachycardia in pediatrics influenced by age, gender or ethnicity? *Congenit Heart Dis*. 2009;4:464–468. doi: 10.1111/j.1747-0803.2009.00336.x
40. Quattrocelli A, Lang J, Davis A, Pflaumer A. Age makes a difference: symptoms in pediatric supraventricular tachycardia. *J Arrhythm*. 2018;34:565–571. doi: 10.1002/joa3.12103
41. Yu L, Ye X, Yang Z, Yang W, Zhang B, China National Diabetes and Metabolic Disorders Study Group. Prevalences and associated factors of electrocardiographic abnormalities in Chinese adults: a cross-sectional study. *BMC Cardiovasc Disord*. 2020;20:414. doi: 10.1186/s12872-020-01698-5
42. Sano S, Komori S, Amano T, Kohno I, Ishihara T, Sawanobori T, Ijiri H, Tamura K. Prevalence of ventricular preexcitation in Japanese schoolchildren. *Heart*. 1998;79:374–378. doi: 10.1136/hrt.79.4.374
43. Arnar DO, Mairesse GH, Boriani G, Calkins H, Chin A, Coats A, Deharo JC, Svendsen JH, Heidbuchel H, Isa R, et al; ESC Scientific Document Group. Management of asymptomatic arrhythmias: a European Heart Rhythm Association (EHRA) consensus document. *Europace*. 2019;21:844–845. doi: 10.1093/europace/euz046
44. Bunch TJ, May HT, Bair TL, Anderson JL, Crandall BG, Cutler MJ, Jacobs V, Mallender C, Muhlestein JB, Osborn JS, et al. Long-term natural history of adult Wolff-Parkinson-White syndrome patients treated with and without catheter ablation. *Circ Arrhythm Electrophysiol*. 2015;8:1465–1471. doi: 10.1161/CIRCEP.115.003013
45. Pappone C, Vicedomini G, Manguso F, Saviano M, Baldi M, Pappone A, Ciaccio C, Giannelli L, Ionescu B, Petretta A, et al. Wolff-Parkinson-White syndrome in the era of catheter ablation: insights from a registry study of 2169 patients. *Circulation*. 2014;130:811–819. doi: 10.1161/CIRCULATIONAHA.114.011154
46. Escudero CA, Ceresnak SR, Collins KK, Pass RH, Aziz PF, Blaufox AD, Ortega MC, Cannon BC, Cohen MI, Dechert BE, et al. Loss of ventricular preexcitation during noninvasive testing does not exclude high-risk accessory pathways: a multicenter study of WPW in children. *Heart Rhythm*. 2020;17:1729–1737. doi: 10.1016/j.hrthm.2020.05.035
47. Colilla S, Crow A, Petkun W, Singer DE, Simon T, Liu X. Estimates of current and future incidence and prevalence of atrial fibrillation in the US adult population. *Am J Cardiol*. 2013;112:1142–1147. doi: 10.1016/j.amjcard.2013.05.063
48. Turakhia MP, Guo JD, Keshishian A, Delinger R, Sun X, Ferri M, Russ C, Cato M, Yuce H, Hlavacek P. Contemporary prevalence estimates of undiagnosed and diagnosed atrial fibrillation in the United States. *Clin Cardiol*. 2023;46:484–493. doi: 10.1002/clc.23983
49. Krijthe BP, Kunst A, Benjamin EJ, Lip GY, Franco OH, Hofman A, Witteman JC, Stricker BH, Heeringa J. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *Eur Heart J*. 2013;34:2746–2751. doi: 10.1093/eurheartj/eht280
50. Albertsen N, Riahi S, Pedersen ML, Skovgaard N, Andersen S. The prevalence of atrial fibrillation in Greenland: a register-based cross-sectional study based on disease classifications and prescriptions of oral anticoagulants. *Int J Circumpolar Health*. 2022;81:2030522. doi: 10.1080/22423982.2022.2030522
51. Williams BA, Chamberlain AM, Blankenship JC, Hylek EM, Voyce S. Trends in atrial fibrillation incidence rates within an integrated health care delivery system, 2006 to 2018. *JAMA Netw Open*. 2020;3:e2014874. doi: 10.1001/jamanetworkopen.2020.14874
52. Heckbert SR, Austin TR, Jensen PN, Chen LY, Post WS, Floyd JS, Soliman EZ, Kronmal RA, Psaty BM. Differences by race/ethnicity in the prevalence of clinically detected and monitor-detected atrial fibrillation: MESA. *Circ Arrhythm Electrophysiol*. 2020;13:e007698. doi: 10.1161/CIRCEP.119.007698
53. Kim D, Yang PS, Jang E, Yu HT, Kim TH, Uhm JS, Kim JY, Pak HN, Lee MH, Joung B, et al. 10-Year nationwide trends of the incidence, prevalence, and adverse outcomes of non-valvular atrial fibrillation nationwide health insurance data covering the entire Korean population. *Am Heart J*. 2018;202:20–26. doi: 10.1016/j.ahj.2018.04.017
54. Khurshid S, Ashburner JM, Ellinor PT, McManus DD, Atlas SJ, Singer DE, Lubitz SA. Prevalence and incidence of atrial fibrillation among older primary care patients. *JAMA Netw Open*. 2023;6:e2255838. doi: 10.1001/jamanetworkopen.2022.55838
55. Wu J, Nadarajah R, Nakao YM, Nakao K, Wilkinson C, Mamas MA, Camm AJ, Gale CP. Temporal trends and patterns in atrial fibrillation incidence: a population-based study of 34 million individuals. *Lancet Reg Health Eur*. 2022;17:100386. doi: 10.1016/j.lanepe.2022.100386
56. Sanchez JM, Jolly SE, Dewland TA, Tseng ZH, Nah G, Vittinghoff E, Marcus GM. Incident atrial fibrillation among American Indians in California. *Circulation*. 2019;140:1605–1606. doi: 10.1161/CIRCULATIONAHA.119.042882
57. Mou L, Norby FL, Chen LY, O'Neal WT, Lewis TT, Loehr LR, Soliman EZ, Alonso A. Lifetime risk of atrial fibrillation by race and socioeconomic status: ARIC study (Atherosclerosis Risk in Communities). *Circ Arrhythm Electrophysiol*. 2018;11:e006350. doi: 10.1161/CIRCEP.118.006350
58. Chao TF, Liu CJ, Tuan TC, Chen TJ, Hsieh MH, Lip GYH, Chen SA. Lifetime risks, projected numbers, and adverse outcomes in Asian patients with

atrial fibrillation: a report from the Taiwan Nationwide AF Cohort Study. *Chest*. 2018;153:453–466. doi: 10.1016/j.chest.2017.10.001
59. Magnussen C, Niiranen TJ, Ojeda FM, Gianfagna F, Blankenberg S, Njolstad I, Vartiainen E, Sans S, Pasterkamp G, Hughes M, et al; BiomarCaRE Consortium. Sex differences and similarities in atrial fibrillation epidemiology, risk factors, and mortality in community cohorts: results from the BiomarCaRE Consortium (Biomarker for Cardiovascular Risk Assessment in Europe). *Circulation*. 2017;136:1588–1597. doi: 10.1161/CIRCULATIONAHA.117.028981
60. Weng LC, Preis SR, Hulme OL, Larson MG, Choi SH, Wang B, Trinquart L, McManus DD, Staerk L, Lin H, et al. Genetic predisposition, clinical risk factor burden, and lifetime risk of atrial fibrillation. *Circulation*. 2018;137:1027–1038. doi: 10.1161/CIRCULATIONAHA.117.031431
61. Staerk L, Wang B, Preis SR, Larson MG, Lubitz SA, Ellinor PT, McManus DD, Ko D, Weng LC, Lunetta KL, et al. Lifetime risk of atrial fibrillation according to optimal, borderline, or elevated levels of risk factors: cohort study based on longitudinal data from the Framingham Heart Study. *BMJ*. 2018;361:k1453. doi: 10.1136/bmj.k1453
62. Schnabel RB, Yin X, Gona P, Larson MG, Beiser AS, McManus DD, Newton-Cheh C, Lubitz SA, Magnani JW, Ellinor PT, et al. 50 Year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *Lancet*. 2015;386:154–162. doi: 10.1016/S0140-6736(14)61774-8
63. Holt A, Gislason GH, Schou M, Zareini B, Biering-Sørensen T, Phelps M, Kragholm K, Andersson C, Fosbøl EL, Hansen ML, et al. New-onset atrial fibrillation: incidence, characteristics, and related events following a national COVID-19 lockdown of 56 million people. *Eur Heart J*. 2020;41:3072–3079. doi: 10.1093/eurheartj/ehaa494
64. Hernandez I, Gabriel N, He M, Guo J, Tadrous M, Suda KJ, Magnani JW. Effect of the COVID-19 pandemic on adversity in individuals receiving anticoagulation for atrial fibrillation: a nationally representative administrative health claims analysis. *Am Heart J Plus*. 2022;13:100096. doi: 10.1016/j.ahjo.2022.100096
65. Matsuoka S, Kaneko H, Okada A, Morita K, Itoh H, Michihata N, Jo T, Takeda N, Morita H, Fujiu K, et al. Age modified relationship between modifiable risk factors and the risk of atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2022;15:e010409. doi: 10.1161/CIRCEP.121.010409
66. Shulman E, Chudow JJ, Essien UR, Shanbhag A, Kargoli F, Romero J, Di Biase L, Fisher J, Krumerman A, Ferrick KJ. Relative contribution of modifiable risk factors for incident atrial fibrillation in Hispanics, African Americans and non-Hispanic Whites. *Int J Cardiol*. 2019;275:89–94. doi: 10.1016/j.ijcard.2018.10.028
67. Kim YG, Han KD, Choi JI, Yung Boo K, Kim DY, Oh SK, Lee KN, Shim J, Kim JS, Kim YH. Impact of the duration and degree of hypertension and body weight on new-onset atrial fibrillation: a nationwide population-based study. *Hypertension*. 2019;74:e45–e51. doi: 10.1161/HYPERTENSIONAHA.119.13672
68. Asad Z, Abbas M, Javed I, Korantzopoulos P, Stavrakis S. Obesity is associated with incident atrial fibrillation independent of gender: a meta-analysis. *J Cardiovasc Electrophysiol*. 2018;29:725–732. doi: 10.1111/jce.13458
69. Aune D, Sen A, Schlesinger S, Norat T, Janszky I, Romundstad P, Tonstad S, Riboli E, Vatten LJ. Body mass index, abdominal fatness, fat mass and the risk of atrial fibrillation: a systematic review and dose-response meta-analysis of prospective studies. *Eur J Epidemiol*. 2017;32:181–192. doi: 10.1007/s10654-017-0232-4
70. Jones NR, Taylor KS, Taylor CJ, Aveyard P. Weight change and the risk of incident atrial fibrillation: a systematic review and meta-analysis. *Heart*. 2019;105:1799–1805. doi: 10.1136/heartjnl-2019-314931
71. Chatterjee NA, Giulianini F, Geelhoed B, Lunetta KL, Misialek JR, Niemeijer MN, Rienstra M, Rose LM, Smith AV, Arking DE, et al. Genetic obesity and the risk of atrial fibrillation: causal estimates from mendelian randomization. *Circulation*. 2017;135:741–754. doi: 10.1161/CIRCULATIONAHA.116.024921
72. Aune D, Schlesinger S, Norat T, Riboli E. Tobacco smoking and the risk of atrial fibrillation: a systematic review and meta-analysis of prospective studies. *Eur J Prev Cardiol*. 2018;25:1437–1451. doi: 10.1177/2047487318780435
73. Qi W, Zhang N, Korantzopoulos P, Letsas KP, Cheng M, Di F, Tse G, Liu T, Li G. Serum glycated hemoglobin level as a predictor of atrial fibrillation: a systematic review with meta-analysis and meta-regression. *PLoS One*. 2017;12:e0170955. doi: 10.1371/journal.pone.0170955
74. Aune D, Feng T, Schlesinger S, Janszky I, Norat T, Riboli E. Diabetes mellitus, blood glucose and the risk of atrial fibrillation: a systematic review and meta-analysis of cohort studies. *J Diabetes Complications*. 2018;32:501–511. doi: 10.1016/j.jdiacomp.2018.02.004
75. Xiong Z, Liu T, Tse G, Gong M, Gladding PA, Smaill BH, Stiles MK, Gillis AM, Zhao J. A machine learning aided systematic review and meta-analysis of the relative risk of atrial fibrillation in patients with diabetes mellitus. *Front Physiol*. 2018;9:835. doi: 10.3389/fphys.2018.00835
76. Anagnostopoulos I, Kousta M, Kossyvakis C, Lakka E, Vrachatis D, Deftereos S, Vassilikos VP, Giannopoulos G. Weekly physical activity and incident atrial fibrillation in females: a dose-response meta-analysis. *Int J Cardiol*. 2023;370:191–196. doi: 10.1016/j.ijcard.2022.11.007
77. Ahn HJ, Lee SR, Choi EK, Han KD, Jung JH, Lim JH, Yun JP, Kwon S, Oh S, Lip GYH. Association between exercise habits and stroke, heart failure, and mortality in Korean patients with incident atrial fibrillation: a nationwide population-based cohort study. *PLoS Med*. 2021;18:e1003659. doi: 10.1371/journal.pmed.1003659
78. Li X, Cui S, Xuan D, Xuan C, Xu D. Atrial fibrillation in athletes and general population: a systematic review and meta-analysis. *Medicine (Baltimore)*. 2018;97:e13405. doi: 10.1097/MD.0000000000013405
79. Guo L, Huang W, Dai W, Yang J. Cross-country skiing and risk of atrial fibrillation: a meta-analysis of cohort studies. *Sci Sports*. 2022;37:294–302. doi: 10.1016/j.scispo.2021.08.006
80. Kunutsor SK, Seidu S, Mäkikallio TH, Dey RS, Laukkanen JA. Physical activity and risk of atrial fibrillation in the general population: meta-analysis of 23 cohort studies involving about 2 million participants. *Eur J Epidemiol*. 2021;36:259–274. doi: 10.1007/s10654-020-00714-4
81. Santhanakrishnan R, Wang N, Larson MG, Magnani JW, McManus DD, Lubitz SA, Ellinor PT, Cheng S, Vasan RS, Lee DS, et al. Atrial fibrillation begets heart failure and vice versa: temporal associations and differences in preserved versus reduced ejection fraction. *Circulation*. 2016;133:484–492. doi: 10.1161/CIRCULATIONAHA.115.018614
82. Mandalenakis Z, Rosengren A, Lappas G, Eriksson P, Gilljam T, Hansson PO, Skoglund K, Fedchenko M, Dellborg M. Atrial fibrillation burden in young patients with congenital heart disease. *Circulation*. 2018;137:928–937. doi: 10.1161/CIRCULATIONAHA.117.029590
83. Baumgartner C, da Costa BR, Collet TH, Feller M, Floriani C, Bauer DC, Cappola AR, Heckbert SR, Ceresini G, Gussekloo J, et al; Thyroid Studies Collaboration. Thyroid function within the normal range, subclinical hypothyroidism, and the risk of atrial fibrillation. *Circulation*. 2017;136:2100–2116. doi: 10.1161/CIRCULATIONAHA.117.028753
84. Bansal N, Zelnick LR, Alonso A, Benjamin EJ, de Boer IH, Deo R, Katz R, Kestenbaum B, Mathew J, Robinson-Cohen C, et al. eGFR and albuminuria in relation to risk of incident atrial fibrillation: a meta-analysis of the Jackson Heart Study, the Multi-Ethnic Study of Atherosclerosis, and the Cardiovascular Health Study. *Clin J Am Soc Nephrol*. 2017;12:1386–1398. doi: 10.2215/CJN.01860217
85. Gallagher C, Hendriks JML, Elliott AD, Wong CX, Rangnekar G, Middeldorp ME, Mahajan R, Lau DH, Sanders P. Alcohol and incident atrial fibrillation: a systematic review and meta-analysis. *Int J Cardiol*. 2017;246:46–52. doi: 10.1016/j.ijcard.2017.05.133
86. Marcus GM, Vittinghoff E, Whitman IR, Joyce S, Yang V, Nah G, Gerstenfeld EP, Moss JD, Lee RJ, Lee BK, et al. Acute consumption of alcohol and discrete atrial fibrillation events. *Ann Intern Med*. 2021;174:1503–1509. doi: 10.7326/M21-0228
87. Zhao E, Chen S, Du Y, Zhang Y. Association between sleep apnea hypopnea syndrome and the risk of atrial fibrillation: a meta-analysis of cohort study. *Biomed Res Int*. 2018;2018:5215868. doi: 10.1155/2018/5215868
88. Chokesuwattanaskul R, Thongprayoon C, Sharma K, Congrete S, Tanawuttiwat T, Cheungpasitporn W. Associations of sleep quality with incident atrial fibrillation: a meta-analysis. *Intern Med J*. 2018;48:964–972. doi: 10.1111/imj.13764
89. Arafa A, Kokubo Y, Shimamoto K, Kashima R, Watanabe E, Sakai Y, Li J, Teramoto M, Sheerah HA, Kusano K. Sleep duration and atrial fibrillation risk in the context of predictive, preventive, and personalized medicine: the Suita Study and meta-analysis of prospective cohort studies. *EPMA J*. 2022;13:77–86. doi: 10.1007/s13167-022-00275-4
90. Yue C, Yang F, Li F, Chen Y. Association between air pollutants and atrial fibrillation in general population: a systematic review and meta-analysis. *Ecotoxicol Environ Saf*. 2021;208:111508. doi: 10.1016/j.ecoenv.2020.111508
91. Bazal P, Gea A, Navarro AM, Salas-Salvadó J, Corella D, Alonso-Gómez A, Fitó M, Muñoz-Bravo C, Estruch R, Fiol M, et al. Caffeinated coffee consumption and risk of atrial fibrillation in two Spanish cohorts. *Eur J Prev Cardiol*. 2021;28:648–657. doi: 10.1177/2047487320909065
92. Rosman L, Lampert R, Ramsey CM, Dziura J, Chui PW, Brandt C, Haskell S, Burg MM. Posttraumatic stress disorder and risk for early incident atrial fibrillation: a prospective cohort study of 11 million young adults. *J Am Heart Assoc*. 2019;8:e013741. doi: 10.1161/JAHA.119.013741

93. Garg PK, O'Neal WT, Diez-Roux AV, Alonso A, Soliman EZ, Heckbert S. Negative affect and risk of atrial fibrillation: MESA. *J Am Heart Assoc*. 2019;8:e010603. doi: 10.1161/JAHA.118.010603
94. Garg PK, Claxton JS, Soliman EZ, Chen LY, Lewis TT, Mosley T Jr, Alonso A. Associations of anger, vital exhaustion, anti-depressant use, and poor social ties with incident atrial fibrillation: the Atherosclerosis Risk in Communities Study. *Eur J Prev Cardiol*. 2020;28:633–640. doi: 10.1177/2047487319897163
95. Fransson EI, Nordin M, Magnusson Hanson LL, Westerlund H. Job strain and atrial fibrillation: results from the Swedish Longitudinal Occupational Survey of Health and meta-analysis of three studies. *Eur J Prev Cardiol*. 2018;25:1142–1149. doi: 10.1177/2047487318777387
96. Filardo G, Damiano RJ Jr, Ailawadi G, Thourani VH, Pollock BD, Sass DM, Phan TK, Nguyen H, da Graca B. Epidemiology of new-onset atrial fibrillation following coronary artery bypass graft surgery. *Heart*. 2018;104:985–992. doi: 10.1136/heartjnl-2017-312150
97. Cikes M, Planinc I, Claggett B, Cunningham J, Milicic D, Sweitzer N, Senni M, Gori M, Linssen G, Shah SJ, et al. Atrial fibrillation in heart failure with preserved ejection fraction: the PARAGON-HF trial. *JACC Heart Fail*. 2022;10:336–346. doi: 10.1016/j.jchf.2022.01.018
98. Chebbout R, Heywood EG, Drake TM, Wild JRL, Lee J, Wilson M, Lee MJ. A systematic review of the incidence of and risk factors for postoperative atrial fibrillation following general surgery. *Anaesthesia*. 2018;73:490–498. doi: 10.1111/anae.14118
99. Xiao FP, Chen MY, Wang L, He H, Jia ZQ, Kuai L, Zhou HB, Liu M, Hong M. Outcomes of new-onset atrial fibrillation in patients with sepsis: a systematic review and meta-analysis of 225,841 patients. *Am J Emerg Med*. 2021;42:23–30. doi: 10.1016/j.ajem.2020.12.062
100. Liao SC, Shao SC, Cheng CW, Chen YC, Hung MJ. Incidence rate and clinical impacts of arrhythmia following COVID-19: a systematic review and meta-analysis of 17,435 patients. *Crit Care*. 2020;24:690. doi: 10.1186/s13054-020-03368-6
101. Szarpak L, Filipiak KJ, Skwarek A, Pruc M, Rahnama M, Denegri A, Jachowicz M, Dawidowska M, Gasecka A, Jaguszewski MJ, et al. Outcomes and mortality associated with atrial arrhythmias among patients hospitalized with COVID-19: a systematic review and meta-analysis. *Cardiol J*. 2022;29:33–43. doi: 10.5603/CJ.a2021.0167
102. Caldeira D, Alves D, Costa J, Ferreira JJ, Pinto FJ. Ibrutinib increases the risk of hypertension and atrial fibrillation: systematic review and meta-analysis.*PLoSOne*.2019;14:e0211228.doi:10.1371/journal.pone.0211228
103. Zhang M, Li LL, Zhao QQ, Peng XD, Wu K, Li X, Ruan YF, Bai R, Liu N, Ma CS. The association of new-onset atrial fibrillation and risk of cancer: a systematic review and meta-analysis. *Cardiol Res Pract*. 2020;2020:2372067. doi: 10.1155/2020/2372067
104. Essien UR, Kornej J, Johnson AE, Schulson LB, Benjamin EJ, Magnani JW. Social determinants of atrial fibrillation. *Nat Rev Cardiol*. 2021;18:763–773. doi: 10.1038/s41569-021-00561-0
105. Essien UR, McCabe ME, Kershaw KN, Youmans QR, Fine MJ, Yancy CW, Khan SS. Association between neighborhood-level poverty and incident atrial fibrillation: a retrospective cohort study. *J Gen Intern Med*. 2021;37:1436–1443. doi: 10.1007/s11606-021-06976-2
106. Abdel-Qadir H, Akioyamen LE, Fang J, Pang A, Ha ACT, Jackevicius CA, Alter DA, Austin PC, Atzema CL, Bhatia RS, et al. Association of neighborhood-level material deprivation with atrial fibrillation care in a single-payer health care system: a population-based cohort study. *Circulation*. 2022;146:159–171. doi: 10.1161/CIRCULATIONAHA.122.058949
107. LaRosa AR, Claxton J, O'Neal WT, Lutsey PL, Chen LY, Bengtson L, Chamberlain AM, Alonso A, Magnani JW. Association of household income and adverse outcomes in patients with atrial fibrillation. *Heart*. 2020;106:1679–1685. doi: 10.1136/heartjnl-2019-316065
108. Tertulien T, Chen Y, Althouse AD, Essien UR, Johnson A, Magnani JW. Association of income and educational attainment in hospitalization events in atrial fibrillation. *Am J Prev Cardiol*. 2021;7:100201. doi: 10.1016/j.ajpc.2021.100201
109. Garg PK, O'Neal WT, Ogunsua A, Thacker EL, Howard G, Soliman EZ, Cushman M. Usefulness of the American Heart Association's Life Simple 7 to predict the risk of atrial fibrillation (from the REasons for Geographic And Racial Differences in Stroke [REGARDS] Study). *Am J Cardiol*. 2018;121:199–204. doi: 10.1016/j.amjcard.2017.09.033
110. Garg PK, O'Neal WT, Chen LY, Loehr LR, Sotoodehnia N, Soliman EZ, Alonso A. American Heart Association's Life Simple 7 and risk of atrial fibrillation in a population without known cardiovascular disease: the ARIC (Atherosclerosis Risk in Communities) study. *J Am Heart Assoc*. 2018;7:e008424. doi: 10.1161/JAHA.117.008424
111. Wang W, Norby FL, Rooney MR, Zhang M, Gutierrez A, Garg P, Soliman EZ, Alonso A, Dudley SC Jr., Lutsey PL, et al. Association of Life's Simple 7 with atrial fibrillation burden (from the Atherosclerosis Risk in Communities Study). *Am J Cardiol*. 2020;137:31–38. doi: 10.1016/j.amjcard.2020.09.033
112. Ogunmoroti O, Michos ED, Aronis KN, Salami JA, Blankstein R, Virani SS, Spatz ES, Allen NB, Rana JS, Blumenthal RS, et al. Life's Simple 7 and the risk of atrial fibrillation: the Multi-Ethnic Study of Atherosclerosis. *Atherosclerosis*. 2018;275:174–181. doi: 10.1016/j.atherosclerosis.2018.05.050
113. Chamberlain AM, Agarwal SK, Folsom AR, Soliman EZ, Chambless LE, Crow R, Ambrose M, Alonso A. A clinical risk score for atrial fibrillation in a biracial prospective cohort (from the Atherosclerosis Risk in Communities [ARIC] study). *Am J Cardiol*. 2011;107:85–91. doi: 10.1016/j.amjcard.2010.08.049
114. Schnabel RB, Aspelund T, Li G, Sullivan LM, Suchy-Dicey A, Harris TB, Pencina MJ, D'Agostino RB Sr, Levy D, Kannel WB, et al. Validation of an atrial fibrillation risk algorithm in Whites and African Americans. *Arch Intern Med*. 2010;170:1909–1917. doi: 10.1001/archinternmed.2010.434
115. Everett BM, Cook NR, Conen D, Chasman DI, Ridker PM, Albert CM. Novel genetic markers improve measures of atrial fibrillation risk prediction. *Eur Heart J*. 2013;34:2243–2251. doi: 10.1093/eurheartj/eht033
116. Segan L, Canovas R, Nanayakkara S, Chieng D, Prabhu S, Voskoboinik A, Sugumar H, Ling LH, Lee G, Morton J, et al. New-onset atrial fibrillation prediction: the HARMS2-AF risk score. *Eur Heart J*. 2023;44:3443–3452. doi: 10.1093/eurheartj/ehad375
117. Shulman E, Kargoli F, Aagaard P, Hoch E, Di Biase L, Fisher J, Gross J, Kim S, Krumerman A, Ferrick KJ. Validation of the Framingham Heart Study and CHARGE-AF risk scores for atrial fibrillation in Hispanics, African-Americans, and Non-Hispanic Whites. *Am J Cardiol*. 2016;117:76–83. doi: 10.1016/j.amjcard.2015.10.009
118. Bundy JD, Heckbert SR, Chen LY, Lloyd-Jones DM, Greenland P. Evaluation of risk prediction models of atrial fibrillation (from the Multi-Ethnic Study of Atherosclerosis [MESA]). *Am J Cardiol*. 2020;125:55–62. doi: 10.1016/j.amjcard.2019.09.032
119. Pfister R, Bragelmann J, Michels G, Wareham NJ, Luben R, Khaw KT. Performance of the CHARGE-AF risk model for incident atrial fibrillation in the EPIC Norfolk cohort. *Eur J Prev Cardiol*. 2015;22:932–939. doi: 10.1177/2047487314544045
120. Pollock BD, Filardo G, da Graca B, Phan TK, Ailawadi G, Thourani V, Damiano RJ Jr, Edgerton JR. Predicting new-onset post-coronary artery bypass graft atrial fibrillation with existing risk scores. *Ann Thorac Surg*. 2018;105:115–121. doi: 10.1016/j.athoracsur.2017.06.075
121. Himmelreich JCL, Lucassen WAM, Harskamp RE, Aussems C, van Weert HCPM, Nielen MMJ. CHARGE-AF in a national routine primary care electronic health records database in the Netherlands: validation for 5-year risk of atrial fibrillation and implications for patient selection in atrial fibrillation screening. *Open Heart*. 2021;8:e001459. doi: 10.1136/openhrt-2020-001459
122. Tiwari P, Colborn KL, Smith DE, Xing F, Ghosh D, Rosenberg MA. Assessment of a machine learning model applied to harmonized electronic health record data for the prediction of incident atrial fibrillation. *JAMA Netw Open*. 2020;3:e1919396. doi: 10.1001/jamanetworkopen.2019.19396
123. Belkin MN, Soria CE, Waldo AL, Borleffs CJW, Hayes DL, Tung R, Singh JP, Upadhyay GA. Incidence and clinical significance of new-onset device-detected atrial tachyarrhythmia: a meta-analysis. *Circ Arrhythm Electrophysiol*. 2018;11:e005393. doi: 10.1161/CIRCEP.117.005393
124. Vitolo M, Imberti JF, Maisano A, Albini A, Bonini N, Valenti AC, Malavasi VL, Proietti M, Healey JS, Lip GY, et al. Device-detected atrial high rate episodes and the risk of stroke/thrombo-embolism and atrial fibrillation incidence: a systematic review and meta-analysis. *Eur J Intern Med*. 2021;92:100–106. doi: 10.1016/j.ejim.2021.05.038
125. Meng Y, Zhang Y, Zhu C, Nie C, Liu P, Chang S, Wang S. Atrial high-rate episode burden and stroke risks for patients with device-detected subclinical atrial fibrillation: a systematic review and meta-analysis. *Int J Cardiol*. 2023;371:211–220. doi: 10.1016/j.ijcard.2022.09.046
126. Freedman B, Camm J, Calkins H, Healey JS, Rosenqvist M, Wang J, Albert CM, Anderson CS, Antoniou S, Benjamin EJ, et al; AF-Screen Collaborators. Screening for atrial fibrillation: a report of the AF-SCREEN international collaboration. *Circulation*. 2017;135:1851–1867. doi: 10.1161/CIRCULATIONAHA.116.026693
127. Benjamin EJ, Go AS, Desvigne-Nickens P, Anderson CD, Casadei B, Chen LY, Crijns H, Freedman B, Hills MT, Healey JS, et al. Research priorities in atrial fibrillation screening: a report from a National Heart, Lung, and Blood Institute virtual workshop. *Circulation*. 2021;143:372–388. doi: 10.1161/CIRCULATIONAHA.120.047633

128. Turakhia MP, Shafrin J, Bognar K, Trocio J, Abdulsattar Y, Wiederkehr D, Goldman DP. Estimated prevalence of undiagnosed atrial fibrillation in the United States. *PLoS One*. 2018;13:e0195088. doi: 10.1371/journal.pone.0195088
129. Himmelreich JCL, Lucassen WA, Coutinho JM, Harskamp RE, de Groot JR, Cpm van Weert H. 14-Day Holter monitoring for atrial fibrillation after ischemic stroke: the yield of guideline-recommended monitoring duration. *Eur Stroke J*. 2023;8:157–167. doi: 10.1177/23969873221146027
130. Gladstone DJ, Wachter R, Schmalstieg-Bahr K, Quinn FR, Hummers E, Ivers N, Marsden T, Thornton A, Djuric A, Suerbaum J, et al. Screening for atrial fibrillation in the older population: a randomized clinical trial. *JAMA Cardiol*. 2021;6:558–567. doi: 10.1001/jamacardio.2021.0038
131. Svendsen JH, Diederichsen SZ, Hojberg S, Krieger DW, Graff C, Kronborg C, Olesen MS, Nielsen JB, Holst AG, Brandes A, et al. Implantable loop recorder detection of atrial fibrillation to prevent stroke (the LOOP study): a randomised controlled trial. *Lancet*. 2021;398:1507–1516. doi: 10.1016/S0140-6736(21)01698-6
132. Svennberg E, Friberg L, Frykman V, Al-Khalili F, Engdahl J, Rosenqvist M. Clinical outcomes in systematic screening for atrial fibrillation (STROKESTOP): a multicentre, parallel group, unmasked, randomised controlled trial. *Lancet*. 2021;398:1498–1506. doi: 10.1016/S0140-6736(21)01637-8
133. Lyth J, Svennberg E, Bernfort L, Aronsson M, Frykman V, Al-Khalili F, Friberg L, Rosenqvist M, Engdahl J, Levin L. Cost-effectiveness of population screening for atrial fibrillation: the STROKESTOP study. *Eur Heart J*. 2023;44:196–204. doi: 10.1093/eurheartj/ehac547
134. Lubitz SA, Atlas SJ, Ashburner JM, Lipsanopoulos ATT, Borowsky LH, Guan W, Khurshid S, Ellinor PT, Chang Y, McManus DD, et al. Screening for atrial fibrillation in older adults at primary care visits: VITAL-AF randomized controlled trial. *Circulation*. 2022;145:946–954. doi: 10.1161/CIRCULATIONAHA.121.057014
135. Jonas DE, Kahwati LC, Yun JDY, Middleton JC, Coker-Schwimmer M, Asher GN. Screening for atrial fibrillation with electrocardiography: evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2018;320:485–498. doi: 10.1001/jama.2018.4190
136. Davidson KW, Barry MJ, Mangione CM, Cabana M, Caughey AB, Davis EM, Donahue KE, Doubeni CA, Epling JW Jr, Kubik M, et al; US Preventive Services Task Force. Screening for atrial fibrillation: US Preventive Services Task Force recommendation statement. *JAMA*. 2022;327:360–367. doi: 10.1001/jama.2021.23732
137. Lowres N, Olivier J, Chao TF, Chen SA, Chen Y, Diederichsen A, Fitzmaurice DA, Gomez-Doblas JJ, Harbison J, Healey JS, et al. Estimated stroke risk, yield, and number needed to screen for atrial fibrillation detected through single time screening: a multicountry patient-level meta-analysis of 141,220 screened individuals. *PLoS Med*. 2019;16:e1002903. doi: 10.1371/journal.pmed.1002903
138. Petryszyn P, Niewinski P, Staniak A, Piotrowski P, Well A, Well M, Jeskowiak I, Lip G, Ponikowski P. Effectiveness of screening for atrial fibrillation and its determinants: a meta-analysis. *PLoS One*. 2019;14:e0213198. doi: 10.1371/journal.pone.0213198
139. Elbadawi A, Sedhom R, Gad M, Hamed M, Elwagdy A, Barakat AF, Khalid U, Mamas MA, Birnbaum Y, Elgendy IY, et al. Screening for atrial fibrillation in the elderly: a network meta-analysis of randomized trials. *Eur J Intern Med*. 2022;105:38–45. doi: 10.1016/j.ejim.2022.07.015
140. Perez MV, Mahaffey KW, Hedlin H, Rumsfeld JS, Garcia A, Ferris T, Balasubramanian V, Russo AM, Rajmane A, Cheung L, et al; Apple Heart Study Investigators. Large-scale assessment of a smartwatch to identify atrial fibrillation. *N Engl J Med*. 2019;381:1909–1917. doi: 10.1056/NEJMoa1901183
141. Kaplan RM, Koehler J, Ziegler PD, Sarkar S, Zweibel S, Passman RS. Stroke risk as a function of atrial fibrillation duration and CHA2DS2-VASc score. *Circulation*. 2019;140:1639–1646. doi: 10.1161/CIRCULATIONAHA.119.041303
142. Lopez-Sainz A, Dominguez F, Lopes LR, Ochoa JP, Barriales-Villa R, Climent V, Linschoten M, Tiron C, Chiriatti C, Marques N, et al; European Genetic Cardiomyopathies Initiative Investigators. Clinical features and natural history of *PRKAG2* variant cardiac glycogenosis. *J Am Coll Cardiol*. 2020;76:186–197. doi: 10.1016/j.jacc.2020.05.029
143. Akhtar MM, Lorenzini M, Cicerchia M, Ochoa JP, Hey TM, Sabater Molina M, Restrepo-Cordoba MA, Dal Ferro M, Stolfo D, Johnson R, et al. Clinical phenotypes and prognosis of dilated cardiomyopathy caused by truncating variants in the *TTN* gene. *Circ Heart Fail*. 2020;13:e006832. doi: 10.1161/CIRCHEARTFAILURE.119.006832
144. Yoneda ZT, Anderson KC, Quintana JA, O'Neill MJ, Sims RA, Glazer AM, Shaffer CM, Crawford DM, Stricker T, Ye F, et al. Early-onset atrial fibrillation and the prevalence of rare variants in cardiomyopathy and arrhythmia genes. *JAMA Cardiol*. 2021;6:1371–1379. doi: 10.1001/jamacardio.2021.3370
145. Alzahrani Z, Ornelas-Loredo A, Darbar SD, Farooqui A, Mol D, Chalazan B, Villagrana NE, McCauley M, Lazar S, Wissner E, et al. Association between family history and early-onset atrial fibrillation across racial and ethnic groups. *JAMA Netw Open*. 2018;1:e182497. doi: 10.1001/jamanetworkopen.2018.2497
146. Chang SH, Kuo CF, Chou IJ, See LC, Yu KH, Luo SF, Huang LH, Zhang W, Doherty M, Wen MS, et al. Association of a family history of atrial fibrillation with incidence and outcomes of atrial fibrillation: a population-based family cohort study. *JAMA Cardiol*. 2017;2:863–870. doi: 10.1001/jamacardio.2017.1855
147. Roselli C, Chaffin MD, Weng LC, Aeschbacher S, Ahlberg G, Albert CM, Almgren P, Alonso A, Anderson CD, Aragam KG, et al. Multi-ethnic genome-wide association study for atrial fibrillation. *Nat Genet*. 2018;50:1225–1233. doi: 10.1038/s41588-018-0133-9
148. Nielsen JB, Thorolfsdottir RB, Fritsche LG, Zhou W, Skov MW, Graham SE, Herron TJ, McCarthy S, Schmidt EM, Sveinbjornsson G, et al. Biobank-driven genomic discovery yields new insight into atrial fibrillation biology. *Nat Genet*. 2018;50:1234–1239. doi: 10.1038/s41588-018-0171-3
149. Gudbjartsson DF, Helgason H, Gudjonsson SA, Zink F, Oddson A, Gylfason A, Besenbacher S, Magnusson G, Halldorsson BV, Hjartarson E, et al. Large-scale whole-genome sequencing of the Icelandic population. *Nat Genet*. 2015;47:435–444. doi: 10.1038/ng.3247
150. Xiong H, Yang Q, Zhang X, Wang P, Chen F, Liu Y, Wang P, Zhao Y, Li S, Huang Y, et al. Significant association of rare variant pGly8Ser in cardiac sodium channel beta4-subunit *SCN4B* with atrial fibrillation. *Ann Hum Genet*. 2019;83:239–248. doi: 10.1111/ahg.12305
151. Olson TM, Alekseev AE, Liu XK, Park S, Zingman LV, Bienengraeber M, Sattiraju S, Ballew JD, Jahangir A, Terzic A. Kv15 channelopathy due to *KCNA5* loss-of-function mutation causes human atrial fibrillation. *Hum Mol Genet*. 2006;15:2185–2191. doi: 10.1093/hmg/ddl143
152. Ahlberg G, Refsgaard L, Lundegaard PR, Andreasen L, Ranthe MF, Linscheid N, Nielsen JB, Melbye M, Haunso S, Sajadieh A, et al. Rare truncating variants in the sarcomeric protein titin associate with familial and early-onset atrial fibrillation. *Nat Commun*. 2018;9:4316. doi: 10.1038/s41467-018-06618-y
153. Choi SH, Weng LC, Roselli C, Lin H, Haggerty CM, Shoemaker MB, Barnard J, Arking DE, Chasman DI, Albert CM, et al; DiscovEHR study and the NHLBI Trans-Omics for Precision Medicine (TOPMed) Consortium. Association between titin loss-of-function variants and early-onset atrial fibrillation. *JAMA*. 2018;320:2354–2364. doi: 10.1001/jama.2018.18179
154. Norby FL, Tang W, Pankow JS, Lutsey PL, Alonso A, Steffan B, Chen LY, Zhang M, Shippee ND, Ballantyne CM, et al. Proteomics and risk of atrial fibrillation in older adults (from the Atherosclerosis Risk in Communities [ARIC] Study). *Am J Cardiol*. 2021;161:42–50. doi: 10.1016/j.amjcard.2021.08.064
155. Mars N, Koskela JT, Ripatti P, Kiiskinen TTJ, Havulinna AS, Lindbohm JV, Ahola-Olli A, Kurki M, Karjalainen J, Palta P, et al. Polygenic and clinical risk scores and their impact on age at onset and prediction of cardiometabolic diseases and common cancers. *Nat Med*. 2020;26:549–557. doi: 10.1038/s41591-020-0800-0
156. Lubitz SA, Yin X, Lin HJ, Kolek M, Smith JG, Trompet S, Rienstra M, Rost NS, Teixeira PL, Almgren P, et al; AFGen Consortium. Genetic risk prediction of atrial fibrillation. *Circulation*. 2017;135:1311–1320. doi: 10.1161/CIRCULATIONAHA.116.024143
157. Miyazawa K, Ito K, Ito M, Zou Z, Kubota M, Nomura S, Matsunaga H, Koyama S, Ieki H, Akiyama M, et al. Cross-ancestry genome-wide analysis of atrial fibrillation unveils disease biology and enables cardioembolic risk prediction. *Nat Genet*. 2023;55:187–197. doi: 10.1038/s41588-022-01284-9
158. Norland K, Sveinbjornsson G, Thorolfsdottir RB, Davidsson OB, Tragante V, Rajamani S, Helgadottir A, Gretarsdottir S, van Setten J, Asselbergs FW, et al. Sequence variants with large effects on cardiac electrophysiology and disease. *Nat Commun*. 2019;10:4803. doi: 10.1038/s41467-019-12682-9
159. Ntalla I, Weng LC, Cartwright JH, Hall AW, Sveinbjornsson G, Tucker NR, Choi SH, Chaffin MD, Roselli C, Barnes MR, et al. Multi-ancestry GWAS of the electrocardiographic PR interval identifies 202 loci underlying cardiac conduction. *Nat Commun*. 2020;11:2542. doi: 10.1038/s41467-020-15706-x
160. Zhao D, Bartz TM, Sotoodehnia N, Post WS, Heckbert SR, Alonso A, Longchamps RJ, Castellani CA, Hong YS, Rotter JI, et al. Mitochondrial DNA copy number and incident atrial fibrillation. *BMC Med*. 2020;18:246. doi: 10.1186/s12916-020-01715-6
161. Jamaly S, Carlsson L, Peltonen M, Jacobson P, Sjostrom L, Karason K. Bariatric surgery and the risk of new-onset atrial fibrillation in

Swedish obese subjects. *J Am Coll Cardiol*. 2016;68:2497–2504. doi: 10.1016/j.jacc.2016.09.940
162. Höskuldsdóttir G, Sattar N, Miftaraj M, Näslund I, Ottosson J, Franzén S, Svensson AM, Eliasson B. Potential effects of bariatric surgery on the incidence of heart failure and atrial fibrillation in patients with type 2 diabetes mellitus and obesity and on mortality in patients with preexisting heart failure: a nationwide, matched, observational cohort study. *J Am Heart Assoc*. 2021;10:e019323. doi: 10.1161/JAHA.120.019323
163. Pathak R, Evans M, Middeldorpa M, Mahajan R, Mehta A, Megan M, Twomey D, Wong C, Hendriks J, Abhayaratna W. Cost-effectiveness and clinical effectiveness of the risk factor management clinic in atrial fibrillation. *JACC Clin Electrophysiol*. 2017;3:436–447. doi: 10.1016/j.jacep.2016.12.015
164. Mehra R, Chung MK, Olshansky B, Dobrev D, Jackson CL, Kundel V, Linz D, Redeker NS, Redline S, Sanders P, et al; on behalf of the American Heart Association Electrocardiography and Arrhythmias Committee of the Council on Clinical Cardiology; and Stroke Council. Sleep-disordered breathing and cardiac arrhythmias in adults: mechanistic insights and clinical implications: a scientific statement from the American Heart Association. *Circulation*. 2022;146:e119–e136. doi: 10.1161/CIR.0000000000001082
165. Traaen GM, Aakerøy L, Hunt TE, Øverland B, Bendz C, Sande L, Aakhus S, Fagerland MW, Steinshamn S, Anfinsen OG, et al. Effect of continuous positive airway pressure on arrhythmia in atrial fibrillation and sleep apnea: a randomized controlled trial. *Am J Respir Crit Care Med*. 2021;204:573–582. doi: 10.1164/rccm.202011-4133OC
166. Deleted in proof
167. Silberberg A, Tan MK, Yan AT, Angaran P, Dorian P, Bucci C, Gregoire JC, Bell AD, Gladstone DJ, Green MS, et al; FREEDOM AF and CONNECT AF Investigators. Use of evidence-based therapy for cardiovascular risk factors in Canadian outpatients with atrial fibrillation: from the Facilitating Review and Education to Optimize Stroke Prevention in Atrial Fibrillation (FREEDOM AF) and Co-ordinated National Network to Engage Physicians in the Care and Treatment of Patients With Atrial Fibrillation (CONNECT AF). *Am J Cardiol*. 2017;120:582–587. doi: 10.1016/j.amjcard.2017.05.027
168. Fatemi O, Yuriditsky E, Tsioufis C, Tsachris D, Morgan T, Basile J, Bigger T, Cushman W, Goff D, Soliman EZ, et al. Impact of intensive glycemic control on the incidence of atrial fibrillation and associated cardiovascular outcomes in patients with type 2 diabetes mellitus (from the Action to Control Cardiovascular Risk in Diabetes Study). *Am J Cardiol*. 2014;114:1217–1222. doi: 10.1016/j.amjcard.2014.07.045
169. Emdin CA, Callender T, Cao J, Rahimi K. Effect of antihypertensive agents on risk of atrial fibrillation: a meta-analysis of large-scale randomized trials. *Europace*. 2015;17:701–710. doi: 10.1093/europace/euv021
170. Soliman EZ, Rahman AF, Zhang ZM, Rodriguez CJ, Chang TI, Bates JT, Ghazi L, Blackshear JL, Chonchol M, Fine LJ, et al. Effect of intensive blood pressure lowering on the risk of atrial fibrillation. *Hypertension*. 2020;75:1491–1496. doi: 10.1161/HYPERTENSIONAHA.120.14766
171. Garnvik LE, Malmo V, Janszky I, Wisløff U, Loennechen JP, Nes BM. Physical activity modifies the risk of atrial fibrillation in obese individuals: the HUNT3 study. *Eur J Prev Cardiol*. 2020;25:1646–1652. doi: 10.1177/2047487318784365
172. Garg PK, Wilson N, Levitan EB, Shikany JM, Howard VJ, Newby PK, Judd S, Howard G, Cushman M, Soliman EZ. Associations of dietary patterns with risk of incident atrial fibrillation in the REasons for Geographic And Racial Differences in Stroke (REGARDS). *Eur J Nutr*. 2023;62:2441–2448. doi: 10.1007/s00394-023-03159-z
173. Oliveri F, Bongiorno A, Compagnoni S, Fasolino A, Gentile FR, Pepe A, Tua L. Statin and postcardiac surgery atrial fibrillation prevention: a systematic review and meta-analysis. *J Cardiovasc Pharmacol*. 2022;80:180–186. doi: 10.1097/FJC.0000000000001294
174. Voskoboinik A, Kalman JM, De Silva A, Nicholls T, Costello B, Nanayakkara S, Prabhu S, Stub D, Azzopardi S, Vizi D, et al. Alcohol abstinence in drinkers with atrial fibrillation. *N Engl J Med*. 2020;382:20–28. doi: 10.1056/NEJMoa1817591
175. Rienstra M, Hobbelt AH, Alings M, Tijssen JGP, Smit MD, Brügemann J, Geelhoed B, Tieleman RG, Hillege HL, Tukkie R, et al; RACE 3 Investigators. Targeted therapy of underlying conditions improves sinus rhythm maintenance in patients with persistent atrial fibrillation: results of the RACE 3 trial. *Eur Heart J*. 2018;39:2987–2996. doi: 10.1093/eurheartj/ehx739
176. O'Neal WT, Efird JT, Judd SE, McClure LA, Howard VJ, Howard G, Soliman EZ. Impact of awareness and patterns of nonhospitalized atrial fibrillation on the risk of mortality: the Reasons for Geographic And Racial Differences in Stroke (REGARDS) Study. *Clin Cardiol*. 2016;39:103–110. doi: 10.1002/clc.22501
177. Reading SR, Go AS, Fang MC, Singer DE, Liu IA, Black MH, Udaltsova N, Reynolds K; Anticoagulation and Risk Factors in Atrial Fibrillation–Cardiovascular Research Network (ATRIA-CVRN) Investigators. Health literacy and awareness of atrial fibrillation. *J Am Heart Assoc*. 2017;6:e005128. doi: 10.1161/JAHA.116.005128
178. Xian Y, O'Brien EC, Liang L, Xu H, Schwamm LH, Fonarow GC, Bhatt DL, Smith EE, Olson DM, Maisch L, et al. Association of preceding antithrombotic treatment with acute ischemic stroke severity and in-hospital outcomes among patients with atrial fibrillation. *JAMA*. 2017;317:1057–1067. doi: 10.1001/jama.2017.1371
179. Hsu JC, Maddox TM, Kennedy KF, Katz DF, Marzec LN, Lubitz SA, Gehi AK, Turakhia MP, Marcus GM. Oral anticoagulant therapy prescription in patients with atrial fibrillation across the spectrum of stroke risk: insights from the NCDR PINNACLE registry. *JAMA Cardiol*. 2016;1:55–62. doi: 10.1001/jamacardio.2015.0374
180. Marzec LN, Wang J, Shah ND, Chan PS, Ting HH, Gosch KL, Hsu JC, Maddox TM. Influence of direct oral anticoagulants on rates of oral anticoagulation for atrial fibrillation. *J Am Coll Cardiol*. 2017;69:2475–2484. doi: 10.1016/j.jacc.2017.03.540
181. Thompson LE, Maddox TM, Lei L, Grunwald GK, Bradley SM, Peterson PN, Masoudi FA, Turchin A, Song Y, Doros G, et al. Sex Differences in the use of oral anticoagulants for atrial fibrillation: a report from the National Cardiovascular Data Registry (NCDR) PINNACLE registry. *J Am Heart Assoc*. 2017;6:e005801. doi: 10.1161/JAHA.117.005801
182. Yong CM, Liu Y, Apruzzese P, Doros G, Cannon CP, Maddox TM, Gehi A, Hsu JC, Lubitz SA, Virani S, et al; ACC PINNACLE Investigators. Association of insurance type with receipt of oral anticoagulation in insured patients with atrial fibrillation: a report from the American College of Cardiology NCDR PINNACLE registry. *Am Heart J*. 2018;195:50–59. doi: 10.1016/j.ahj.2017.08.010
183. McIntyre WF, Conen D, Olshansky B, Halperin JL, Hayek E, Huisman MV, Lip GYH, Lu S, Healey JS. Stroke-prevention strategies in North American patients with atrial fibrillation: the GLORIA-AF registry program. *Clin Cardiol*. 2018;41:744–751. doi: 10.1002/clc.22936
184. Essien UR, Magnani JW, Chen N, Gellad WF, Fine MJ, Hernandez I. Race/ethnicity and sex-related differences in direct oral anticoagulant initiation in newly diagnosed atrial fibrillation: a retrospective study of Medicare data. *J Natl Med Assoc*. 2020;112:103–108. doi: 10.1016/j.jnma.2019.10.003
185. Essien UR, Holmes DN, Jackson LR 2nd, Fonarow GC, Mahaffey KW, Reiffel JA, Steinberg BA, Allen LA, Chan PS, Freeman JV, et al. Association of race/ethnicity with oral anticoagulant use in patients with atrial fibrillation: findings from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II. *JAMA Cardiol*. 2018;3:1174–1182. doi: 10.1001/jamacardio.2018.3945
186. Essien UR, Chiswell K, Kaltenbach LA, Wang TY, Fonarow GC, Thomas KL, Turakhia MP, Benjamin EJ, Rodriguez F, Fang MC, et al. Association of race and ethnicity with oral anticoagulation and associated outcomes in patients with atrial fibrillation: findings from the Get With The Guidelines-Atrial Fibrillation Registry. *JAMA Cardiol*. 2022;7:1207–1217. doi: 10.1001/jamacardio.2022.3704
187. Sur NB, Wang K, Di Tullio MR, Gutierrez CM, Dong C, Koch S, Gardener H, García-Rivera EJ, Zevallos JC, Burgin WS, et al. Disparities and temporal trends in the use of anticoagulation in patients with ischemic stroke and atrial fibrillation. *Stroke*. 2019;50:1452–1459. doi: 10.1161/STROKEAHA.118.023959
188. Gallagher C, Elliott AD, Wong CX, Rangnekar G, Middeldorp ME, Mahajan R, Lau DH, Sanders P, Hendriks JML. Integrated care in atrial fibrillation: a systematic review and meta-analysis. *Heart*. 2017;103:1947–1953. doi: 10.1136/heartjnl-2016-310952
189. Centers for Disease Control and Prevention and National Center for Health Statistics. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death micro-data files. Accessed April 8, 2023. https://cdc.gov/nchs/nvss/mortality_public_use_data.htm
190. Centers for Disease Control and Prevention and National Center for Health Statistics. Multiple cause of death, CDC WONDER online database. Accessed April 1, 2023. https://wonder.cdc.gov/mcd-icd10.html
191. Emdin CA, Wong CX, Hsiao AJ, Altman DG, Peters SA, Woodward M, Odutayo AA. Atrial fibrillation as risk factor for cardiovascular disease and death in women compared with men: systematic review and meta-analysis of cohort studies. *BMJ*. 2016;532:h7013. doi: 10.1136/bmj.h7013
192. DeLago AJ, Essa M, Ghajar A, Hammond-Haley M, Parvez A, Nawaz I, Shalhoub J, Marshall DC, Nazarian S, Calkins H, et al. Incidence and mortality trends of atrial fibrillation/atrial flutter in the United States 1990 to 2017. *Am J Cardiol*. 2021;148:78–83. doi: 10.1016/j.amjcard.2021.02.014

193. Chamberlain AM, Gersh BJ, Alonso A, Chen LY, Berardi C, Manemann SM, Killian JM, Weston SA, Roger VL. Decade-long trends in atrial fibrillation incidence and survival: a community study. *Am J Med*. 2015;128:260–267. e1. doi: 10.1016/j.amjmed.2014.10.030
194. Vinter N, Huang Q, Fenger-Grøn M, Frost L, Benjamin EJ, Trinquart L. Trends in excess mortality associated with atrial fibrillation over 45 years (Framingham Heart Study): community based cohort study. *BMJ*. 2020;370:m2724. doi: 10.1136/bmj.m2724
195. Masri A, Kanj M, Thamilarasan M, Wazni O, Smedira NG, Lever HM, Desai MY. Outcomes in hypertrophic cardiomyopathy patients with and without atrial fibrillation: a survival meta-analysis. *Cardiovasc Diagn Ther*. 2017;7:36–44. doi: 10.21037/cdt.2016.11.23
196. Alphonse P, Virk S, Collins J, Campbell T, Thomas SP, Semsarian C, Kumar S. Prognostic impact of atrial fibrillation in hypertrophic cardiomyopathy: a systematic review. *Clin Res Cardiol*. 2021;110:544–554. doi: 10.1007/s00392-020-01730-w
197. Camen S, Csengeri D, Geelhoed B, Niiranen T, Gianfagna F, Vishram-Nielsen JK, Costanzo S, Söderberg S, Vartiainen E, Börschel CS, et al. Risk factors, subsequent disease onset, and prognostic impact of myocardial infarction and atrial fibrillation. *J Am Heart Assoc*. 2022;11:e024299. doi: 10.1161/JAHA.121.024299
198. Saxena A, Virk SA, Bowman S, Chan L, Jeremy R, Bannon PG. Preoperative atrial fibrillation portends poor outcomes after coronary bypass graft surgery: a systematic review and meta-analysis. *J Thorac Cardiovasc Surg*. 2018;155:1524–1533.e2. doi: 10.1016/j.jtcvs.2017.11.048
199. Kaw R, Hernandez AV, Masood I, Gillinov AM, Saliba W, Blackstone EH. Short- and long-term mortality associated with new-onset atrial fibrillation after coronary artery bypass grafting: a systematic review and meta-analysis. *J Thorac Cardiovasc Surg*. 2011;141:1305–1312. doi: 10.1016/j.jtcvs.2010.10.040
200. Phan K, Ha HS, Phan S, Medi C, Thomas SP, Yan TD. New-onset atrial fibrillation following coronary bypass surgery predicts long-term mortality: a systematic review and meta-analysis. *Eur J Cardiothorac Surg*. 2015;48:817–824. doi: 10.1093/ejcts/ezu551
201. Brener MI, George I, Kosmidou I, Nazif T, Zhang Z, Dizon JM, Garan H, Malaisrie SC, Makkar R, Mack M, et al. Atrial fibrillation is associated with mortality in intermediate surgical risk patients with severe aortic stenosis: analyses from the PARTNER 2A and PARTNER S3i trials. *J Am Heart Assoc*. 2021;10:e019584. doi: 10.1161/JAHA.120.019584
202. Mojoli M, Gersh BJ, Barioli A, Masiero G, Tellaroli P, D'Amico G, Tarantini G. Impact of atrial fibrillation on outcomes of patients treated by transcatheter aortic valve implantation: a systematic review and meta-analysis. *Am Heart J*. 2017;192:64–75. doi: 10.1016/j.ahj.2017.07.005
203. Vitalis A, Shantsila A, Proietti M, Vohra RK, Kay M, Olshansky B, Lip GYH. Peripheral arterial disease in patients with atrial fibrillation: the AFFIRM study. *Am J Med*. 2021;134:514–518. doi: 10.1016/j.amjmed.2020.08.026
204. Vrsalovic M, Presecki AV. Atrial fibrillation and risk of cardiovascular events and mortality in patients with symptomatic peripheral artery disease: a meta-analysis of prospective studies. *Clin Cardiol*. 2017;40:1231–1235. doi: 10.1002/clc.22813
205. Lin HJ, Wolf PA, Kelly-Hayes M, Beiser AS, Kase CS, Benjamin EJ, D'Agostino RB. Stroke severity in atrial fibrillation: the Framingham study. *Stroke*. 1996;27:1760–1764. doi: 10.1161/01.str.27.10.1760
206. Cheng M, Lu X, Huang J, Zhang J, Zhang S, Gu D. The prognostic significance of atrial fibrillation in heart failure with a preserved and reduced left ventricular function: insights from a meta-analysis. *Eur J Heart Fail*. 2014;16:1317–1322. doi: 10.1002/ejhf.187
207. Odutayo A, Wong CX, Williams R, Hunn B, Emdin CA. Prognostic importance of atrial fibrillation timing and pattern in adults with congestive heart failure: a systematic review and meta-analysis. *J Card Fail*. 2017;23:56–62. doi: 10.1016/j.cardfail.2016.08.005
208. Weber C, Hung J, Hickling S, Nedkoff L, Murray K, Li I, Briffa TG. Incidence, predictors and mortality risk of new heart failure in patients hospitalised with atrial fibrillation. *Heart*. 2021;107:1320–1326. doi: 10.1136/heartjnl-2020-318648
209. Echouffo-Tcheugui JB, Shrader P, Thomas L, Gersh BJ, Kowey PR, Mahaffey KW, Singer DE, Hylek EM, Go AS, Peterson ED, et al. Care patterns and outcomes in atrial fibrillation patients with and without diabetes: ORBIT-AF Registry. *J Am Coll Cardiol*. 2017;70:1325–1335. doi: 10.1016/j.jacc.2017.07.755
210. Walkey AJ, Hammill BG, Curtis LH, Benjamin EJ. Long-term outcomes following development of new-onset atrial fibrillation during sepsis. *Chest*. 2014;146:1187–1195. doi: 10.1378/chest.14-0003
211. Kanjanahattakij N, Rattanawong P, Krishnamoorthy P, Horn B, Chongsathidkiet P, Garvia V, Putthapiban P, Sirinvaravong N, Figueredo VM. New-onset atrial fibrillation is associated with increased mortality in critically ill patients: a systematic review and meta-analysis. *Acta Cardiol*. 2019;74:162–169. doi: 10.1080/00015385.2018.1477035
212. Garg L, Agrawal S, Agarwal M, Shah M, Garg A, Patel B, Agarwal N, Nanda S, Sharma A, Cox D. Influence of atrial fibrillation on outcomes in patients who underwent primary percutaneous coronary intervention for ST-Segment elevation myocardial infarction. *Am J Cardiol*. 2018;121:684–689. doi: 10.1016/j.amjcard.2017.12.003
213. Antikainen RL, Peters R, Beckett NS, Rajkumar C, Bulpitt CJ. Atrial fibrillation and the risk of cardiovascular disease and mortality in the Hypertension in the Very Elderly Trial. *J Hypertens*. 2020;38:839–844. doi: 10.1097/HJH.0000000000002346
214. Magnani JW, Norby FL, Agarwal SK, Soliman EZ, Chen LY, Loehr LR, Alonso A. Racial differences in atrial fibrillation-related cardiovascular disease and mortality: the Atherosclerosis Risk in Communities (ARIC) study. *JAMA Cardiol*. 2016;1:433–441. doi: 10.1001/jamacardio.2016.1025
215. Roth GA, Dwyer-Lindgren L, Bertozzi-Villa A, Stubbs RW, Morozoff C, Naghavi M, Mokdad AH, Murray CJL. Trends and patterns of geographic variation in cardiovascular mortality among US counties, 1980-2014. *JAMA*. 2017;317:1976–1992. doi: 10.1001/jama.2017.4150
216. Doshi R, Al-Khafaji JF, Dave M, Taha M, Patel K, Goyal H, Gullapalli N. Comparison of baseline characteristics and in-hospital outcomes in Medicaid versus private insurance hospitalizations for atrial fibrillation. *Am J Cardiol*. 2019;123:776–781. doi: 10.1016/j.amjcard.2018.11.045
217. Tanaka Y, Shah NS, Passman R, Greenland P, Lloyd-Jones DM, Khan SS. Trends in cardiovascular mortality related to atrial fibrillation in the United States, 2011 to 2018. *J Am Heart Assoc*. 2021;10:e020163. doi: 10.1161/JAHA.120.020163
218. O'Neal WT, Sandesara PB, Kelli HM, Venkatesh S, Soliman EZ. Urban-rural differences in mortality for atrial fibrillation hospitalizations in the United States. *Heart Rhythm*. 2018;15:175–179. doi: 10.1016/j.hrthm.2017.10.019
219. Yang H, Liang X, Xu J, Hou H, Wang Y. Meta-analysis of atrial fibrillation in patients with COVID-19. *Am J Cardiol*. 2021;144:152–156. doi: 10.1016/j.amjcard.2021.01.010
220. Wandell P, Carlsson AC, Gasevic D, Sundquist J, Sundquist K. Neighbourhood socio-economic status and all-cause mortality in adults with atrial fibrillation: a cohort study of patients treated in primary care in Sweden. *Int J Cardiol*. 2016;202:776–781. doi: 10.1016/j.ijcard.2015.09.027
221. Wändell P, Carlsson AC, Gasevic D, Holzmann MJ, Ärnlöv J, Sundquist J, Sundquist K. Socioeconomic factors and mortality in patients with atrial fibrillation: a cohort study in Swedish primary care. *Eur J Public Health*. 2018;28:1103–1109. doi: 10.1093/eurpub/cky075
222. Shi M, Chen LY, Bekwelem W, Norby FL, Soliman EZ, Alam AB, Alonso A. Association of atrial fibrillation with incidence of extracranial systemic embolic events: the ARIC study. *J Am Heart Assoc*. 2020;9:e016724. doi: 10.1161/JAHA.120.016724
223. Quinn GR, Severdija ON, Chang Y, Singer DE. Wide Variation in reported rates of stroke across cohorts of patients with atrial fibrillation. *Circulation*. 2017;135:208–219. doi: 10.1161/CIRCULATIONAHA.116.024057
224. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham study. *Stroke*. 1991;22:983–988. doi: 10.1161/01.str.22.8.983
225. Kabra R, Cram P, Girotra S, Vaughan Sarrazin M. Effect of race on outcomes (stroke and death) in patients >65 years with atrial fibrillation. *Am J Cardiol*. 2015;116:230–235. doi: 10.1016/j.amjcard.2015.04.012
226. Kabra R, Girotra S, Vaughan Sarrazin M. Refining stroke prediction in atrial fibrillation patients by addition of African-American ethnicity to CHA2DS2-VASc score. *J Am Coll Cardiol*. 2016;68:461–470. doi: 10.1016/j.jacc.2016.05.044
227. Patel PJ, Katz R, Borovskiy Y, Killian A, Levine JM, McNaughton NW, Callans D, Supple G, Dixit S, Epstein AE, et al. Race and stroke in an atrial fibrillation inception cohort: findings from the Penn Atrial Fibrillation Free study. *Heart Rhythm*. 2018;15:487–493. doi: 10.1016/j.hrthm.2017.11.025
228. Harrison SL, Fazio-Eynullayeva E, Lane DA, Underhill P, Lip GYH. Atrial fibrillation and the risk of 30-day incident thromboembolic events, and mortality in adults >/= 50 years with COVID-19. *J Arrhythm*. 2021;37:231–237. doi: 10.1002/joa3.12458
229. Liu DS, Chen J, Jian WM, Zhang GR, Liu ZR. The association of atrial fibrillation and dementia incidence: a meta-analysis of prospective cohort studies. *J Geriatr Cardiol*. 2019;16:298–306. doi: 10.11909/j.issn.1671-5411.2019.03.006
230. Islam MM, Poly TN, Walther BA, Yang HC, Wu CC, Lin MC, Chien SC, Li YC. Association between atrial fibrillation and dementia: a meta-analysis. *Front Aging Neurosci*. 2019;11:305. doi: 10.3389/fnagi.2019.00305

231. Giannone ME, Filippini T, Whelton PK, Chiari A, Vitolo M, Boriani G, Vinceti M. Atrial fibrillation and the risk of early-onset dementia: a systematic review and meta-analysis. *J Am Heart Assoc*. 2022;11:e025653. doi: 10.1161/JAHA.122.025653
232. Conen D, Rodondi N, Muller A, Beer JH, Ammann P, Moschovitis G, Auricchio A, Hayoz D, Kobza R, Shah D, et al; Swiss-AF Study Investigators. Relationships of overt and silent brain lesions with cognitive function in patients with atrial fibrillation. *J Am Coll Cardiol*. 2019;73:989–999. doi: 10.1016/j.jacc.2018.12.039
233. Bailey MJ, Soliman EZ, McClure LA, Howard G, Howard VJ, Judd SE, Unverzagt FW, Wadley V, Sachs BC, Hughes TM. Relation of atrial fibrillation to cognitive decline (from the REasons for Geographic and Racial Differences in Stroke [REGARDS] study). *Am J Cardiol*. 2021;148:60–68. doi: 10.1016/j.amjcard.2021.02.036
234. Cadogan SL, Powell E, Wing K, Wong AY, Smeeth L, Warren-Gash C. Anticoagulant prescribing for atrial fibrillation and risk of incident dementia. *Heart*. 2021;107:1898–1904. doi: 10.1136/heartjnl-2021-319672
235. Rienstra M, Lyass A, Murabito JM, Magnani JW, Lubitz SA, Massaro JM, Ellinor PT, Benjamin EJ. Reciprocal relations between physical disability, subjective health, and atrial fibrillation: the Framingham Heart Study. *Am Heart J*. 2013;166:171–178. doi: 10.1016/j.ahj.2013.02.025
236. Zhang L, Gallagher R, Neubeck L. Health-related quality of life in atrial fibrillation patients over 65 years: a review. *Eur J Prev Cardiol*. 2015;22:987–1002. doi: 10.1177/2047487314538855
237. Piccini JP, Simon DN, Steinberg BA, Thomas L, Allen LA, Fonarow GC, Gersh B, Hylek E, Kowey PR, Reiffel JA, et al; Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) Investigators and Patients. Differences in clinical and functional outcomes of atrial fibrillation in women and men: two-year results from the ORBIT-AF registry. *JAMA Cardiol*. 2016;1:282–291. doi: 10.1001/jamacardio.2016.0529
238. Silva RL, Guhl EN, Althouse AD, Herbert B, Sharbaugh M, Essien UR, Hausmann LRM, Magnani JW. Sex differences in atrial fibrillation: patient-reported outcomes and the persistent toll on women. *Am J Prev Cardiol*. 2021;8:100252. doi: 10.1016/j.ajpc.2021.100252
239. Malik V, Gallagher C, Linz D, Elliott AD, Emami M, Kadhim K, Mishima R, Hendriks JML, Mahajan R, Arnolda L, et al. Atrial fibrillation is associated with syncope and falls in older adults: a systematic review and meta-analysis. *Mayo Clin Proc*. 2020;95:676–687. doi: 10.1016/j.mayocp.2019.09.029
240. Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, D'Agostino RB, Murabito JM, Kannel WB, Benjamin EJ. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation*. 2003;107:2920–2925. doi: 10.1161/01.CIR.0000072767.89944.6E
241. Chamberlain AM, Gersh BJ, Alonso A, Kopecky SL, Killian JM, Weston SA, Roger VL. No decline in the risk of heart failure after incident atrial fibrillation: a community study assessing trends overall and by ejection fraction. *Heart Rhythm*. 2017;14:791–798. doi: 10.1016/j.hrthm.2017.01.031
242. Steinberg BA, Li Z, O'Brien EC, Pritchard J, Chew DS, Bunch TJ, Mark DB, Nabutovsky Y, Greiner MA, Piccini JP. Atrial fibrillation burden and heart failure: data from 39,710 individuals with cardiac implanted electronic devices. *Heart Rhythm*. 2021;18:709–716. doi: 10.1016/j.hrthm.2021.01.021
243. Nicoli CD, O'Neal WT, Levitan EB, Singleton MJ, Judd SE, Howard G, Safford MM, Soliman EZ. Atrial fibrillation and risk of incident heart failure with reduced versus preserved ejection fraction. *Heart*. 2022;108:353–359. doi: 10.1136/heartjnl-2021-319122
244. Ruddox V, Sandven I, Munkhaugen J, Skattebu J, Edvardsen T, Otterstad JE. Atrial fibrillation and the risk for myocardial infarction, all-cause mortality and heart failure: a systematic review and meta-analysis. *Eur J Prev Cardiol*. 2017;24:1555–1566. doi: 10.1177/2047487317715769
245. Soliman EZ, Safford MM, Muntner P, Khodneva Y, Dawood FZ, Zakai NA, Thacker EL, Judd S, Howard VJ, Howard G, et al. Atrial fibrillation and the risk of myocardial infarction. *JAMA Intern Med*. 2014;174:107–114. doi: 10.1001/jamainternmed.2013.11912
246. Soliman EZ, Lopez F, O'Neal WT, Chen LY, Bengtson L, Zhang ZM, Loehr L, Cushman M, Alonso A. Atrial fibrillation and risk of ST-segment-elevation versus non-ST-segment-elevation myocardial infarction: the Atherosclerosis Risk in Communities (ARIC) study. *Circulation*. 2015;131:1843–1850. doi: 10.1161/CIRCULATIONAHA.114.014145
247. O'Neal WT, Sangal K, Zhang ZM, Soliman EZ. Atrial fibrillation and incident myocardial infarction in the elderly. *Clin Cardiol*. 2014;37:750–755. doi: 10.1002/clc.22339
248. Bansal N, Fan D, Hsu CY, Ordonez JD, Marcus GM, Go AS. Incident atrial fibrillation and risk of end-stage renal disease in adults with chronic kidney disease. *Circulation*. 2013;127:569–574. doi: 10.1161/CIRCULATIONAHA.112.123992
249. Mark PB, Carrero JJ, Matsushita K, Sang Y, Ballew SH, Grams ME, Coresh J, Surapaneni A, Brunskill NJ, Chalmers J, et al. Major cardiovascular events and subsequent risk of kidney failure with replacement therapy: a CKD Prognosis Consortium study. *Eur Heart J*. 2023;44:1157–1166. doi: 10.1093/eurheartj/ehac825
250. Rattanawong P, Upala S, Riangwiwat T, Jaruvongvanich V, Sanguankeo A, Vutthikraivit W, Chung EH. Atrial fibrillation is associated with sudden cardiac death: a systematic review and meta-analysis. *J Interv Card Electrophysiol*. 2018;51:91–104. doi: 10.1007/s10840-017-0308-9
251. Fawzy AM, Bisson A, Bodin A, Herbert J, Lip GYH, Fauchier L. Atrial fibrillation and the risk of ventricular arrhythmias and cardiac arrest: a nationwide population-based study. *J Clin Med*. 2023;12:1075. doi: 10.3390/jcm12031075
252. Ganesan AN, Chew DP, Hartshorne T, Selvanayagam JB, Aylward PE, Sanders P, McGavigan AD. The impact of atrial fibrillation type on the risk of thromboembolism, mortality, and bleeding: a systematic review and meta-analysis. *Eur Heart J*. 2016;37:1591–1602. doi: 10.1093/eurheartj/ehw007
253. Padfield GJ, Steinberg C, Swampillai J, Qian H, Connolly SJ, Dorian P, Green MS, Humphries KH, Klein GJ, Sheldon R, et al. Progression of paroxysmal to persistent atrial fibrillation: 10-year follow-up in the Canadian Registry of Atrial Fibrillation. *Heart Rhythm*. 2017;14:801–807. doi: 10.1016/j.hrthm.2017.01.038
254. Al-Kawaz M, Omran SS, Parikh NS, Elkind MSV, Soliman EZ, Kamel H. Comparative risks of ischemic stroke in atrial flutter versus atrial fibrillation. *J Stroke Cerebrovasc Dis*. 2018;27:839–844. doi: 10.1016/j.jstrokecerebrovasdis.2017.10.025
255. Lin YS, Chen TH, Chi CC, Lin MS, Tung TH, Liu CH, Chen YL, Chen MC. different implications of heart failure, ischemic stroke, and mortality between nonvalvular atrial fibrillation and atrial flutter: a view from a national cohort study. *J Am Heart Assoc*. 2017;6:e006406. doi: 10.1161/JAHA.117.006406
256. Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project (HCUP). Accessed April 1, 2023. http://hcupnet.ahrq.gov/
257. Centers for Disease Control and Prevention and National Center for Health Statistics. National Ambulatory Medical Care Survey (NAMCS) public use data files. Accessed April 1, 2023. https://cdc.gov/nchs/ahcd/datasets_documentation_related.htm#data
258. Jackson SL, Tong X, Yin X, George MG, Ritchey MD. Emergency department, hospital inpatient, and mortality burden of atrial fibrillation in the United States, 2006 to 2014. *Am J Cardiol*. 2017;120:1966–1973. doi: 10.1016/j.amjcard.2017.08.017
259. Meyre P, Blum S, Berger S, Aeschbacher S, Schoepfer H, Briel M, Osswald S, Conen D. Risk of hospital admissions in patients with atrial fibrillation: a systematic review and meta-analysis. *Can J Cardiol*. 2019;35:1332–1343. doi: 10.1016/j.cjca.2019.05.024
260. Jiang S, Seslar SP, Sloan LA, Hansen RN. Health care resource utilization and costs associated with atrial fibrillation and rural-urban disparities. *J Manag Care Spec Pharm*. 2022;28:1321–1330. doi: 10.18553/jmcp.2022.28.11.1321
261. Dieleman JL, Cao J, Chapin A, Chen C, Li Z, Liu A, Horst C, Kaldjian A, Matyasz T, Scott KW, et al. US health care spending by payer and health condition, 1996-2016. *JAMA*. 2020;323:863–884. doi: 10.1001/jama.2020.0734
262. Li X, Tse VC, Au-Doung LW, Wong ICK, Chan EW. The impact of ischaemic stroke on atrial fibrillation-related healthcare cost: a systematic review. *Europace*. 2017;19:937–947. doi: 10.1093/europace/euw093
263. Johnsen SP, Dalby LW, Tackstrom T, Olsen J, Fraschke A. Cost of illness of atrial fibrillation: a nationwide study of societal impact. *BMC Health Serv Res*. 2017;17:714. doi: 10.1186/s12913-017-2652-y
264. Global Burden of Disease Study and Institute for Health Metrics and Evaluation. University of Washington. Accessed August 2, 2023. http://ghdx.healthdata.org/
265. Healey JS, Oldgren J, Ezekowitz M, Zhu J, Pais P, Wang J, Commerford P, Jansky P, Avezum A, Sigamani A, et al. Occurrence of death and stroke in patients in 47 countries 1 year after presenting with atrial fibrillation: a cohort study. *Lancet*. 2016;388:1161–1169. doi: 10.1016/S0140-6736(16)30968-0
266. Huxley RR, Lopez FL, Folsom AR, Agarwal SK, Loehr LR, Soliman EZ, Maclehose R, Konety S, Alonso A. Absolute and attributable risks of atrial fibrillation in relation to optimal and borderline risk factors: the Atherosclerosis Risk in Communities (ARIC) study. *Circulation*. 2011;123:1501–1508. doi: 10.1161/CIRCULATIONAHA.110.009035

# 19. SUDDEN CARDIAC ARREST, VENTRICULAR ARRHYTHMIAS, AND INHERITED CHANNELOPATHIES

*See Tables 19-1 through 19-6 and Charts 19-1 through 19-5*

Click here to return to the Table of Contents

Click here to return to the Abbreviations

## Cardiac Arrest (Including VF and Ventricular Flutter)

***ICD-9 427.4, 427.5; ICD-10 I46.0, I46.1, I46.9, I49.0.***

2021, United States: Underlying cause mortality—20 114. Any-mention mortality—446 757.

## Tachycardia

***ICD-9 427.0, 427.1, 427.2; ICD-10 I47.1, I47.2, I47.9.***

2021, United States: Underlying cause mortality—1245. Any-mention mortality—11 201.

## Sudden Cardiac Arrest

Cardiac arrest is the cessation of cardiac mechanical activity as confirmed by the absence of signs of circulation.[1] An operational definition of SCA is unexpected cardiac arrest that results in attempts to restore circulation. If resuscitation attempts are unsuccessful, this situation is referred to as SCD. SCA results from many disease processes; an ILCOR consensus statement recommends categorizing cardiac arrest into events with external causes (drowning, trauma, asphyxia, electrocution, and drug overdose) or events with medical causes.[2] Because of fundamental differences in the underlying pathogenesis and system of care, epidemiological data for OHCA and IHCA are collected and reported separately. For similar reasons, data for infants (<1 year of age), children (1–18 years of age), and adults are reported separately. To that end, this chapter addresses epidemiology and statistics pertaining to adult OHCA, adult IHCA, pediatric OHCA, pediatric IHCA, SCA/SCD not associated with location, and special circumstances in separate subheadings for ease of use.

The 2024 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2024. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

## OHCA in Adults

### Incidence and Cause

***(See Tables 19-1 through 19-3)***

- The ongoing CARES registry[3] estimates the incidence of EMS-treated OHCA among individuals of any age in >2300 EMS agencies in the United States. Differences in bystander intervention and survival by race and ethnicity, sex, and neighborhood characteristics are listed in Table 19-1.
- Incidence of EMS-treated OHCA in US people of any age is 88.8 individuals per 100 000 population according to the 2022 CARES registry, with great variation between states (range, 49.9–137.0; Table 19-2).
- In 2022, location of OHCA in adults was most often a home or residence (72.1%), followed by public settings (17.3%) and nursing homes (10.6%; Table 19-3).[3]
- The initial recorded cardiac rhythm was VF, VT, or shockable by an automated external defibrillator in 17.3% of EMS-treated adult OHCAs in 2022 (Table 19-3).
- Of 2937 OHCA cases of SCA in people 2 to 45 years of age from 2009 to 2012 in Toronto, 1892 (64.4%) had presumed cardiac cause by Utstein definitions, but after detailed investigation, only 608 (20.7%) had an adjudicated pathology of cardiac cause.[4] Noncardiac causes included 130 (4.4%) blunt, penetrating, or burn injury traumas; 687 (23.4%) suicides; 521 (17.7%) drug overdoses; 288 (9.8%) acute noncardiac illnesses (eg, terminal illness); 218 (7.4%) motor vehicle collisions; 106 (3.6%) noncardiac vascular causes; 32 (1.1%) drownings; and 24 (0.82%) homicides.
- Among 608 OHCAs with a cardiac cause in people 2 to 45 years of age from 2009 to 2012 in Toronto, 243 (40%) were attributed to CHD, 174 (28.6%) were attributed to structural diseases of the myocardium, 98 (16.1%) were attributed to sudden unexplained death, 15 (2.5%) were attributed to other cardiac causes (anomalous coronary arteries, congenital HD, and tamponade), and 78 (12.8%) remained unspecified.[4]
- OHCA has been attributed to various causes, including cardiac (53%), respiratory (18%), neurological (3%), toxicological (6%), other (9%), and unknown (11%) in a multihospital health network observational study.[5]

### COVID-19 Effects on OHCA Incidence

The COVID-19 pandemic has had multiple effects on the incidence of OHCA.

- In New York City, the incidence of OHCA attended by EMS (March 1–April 25, 2020) increased 3-fold over the same period 1 year earlier.[6] Compared with the pre-COVID control period, individuals experiencing OHCA during COVID were older and more likely to be Asian, Black, Hispanic, or of >1 race than White. There was a higher prevalence of asystole and pulseless electric activity (ie, nonshockable rhythms) during the COVID-19 period compared with the control period.
- Early in the COVID-19 pandemic, incidence of OHCA in the United States was higher than in 2019, primarily in communities with high COVID-19 mortality (adjusted mean difference, 38.6 [95% CI, 37.1–40.1] per 1 million residents) and very high COVID-19 mortality (adjusted mean difference, 28.7 [95% CI, 26.7–30.6] per 1 million residents).[7]
- A study of nontraumatic OHCA calls in 3 counties in southeast Michigan between January 1 and May 31 of both 2019 and 2020 showed a 60% increase in OHCA calls during the pandemic months compared with the control period.[8] The increase in OHCA calls slightly lagged but otherwise mirrored the rise and fall of confirmed COVID-19 cases in the counties. OHCA increased disproportionately among individuals ≥85 years of age, Black individuals, and residents of nursing facilities. In 2020, patients with OHCA were 53% less likely to receive an advanced airway device compared with 2019 (397 patients [21.4%] in 2020 versus 529 [45.5%] in 2019; $P<0.001$). Of the calls received, the proportion that were for individuals who died in the field increased by 42% (1400 patients [75.5%] in 2020 versus 619 [53.3%] in 2019; $P<0.001$). A similar significant increase in OHCA and dead-on-arrival EMS responses was observed in Los Angeles, CA, in 2020 starting around the time of California's stay-at-home order compared with 2018 and 2019 ($P<0.001$).[9]
- A meta-analysis that included 10 studies from multiple countries found a 119% increase in OHCA during the pandemic compared with earlier control periods. For the patients with known outcomes (n=10992), mortality was 85% compared with 62% for the control periods.[10]
- In a Swiss study, a significant contribution to the increase in OHCA was attributable to delay in seeking care for AMI. A delay in symptom onset to contact with the medical system was measured during the COVID-19 pandemic compared with control (112 minutes versus 60 minutes; $P=0.049$).[11]
- In a large US registry, rates of sustained return of spontaneous circulation after OHCA were, on average, 28% lower during the first wave of the pandemic (March 16–April 2020) compared with the corresponding period in 2019 (23.0% versus 29.8%; adjusted rate ratio, 0.82 [95% CI, 0.78–0.87]; $P<0.001$).[7] The decline in sustained return of spontaneous circulation paralleled the concurrent rate of COVID-19 mortality in the community, ranging from 11% to 15% in communities with very low or low rates of COVID-19 mortality to 21% to 33% in communities with high or very high rates of COVID mortality.[7]

### Secular Trends

- Crude incidence of OHCA increased significantly from 64.75 to 76.10 per 100000 from 2002 to 2014 in a registry of 30560 patients from Queensland, Australia.[12] Rates of return of spontaneous circulation also increased from 6.31 to 9.99 per 100000.
- A national database of 120365 adult medical OHCAs in the Republic of Korea from 2006 to 2015 reported increases over time in layperson CPR (1.2% to 17.0%), age- and sex-adjusted survival (3.0% to 8.0%), and good functional recovery (0.9% to 5.8%).[13] Layperson CPR rates increased more in the highest socioeconomic quintile (1.6% to 32.5%) than in the lowest socioeconomic quintile (1.6% to 15.3%).

### Risk Factors

- The first 3 to 6 months after AMI are considered a high-risk period for OHCA. However, the actual risk data have been based on older studies that antedated current standards of care for patients with AMI. A survey of >120000 AMI survivors from 2009 to 2017 in the Swedish Cardiopulmonary Resuscitation Registry followed up for up to 90 days after hospital discharge found the incidence of OHCA to be 0.29%, which translates to 116 per 100000 person-years (if everyone was followed up for 90 days; 0.19% at 30 days or 228 per 100000 person-years).[14]
- MI with OHCA or cardiac arrest in the ED occurred in 9682 of 252882 patients (3.8%) from 224 hospitals in the NCDR ACTION Registry (2594 or 1.6% of patients with NSTEMI and 7088 or 7.5% of patients with STEMI).[15]
- Of 4729 patients with STEMI in Los Angeles County, California, from 2011 to 2014, 422 (9%) had OHCA.[16]
- In a clinical trial of a wearable defibrillator in 2302 patients with reduced EF (<35%) after AMI, 44 patients (1.9%) had arrhythmic sudden death, 21 (0.9%) had appropriate defibrillator shock, and 86 (3.7%) had death attributable to any cause during the first 90 days.[17]
- Incidence of OHCA increased with daily atmospheric levels of particulate matter in 249372 OHCAs in Japan from 2014 to 2015 (OR, 1.016 [95% CI, 1.009–1.023] per 10–μg/m3 increase in

PM2.5).[18] Similar findings were reported recently from Israel and Italy.[19,20]

### Sex

Variability in survival and neurological recovery after OHCA by sex has been reported by the studies below.

- Females compared with males with OHCA are older, less likely to present with shockable rhythms, and less likely to collapse in public. Despite these factors that would reduce survival, 1 study found that females have equivalent or higher rates of survival to hospital discharge or to 30 days relative to males.[21]
- In a registry that included 40 159 OHCAs from 2009 to 2012 in Singapore, Japan, the Republic of Korea, Malaysia, Thailand, Taiwan, and the United Arab Emirates, females represented 40% of individuals experiencing an OHCA.[22] Females were older, more often presented in a nonshockable rhythm, and more often received layperson CPR. There was no difference between sexes in survival of the event or survival to hospital discharge after adjustment for measured confounding factors.
- In an EMS-based registry of 3862 OHCAs from 2013 to 2015 that includes 90% of the population of New Zealand, OHCA was more common in males (69%) than females (31%).[23] This study found the same differences between sexes in age, rhythm, location of arrest, and witnessed collapse, as well as the absence of any difference in survival of the event or 30-day survival after adjustment for these factors.
- In contrast to the previous studies, in a prospective multicenter international registry of 2407 patients admitted to ICUs after OHCA from 2012 to 2017, females were less likely to survive to hospital discharge, but the difference was attenuated after adjustment for differences in clinical characteristics (30.1% versus 42.7%; aOR, 0.85 [95% CI, 0.67–1.08]).[24] Females were less likely to have a good neurological outcome at discharge from the index hospitalization (21.4% versus 34.0%; aOR, 0.74 [95% CI, 0.57–0.96]) and at 6 months after arrest (16.7% versus 29.4%; aOR, 0.73 [95% CI, 0.54–0.98]). The use of neuroimaging and other neurophysiological testing did not differ by sex. Females were more likely to undergo withdrawal of lifesaving therapy (55.6% versus 42.8%; aOR, 1.35 [95% CI, 1.09–1.66]).

### Social Determinants of Health/Health Equity

- A study of the NIS from 2006 through 2018 identified patients with OHCA who survived to hospital admission and IHCA.[25] Over the study period, the proportion of patients with SCA who were Black increased from 11.9% to 18.8%. Compared with patients of other races and ethnicities, Black people hospitalized for SCA were younger (61.1 years versus 65.9 years; $P<0.001$), had a slightly higher Charlson Comorbidity Index (1.50 versus 1.47; $P<0.001$), and had a greater proportion of females (49% versus 42%; $P<0.001$). Black people with SCA were less likely to undergo cardiac catheterization (9.5% versus 15.0%; OR, 0.61 [95% CI, 0.59–0.63]; $P<0.001$) compared with patients of other races and ethnicities and were more likely to die during the hospitalization (OR, 1.09 [95% CI, 1.08–1.11]; $P<0.001$). This study was not designed to adequately examine the patient, health system, and structural factors responsible for these differences.
- In a large artificial intelligence–guided statistical and geographic information system analysis of a prospectively collected multicenter data set of adult patients who sequentially presented to Houston metro area hospitals from January 1, 2007, to January 1, 2016, Black people were disproportionately more likely to have OHCA and, compared with White people, were significantly more likely to have poor neurological disposition (OR, 2.21 [95% CI, 1.25–3.92]; $P=0.006$) and to be discharged to a facility instead of home (OR, 1.39 [95% CI, 1.05–1.85]; $P=0.023$).[26] At a zip code level, each additional $10 000 above the median household income was associated with a decrease in the total number of cardiac arrests by 2.86 (95% CI, −4.26 to −1.46; $P<0.001$); zip codes with a median income above $54 600 compared with the FPL (ie, $20 650 in 2007 to $24 300 in 2017 for a family of 4) had 14.62 fewer arrests ($P<0.001$).[27] At an institutional level, compared with the safety-net hospital system, the university hospital serving largely commercially and Medicare-insured patients had the lowest odds of death (OR, 0.45; $P<0.001$), followed by the main private hospital serving primarily commercially insured patients (OR, 0.62; $P=0.017$). Geographic information system maps showed convergence of the greater density of poor neurological outcome cases and greater density of poorer Black residences, suggesting the intersectionality of risk based on race and ethnicity and low income.
- OHCA incidence in 123 municipalities surrounding Paris has strong geographic variations (RR varies from 0.23–2) based on 3414 cases from 2013 to 2015. Municipalities with a high SCA incidence are characterized by a lower SES and more social deprivation as measured with the Human Development Index 2.[28]
- In King County, Washington, the presence of more pharmacies or medical facilities was not associated with lower rates of OHCA or shorter response times; in fact, OHCA was more common in census tracts with more pharmacies or other medical facilities (OR, 1.28 [95% CI, 1.03–1.59]).[29]

- In an analysis of 347 705 SCDs in the United States between 1999 and 2019 from CDC WONDER, age-adjusted mortality rates were higher in rural than in urban counties.[30] In urban counties, rates of SCD declined from 1999 through 2013 (−0.05 [95% CI, −0.09 to −0.01]) but then increased through the end of the study period (0.08 [95% CI, 0.03–0.12]). In rural counties, age-adjusted mortality rates attributable to SCD declined throughout the study period, but the rate of decline slowed after 2013 (−0.29 versus −0.14). Age-adjusted mortality rates for urban-dwelling males increased from 2013 onward from 4.8 to 5.7 per 100 000 population. Age-adjusted mortality rates for rural-dwelling males were unchanged from 2013 onward: 9.3 versus 9.3 per 100 000 population. Age-adjusted mortality rates for urban-dwelling females were unchanged from 2013 onward: 4.2 versus 4.8 per 100 000 population. In contrast, age-adjusted mortality for rural-dwelling females declined from 8.9 to 7.7 per 100 000 population.
- In a national database of 120 365 adult medical OHCAs in the Republic of Korea from 2006 to 2015, there were differences from the lowest to highest socioeconomic quintiles for layperson CPR (5.5%–11.4%), survival to hospital discharge (3.8%–6.1%), and good functional recovery (1.9%–2.9%).[13]

### Awareness and Treatment

- The median annual CPR training rate for US counties was 2.39% (25th–75th percentiles, 0.88%–5.31%) according to training data from the AHA, the American Red Cross, and the Health & Safety Institute, the largest providers of CPR training in the United States.[31] Training rates were lower in rural areas, counties with high proportions of Black or Hispanic residents, and counties with lower median household income.
- Prevalence of reported current training in CPR was 18% and prevalence of having CPR training at some point was 65% in a survey of 9022 people in the United States in 2015.[32] The prevalence of CPR training was lower in Hispanic/Latino people, older people, people with less formal education, and lower-income groups.
- Those with prior CPR training include 90% of citizens in Norway[33]; 68% of citizens in Victoria, Australia[34]; 61.1% of laypeople in the United Kingdom[35]; and 49% of people in the Republic of Korea,[36] according to surveys.
- Prevalence of prior CPR training among 1076 adults in all states and territories in Australia was 540 (55.7%). The majority of respondents replied "unsure" (n=404, 37.6%) or "no" (n=316, 29.4%) when asked if they knew the difference between a cardiac arrest and a heart attack. Of respondents with CPR training, 227 (42%) received training >5 years ago.[37]
- Laypeople with knowledge of automated external defibrillators include 69.3% of people in the United Kingdom; 66% in Philadelphia, PA; and 32.6% in the Republic of Korea.[35,36,38] A total of 58% of Philadelphia respondents,[38] but only 2.1% of UK respondents,[35] reported that they would actually use an automated external defibrillator during a cardiac arrest.
- A survey of 5456 households in Beijing, China, Shanghai, China, and Bangalore, India, found that 26%, 15%, and 3% of respondents, respectively, were trained in CPR.[39]
- A survey of 501 inhabitants of Vienna, Austria, found that 52% would recognize cardiac arrest, 50% were willing to use an automated external defibrillator, and 33% were willing to do CPR.[40]
- Laypeople in the United States initiated CPR in 40% of OHCAs in CARES 2022 data.[3]
- Layperson CPR rates in Asian countries range from 10.5% to 40.9%.[41]
- Layperson CPR among 4525 witnessed pediatric OHCAs was 831 of 1669 (36.9%) for female patients versus 1336 of 2856 (46.8%) for male patients.[42]
- Laypeople in the United States were less likely to initiate CPR for people with OHCA in low-income Black neighborhoods (OR, 0.49 [95% CI, 0.41–0.58])[43] or in predominantly Hispanic neighborhoods (OR, 0.62 [95% CI, 0.44–0.89]) than in high-income White neighborhoods.[44]
- Examining 2013 to 2019 CARES data shows that 32.2% of arrests occurred in Black or Hispanic individuals. Black and Hispanic individuals were less likely to receive layperson CPR at home (aOR, 0.74 [95% CI, 0.72–0.76]) and in public (aOR, 0.63 [95% CI, 0.60–0.66]) compared with White individuals with OHCA.[45] This disparity persisted despite the racial makeup of the community in which they arrested and the economic strata.
- Layperson CPR rates varied from 1.3% to 72% in an international study including 35 communities across 25 countries.[46] Rates of layperson CPR correlated with gross domestic product per capita (0.772; $P<0.01$; $r^2=0.596$). Socioeconomically advantaged communities most likely have more resources to provide CPR education.

### Mortality

### (See Tables 19-2 through 19-4)

- Survival to hospital discharge after EMS-treated adult OHCA was 9.3% in the 2022 CARES registry on the basis of 143 507 adult cases, with variation between states reporting data (range, 5.5%–15.4%; Tables 19-2 and 19-3). Survival to

hospital discharge with good functional status was 7.5% in 2022 (Table 19-3).[3]

- Survival to hospital admission after EMS-treated nontraumatic OHCA in 2022 was 24.9% for all presentations, with higher survival rates in public places (36.9%) and lower survival rates in homes/residences (23.5%) and nursing homes (14.4%) in the 2022 CARES registry (Table 19-4).
- Survival to hospital discharge varied between regions of the United States, being higher in the Midwest (aOR, 1.16 [95% CI, 1.02–1.32]) and the South (aOR, 1.24 [95% CI, 1.09–1.40]) relative to the Northeast, in 154 177 patients hospitalized after OHCA in the NIS (2002–2013).[47]
- Survival at 1, 5, 10, and 15 years was 92.2%, 81.4%, 70.1%, and 62.3%, respectively, among 3449 patients surviving to hospital discharge after OHCA from 2000 to 2014 in Victoria, Australia.[48]
- Patients with STEMI who had OHCA had higher in-hospital mortality (38%) than patients with STEMI without OHCA (6%) in a Los Angeles, CA, registry of 4729 patients with STEMI from 2011 to 2014.[16]
- Survival to 30 days was lower for 2516 patients in nursing homes (1.7% [95% CI, 1.2%–2.2%]) than for 24 483 patients in private homes (4.9% [95% CI, 4.6%–5.2%]) in a national database in Denmark from 2001 to 2014.[49]
- An observational study of 104 patients resuscitated from OHCA without obvious cause underwent a CT scan protocol including noncontrast head CT, cardiac and thoracic CT, and abdominopelvic CT within 1.9±1.0 hours of hospital arrival.[50] Presumed causes of OHCA were identified in 39%. Potentially life-threatening complications of resuscitation were identified in 13% of cases.
- A meta-analysis was conducted to explore long-term survival from OHCA attributable to a suspected cardiac cause.[51] In 11 800 patients with OHCA, the median survival for patients surviving to hospital discharge was 5 years (IQR, 2.3–7.9 years). Survival to 10 years after hospital discharge was 63.9% (95% CI, 62.3%–65.4%).

### Treatment

- Immediate coronary angiography compared with standard of care in patients with OHCA and no STEMI was not associated with improved LV function in short-term measures, regardless of whether PCI was performed.[52] However, in a Korean prospective registry of 678 patients, high-risk patients who had early coronary angiography exhibited improved neurological function at 6 months (OR, 2.36 [95% CI, 1.61–3.46]), whereas low-risk patients showed no benefit (OR, 1.64 [95% CI, 0.57–4.72]).[53]
- A multicenter RCT of 530 patients resuscitated from OHCA with no evidence of STEMI compared outcomes with immediate and delayed coronary angiography.[54] At 30 days, mortality was 54% in the immediate angiography group versus 46% in the delayed angiography group (HR, 1.28 [95% CI, 1.00–1.63]; $P$=0.06). Death or severe neurological deficit occurred in 64.3% of the immediate angiography group versus 55.6% of the delayed angiography group (RR, 1.16 [95% CI, 1.00–1.34]).
- Multiple methods have been examined to predict neurological recovery and overall survival early after resuscitation from OHCA. Elevated serum levels of several biomarkers, including taurine[55] and neuron-specific enolase,[56–58] correlate with poorer outcomes.
- Guidelines recommend targeted temperature management to prevent hypoxic-ischemic brain damage in patients with coma after cardiac arrest.[59] However, the benefit of this treatment has been questioned. An open-label RCT of 1861 comatose adults resuscitated after OHCA with a cardiac cause compared survival with targeted hypothermia for 40 hours and normothermia. Hypothermia treatment did not improve survival ($P$=0.37), neurological status, or quality of life at 6 months..[60] A meta-analysis of multiple trials also found lack of benefit of hypothermia in individuals with OHCA.[61] ILCOR recommends temperature control for comatose survivors of OHCA to a temperature of <37.7°C; however, the ideal target temperature for other subgroups remains unclear.[62]
- Markers of systemic inflammation are commonly elevated in comatose patients resuscitated from OHCA, and higher levels are associated with poorer outcomes. In an RCT of tocilizumab, an interleukin-6 receptor antibody, patients resuscitated from OHCA had reduced circulating levels of CRP at 72 hours by 96% ($P$<0.0001). Leukocyte levels were reduced by 23% at 48 hours ($P$=0.004). In addition, troponin T levels were reduced by 36% at 12 hours ($P$=0.008). However, mortality rates at 6 months were not significantly reduced with tocilizumab ($P$=0.9). In addition, multiple markers of neurological function were not altered by this agent ($P$=0.82).[63]
- An RCT conducted with a 2×2 factorial design explored optimal BP targets (mean arterial pressure, 63 mm Hg versus 77 mm Hg)[64] and optimal oxygen targets (arterial oxygen [$Pa_{O_2}$], 9–10 kPa [68–75 mm Hg] or 13–14 kPa (98–105 mm Hg[65]) in resuscitated patients with OHCA with presumed cardiac cause of arrest. The measured outcome was a composite outcome of death at hospital discharge with a Cerebral Performance Category of 3 or 4. To assess optimal BP, 789 patients were randomized to the 2 arms. There was no difference in the primary outcome event (HR, 1.08 [95% CI, 0.84–1.37];

*P*=0.56) between the 2 target BPs. In assessment of the optimal oxygen target between the liberal and restrictive strategies, no difference was found in the primary outcome event between the 2 oxygen targets (HR, 0.95 [95% CI, 0.75–1.21]; *P*=0.69).
- In a single-center RCT of 256 adults with a witnessed OHCA of presumed cardiac origin without return of spontaneous circulation, early intra-arrest transport, extracorporeal CPR, and invasive assessment and treatment did not significantly improve survival with neurologically favorable outcome at 180 days compared with standard resuscitation (OR, 1.63 [95% CI, 0.93–2.85]; difference, 9.5% [95% CI, −1.3% to 20.1%]; *P*=0.09).[66] However, the trial was possibly underpowered to detect a clinically relevant difference.

### *Other Outcomes*

- Functional recovery continues over the first 6 to 12 months after OHCA in adults.[67,68]
- Of 287 people who survived hospitalization after OHCA, 47% had reduced participation in premorbid activities, and 27% of those who were working before the OHCA were on sick leave at 6 months.[69]
- Of 153 survivors of OHCA 18 to 65 years of age in Paris, France, between 2000 and 2013, 96 (63%) returned to work after a mean of 714 days (SD, 1013 days).[70] Younger patients with a higher-level job and for whom cardiac arrest occurred in the workplace were more likely to return to work.
- Of 206 patients who survived to 1 year after OHCA in Finland, 188 (91.3%) were living at home.[71] Among 95 patients who were employed before the arrest, 69 (72.6%) had returned to work, whereas 23 (24.2) had stopped work specifically because of their medical condition.
- Among 195 family caregivers of cardiac arrest survivors, anxiety was present in 33 caregivers (25%) and depression in 18 caregivers (14%) at 12 months.[72]
- Among OHCA survivors, the prevalence of depression (19%), anxiety (26%), and posttraumatic stress disorder (20%) is significant, highlighting the need for further screening, prevention, and treatment options.[73]
- Among 7321 patients with OHCA in Taiwan who survived to ICU admission, 281 (3.84%) had new-onset HF.[74] Strong predictors of new-onset HF were age (60–75 years; HR, 11.4 [95% CI, 9–14.4]), history of MI (HR, 2.47 [95% CI, 2.05–2.98]), history of cardiomyopathy (HR, 2.94 [95% CI, 1.45–5.94]), or new-onset IHD during admission (HR, 4.5 [95% CI, 3.46–5.86]).

### *Global Burden*

- International comparisons of cardiac arrest epidemiology must take into account differences in case ascertainment. OHCA usually is identified through EMS systems, and regional and cultural differences in the use of EMS affect results.[75]
- A prospective data collection concerning 10 682 OHCA cases from 27 European countries in October 2014 found an incidence of 84 per 100 000 people, with CPR attempted in 19 to 104 cases per 100 000 people.[76] Return of pulse occurred in 28.6% (range for countries, 9%–50%), with 10.3% (range, 1.1%–30.8%) of people on whom CPR was attempted surviving to hospital discharge or 30 days.
- In a systematic review accounting for 133 981 patients with EMS-witnessed OHCA treated in 33 countries, the incidence of EMS-treated cases was 4.1 in 100 000 person-years (95% CI, 3.5–4.7 per 100 000 person-years).[77] Survival to hospital discharge or at 30 days from arrest was 20% in shockable rhythms and 6% in nonshockable rhythms. Significant global variation was appreciated.

## IHCA in Adults

### *Incidence*

### *(See Table 19-3)*

- Incidence of IHCA is 292 000 people each year on the basis of extrapolation of GWTG data to the total population of hospitalized patients in the United States.[78,79]
- Incidence of IHCA among 15 953 rapid response team calls in Australia was 159 cases in 152 individuals or 0.62 IHCAs per 1000 multiday admissions (IQR, 0.50–1.19).[80]
- In the HCUP NIS for 2020 (Unpublished NHLBI tabulation)[81]:
  - There were 25 365 hospital discharges with a primary diagnosis of cardiac arrest.
  - There were 276 360 hospital discharges with all-listed diagnoses of cardiac arrest.
  - There were 202 789 ED discharges with a principal diagnosis of cardiac arrest.
- Incidence of IHCA was 1.7 per 1000 hospital admissions on the basis of 18 069 patients with IHCA in the Swedish Register of CPR between 2006 and 2018.[82]
- After data from GWTG–Resuscitation were combined with Medicare data from 2014 to 2017, 38 630 patients with IHCA were analyzed to determine the incidence of IHCA of Medicare beneficiaries and hospital variation in IHCA.[83] The median risk-adjusted IHCA incidence was 8.5 per 1000 admissions (95% CI, 8.2–9.0 per 1000 admissions). IHCA incidence varied across hospitals after adjustment for differences in case-mix index, from 2.4 per 1000 admissions to 25.5 per 1000 admissions (IQR, 6.6–11.4; median OR, 1.51 [95% CI,

1.44–1.58]). Higher case-mix index, higher nurse staffing, and teaching status were associated with less incidence of IHCA.
- IHCA within the first 24 hours after admission for STEMI occurred in 7.8% (136) of 1754 patients in the ARGEN-IAM-ST. Features associated with IHCA were older age and cardiogenic shock.[84]
- A smaller single-center study found that IHCA within the first 48 hours after PCI for STEMI occurred in 11% (44) of 403 patients reviewed.[85]
- IHCA incidence was 320 (1.50%) of 21 337 patients with ACS admitted to 3 hospitals in China from 2012 to 2016.[86]
- According to 2022 GWTG data, location of adult IHCA was the ICU, operating room, or ED in 60.4% and noncritical care areas in 39.6% among 39 896 events at 379 hospitals (Table 19-3).
- Initial recorded cardiac rhythm was VF or VT in 13.4% of adult IHCAs in 2022 GWTG data (GWTG–Resuscitation, unpublished data, 2022; Table 19-3).
- Intraoperative cardiac arrest in adults occurred with an incidence of 5.7 per 10 000 hospital admissions in which there was an operating room procedure in a 2016 survey of the NIS.[87] In-hospital mortality was 36% in patients experiencing intraoperative cardiac arrest.
- Multiple studies have shown that risk for IHCA is predictable and that focused rapid response teams may reduce the risk of IHCA.[88–91]
- A New York academic medical center review of IHCA from 2012 to 2018 showed lower incidence in females but twice the in-hospital mortality compared with males.[92]

### COVID-19 Effects on IHCA Incidence

- A multicenter prospective report from 68 US hospitals described outcomes of IHCA among 701 adults with COVID-19 in ICUs. Of these, 57% received CPR, and 12% survived to hospital discharge.[93] Among the 48 individuals who survived to hospital discharge, 58.3% had normal or mildly impaired neurological status, whereas 41.7% had moderate to severe neurological dysfunction.
- Compared with 2016 to 2019, patients in the United Kingdom who experienced IHCA during the first wave of the pandemic were younger, male, and of underrepresented race (Asian, Black, multiracial, other).[94] Higher hospital COVID-19 burden was associated with decreased survival to hospital discharge (OR, 0.95 [95% CI, 0.93–0.98]; $P<0.001$).

### Risk Prediction

#### Prodromal Symptoms

- Abnormal vital signs during the 4 hours preceding IHCA occurred in 59.4% and at least 1 severely abnormal vital sign occurred in 13.4% of 7851 patients in the 2007 to 2010 GWTG data.[95]
- Early warning score systems using both clinical criteria and vital signs identified hospitalized patients with a higher risk of IHCA[96] (see also IHCA incidence).
- A comparison using receiver-operating curves of early warning score accuracy for predicting risk of IHCA and other serious events for individual patients in the hospital had AUCs of 0.663 to 0.801.[97]
- Among 1352 surgical patients with postoperative IHCA within 30 days, 746 (55%) had developed a postoperative complication (acute kidney injury, acute respiratory failure, DVT/PE, MI, sepsis/septic shock, stroke, transfusion) before the arrest.[98]

### Mortality

#### (See Table 19-3 and Chart 19-1)

- Survival to hospital discharge was 21.2% of adult patients with pulseless IHCAs in GWTG 2022 data (Table 19-3 and Chart 19-1). Among survivors, 79.9% had good functional status (Cerebral Performance Category 1 or 2) at hospital discharge.
- Unadjusted survival rate after IHCA was 18.4% in the UK National Cardiac Arrest Audit database between 2011 and 2013. Survival was 49% when the initial rhythm was shockable and 10.5% when the initial rhythm was not shockable.[99]
- Unadjusted survival to 30 days after IHCA was 28.3% and survival to 1 year was 25.0% in 18 069 patients from 66 hospitals between 2006 and 2015 in the Swedish register of CPR.[82]
- Survival to hospital discharge after IHCA was lower for males than for females (aOR, 0.90 [95% CI, 0.83–0.99]) in a Swedish registry of 14 933 cases of IHCA from 2007 to 2014.[100]
- Mortality was lower among 348 368 patients with IHCA managed in teaching hospitals (55.3%) than among 376 035 managed in nonteaching hospitals (58.8%), even after adjustment for baseline patient and hospital characteristics (OR, 0.92 [95% CI, 0.90–0.94]).[101]
- A propensity-matched analysis of 2000 to 2018 data from 497 US hospitals participating in the AHA GWTG–Resuscitation registry examined the use of epinephrine before defibrillation for treatment of IHCA with a shockable rhythm.[102] In this evaluation of 34 820 patients, 28% received epinephrine before defibrillation, contrary to current guidelines. Use of epinephrine delayed defibrillation by 3 minutes (median). Patients treated with epinephrine had a significantly lower chance of survival to hospital discharge (25.2% versus 29.9%; $P<0.001$) and were less likely to have favorable neurological outcome (18.6% versus 21.4%; $P<0.001$).
- A multicenter RCT conducted in 10 Danish hospitals compared vasopressin and methylprednisolone with placebo in 501 individuals with IHCA.[103] The

active treatment group experienced significantly higher rate of return of spontaneous circulation (42% versus 33%). However, there was no significant difference in survival at 30 days (9.7% versus 12%, respectively) or achievement of a favorable neurological outcome at 30 days (7.6% versus 7.6%, respectively).

### *Other Outcomes*

- Among 366 patients discharged after IHCA in a Veterans Administration hospital between 2014 and 2015, 55 (15%) endorsed suicidal ideation during the first 12 months.[104]
- In a single-center study, 102 patients experienced IHCA; 50 survived the arrest event and 47 survived to hospital discharge with a good neurological outcome (modified Rankin Scale score, 0–3).[105]

### *Global Burden of Disease*

- Hospitals in Beijing, China, reported an IHCA incidence of 17.5 events per 1000 admissions.[106]
- Among 353 adults after IHCA in 6 Kenyan hospitals in 2014 to 2016, 16 (4.2%) survived to hospital discharge.[107]

## OHCA in Pediatric Patients

### *Incidence*

### *(See Table 19-3)*

- In 2022, the location of EMS-treated OHCA was home for 80.5% of children in the CARES 2022 data. The location was a public place for 19.0% of the children (Table 19-3).[3]
- The annual incidence of pediatric OHCA was 8.7 per 100 000 population in Western Australia from 2011 to 2014.[108]

### *Secular Trends*

- Incidence of pediatric OHCA declined from 1997 to 2014 in Perth, Western Australia, from 14.1 (1997–2000) to 8.7 (2011–2014) per 100 000 population.[108] The incidence was even lower among children <1 year of age.
- Incidence of pediatric (<16 years of age) OHCA that was EMS attended (6.7 per 100 000) or EMS treated (4.9 per 100 000) did not change from 2000 to 2016 in Victoria, Australia.[109] Survival to hospital discharge increased from 9.4% to 17.7%.

### *Awareness and Treatment*

- In an English study of 2363 pediatric OHCA events, layperson CPR was performed in 69.6% of cases (1646) overall.[110] There was variability in provision of CPR across the different regions studied.

### *Mortality*

### *(See Table 19-5)*

- Survival to hospital discharge was 6.6% for 1687 children <1 year of age, 14.7% for 1207 children 1 to 12 years of age, and 17.3% for 898 children 13 to 18 years of age in CARES 2022 data (Table 19-5).
- In a registry including 974 children with OHCA from 2009 to 2012 in Singapore, Japan, the Republic of Korea, Malaysia, Thailand, Taiwan, and the United Arab Emirates, 8.6% (range, 0%–9.7%) of children survived to hospital discharge.[111]
- In Rotterdam, shockable rhythm after 369 pediatric (median age, 3.4 years) OHCAs was associated with significantly higher long-term survival and favorable neurological outcome. Fourteen percent had a shockable rhythm. Of these, 39% survived to hospital discharge. After a median follow-up of 25 months, 81% of hospital survivors had a favorable neurological status.[112]

## IHCA in Pediatric Patients

### *Incidence*

### *(See Table 19-3)*

- Of 660 events of IHCA in children (1–18 years of age) at 118 hospitals, 71.2% occurred in the ICU, operating room, or ED and 28.9% in noncritical care areas per 2022 GWTG data (Table 19-3). Of the 1027 IHCA events in infants (<1 year of age) at 93 hospitals, 68.7% occurred in the ICU, operating room, or ED and 31.4% in noncritical care areas per the 2022 GWTG data (Table 19-3).
- Incidence of IHCA was 1.8 CPR events per 100 pediatric (<18 years of age) ICU admissions (sites ranged from 0.6–2.3 per 100 ICU admissions) in the Collaborative Pediatric Critical Care Research Network data set of 10 078 pediatric ICU admissions from 2011 to 2013.[113]
- In a registry of 23 cardiac ICUs in the Pediatric Critical Care Consortium that included 15 908 children between 2014 and 2016, 3.1% of children in ICUs had a cardiac arrest, with substantial variation between centers (range, 1%–5.5%), for a mean incidence of 4.8 cardiac arrests per 1000 cardiac ICU days (range, 1.1–10.4 per 1000 cardiac ICU days).[114]
- Initial recorded cardiac arrest rhythm was VF or VT in 4.0% of 660 child (1–18 years of age) events at 118 hospitals in GWTG–Resuscitation in 2022 and 2.0% of 1027 infant (<1 year of age) events at 93 hospitals (Table 19-3).
- A retrospective analysis of 3 US pediatric ICUs from 2015 to 2017 found a 7% incidence of cardiac arrest in patients undergoing endotracheal intubation.[115]

### *Secular Trends*

### *(See Chart 19-1)*

- Survival to discharge after pulseless IHCA in pediatric patients (children and infants 0–18 years of age) increased from 18.9% to 44.2% between 2000 and 2022 in GWTG data (Chart 19-1).

- A multicenter observational study of 7433 hospitalized pediatric patients who received CPR from 2000 to 2018 found significant increases in survival, from 19% in 2000 to 38% in 2018.[116] The improvement in survival plateaued after 2010.

### Mortality

*(See Table 19-3)*

- Survival to hospital discharge after pulseless IHCA was 43.9% in children 1 to 18 years of age and 44.5% in infants <1 year of age per 2022 GWTG data (GWTG–Resuscitation, unpublished data; Table 19-3).
- Survival to hospital discharge for children with IHCA in the ICU was 45% in the Collaborative Pediatric Critical Care Research Network from 2011 to 2013.[113]
- In 429 pediatric IHCA events, survival before and during the COVID-19 pandemic was similar (52% versus 60%; *P*=0.12).[117]

### Global Burden of Disease

- Perioperative cardiac arrest and mortality vary between middle- and low-income countries. The global incidence of cardiac arrest that occurred perioperatively was 2.54 (95% CI, 2.23–2.84) per 1000 anesthetic events, and mortality was 41.18 (95% CI, 35.68–46.68) per 1000 anesthetic events.[118]

## SCA or SCD When Location Is Not Specified

### Lifetime Risk and Cumulative Incidence

*(See Table 19-6 and Chart 19-2)*

- SCD appeared among the multiple causes of death on 13.0% of death certificates in 2020 (436 852 of 2 854 838; Table 19-6). Because some people survive SCA, the lifetime risk of cardiac arrest is even higher.
- In 2021, infants had a higher incidence of SCD (11.7 per 100 000) than older children (1.1–2.4 per 100 000). Among adults, risk of SCD increased exponentially with age, surpassing the risk for infants by 30 to 34 years of age (13.0 per 100 000; Chart 19-2).

### Secular Trends

*(See Charts 19-3 and 19-4)*

- Rate of SCD (6.8% versus 11.4% over 4 years) and hazard of SCD in propensity-matched cohorts (sub-HR, 0.46 [95% CI, 0.30–0.70]) decreased over time in outpatients with HFrEF (<40%) on the basis of 2 multicenter prospective registries (MUSIC [n=641; 2003–2004] and REDINSCOR I [n=1710; 2007–2011]).[119] This reduction in SCD was associated with more frequent use of β-blockers (85% versus 71%), mineralocorticoid antagonists (64% versus 44%), ICDs (19% versus 2%), and resynchronization therapy (7.2% versus 4.8%).
- Age-adjusted death rates for any mention of SCD declined from 137.7 per 100 000 population in 1999 to 91.2 per 100 000 population by 2019 and increased to 111.2 in 2021 (Chart 19-3).
- Two prospective autopsy studies of people with SCD have shed new evidence on underlying causes of sudden death. One study followed up patients with HF or reduced EF after a recent MI enrolled in a randomized trial of drug therapy.[120] The second study was a community-based survey of out-of-hospital SCD.[121] In each study, only one-half of the sudden deaths had no specific findings at autopsy. In these cases, the mechanism of death was classified as arrhythmic. However, approximately one-half of the sudden unexpected deaths in each study had specific findings at autopsy, supporting a nonarrhythmic mechanism for the sudden death, including AMI, cardiac rupture, acute HF, and acute pulmonary embolus (Chart 19-4). In addition, acute neurological events and occult drug overdoses were common in the San Francisco community study. EMS data were available for the San Francisco community study. When the initial rhythm recorded by EMS was VT or VF, the autopsy findings were likely to be consistent with sudden arrhythmic death, whereas when the initial finding was pulseless electric activity, the autopsy was likely to result in a classification of nonsudden arrhythmic death.

### Risk Factors

*(See Chart 19-5)*

- SCA and SCD result from many different disease processes, each of which can have different risk factors. Among patients with OHCA resuscitated and hospitalized from 2012 to 2016, ACS and other cardiac causes accounted for the largest proportion of causes. Among patients with IHCA, respiratory failure was the most common cause (Chart 19-5).[122]
- Among patients with DCM considered to be at low arrhythmic risk (LVEF >35% and New York Heart Association class I–III on optimal medical therapy), 14 of 360 (3.9%) had SCD and 16 (4.4%) had major ventricular arrhythmias (SCA or ICD intervention) during a median follow-up of 152 months.[123] Events were associated with larger left atrial end-systolic area and arrhythmogenic profile (history of syncope, nonsustained VT, at least 1000 premature ventricular contractions per 24 hours, or at least 50 ventricular couplets per 24 hours at Holter electrocardiographic monitoring).
- A substudy of the DANISH trial of patients with nonischemic systolic HF (EF ≤35%) demonstrated an association of nonsustained VT (HR, 1.47 [95%

CI, 1.07–2.03]; *P*=0.02 and HR, 1.89 [95% CI, 1.25–2.87]; *P*=0.003) and frequent ventricular premature depolarizations (HR, 1.38 [95% CI, 1.00–1.90]; *P*=0.046 and HR, 1.78 [95% CI, 1.19–2.66]; *P*=0.005) with total and cardiovascular mortality, respectively, but no relation to SCD.[124]

- Among 5869 autopsied individuals with SCD, after exclusion of cases with noncardiac causes of death in Finland between 1998 and 2017, ischemic cardiac disease represented 4392 (74.8%) and nonischemic cardiac diseases represented 1477 (25.2%).[125] Over time, the proportion of ischemic SCD declined from 78.8% (1998–2002) to 72.4% (2013–2017).
- An analysis of 8900 patients enrolled in 3 contemporary therapeutic trials of patients with HFpEF found that those with prior MI had ≈50% increased risk of SCD compared with patients without prior MI.[126]
- Alcohol consumption was not associated with increased risk of ventricular arrhythmia but was associated with SCD in a longitudinal study of 408 712 individuals over a follow-up time of 11.5 years.[127]

### Age

#### (See Chart 19-2)

- In 2021, mortality rates for any mention of SCD decreased with increasing age category (<1, 1–4, and 5–9 years of age) in those 0 to 9 years of age and increased for those ≥10 years of age with each 5-year age category through 84 years of age (Chart 19-2).

### Sex

- In a prospective postmortem study in San Francisco County, all incident presumed SCDs in people 18 to 90 years of age were autopsied through active surveillance of consecutive out-of-hospital deaths between February 1, 2011, and March 1, 2014.[128] Among 525 autopsied presumed SCDs in San Francisco County, after adjustment for age and race, females had more noncardiac causes of presumed SCD, including pulmonary emboli (8% versus 2%) and neurological causes (10% versus 3%; both *P*<0.01). Males had 3-fold higher rates of autopsy-proven sudden arrhythmic deaths (defined as cases in which no extracardiac cause of death or HF was noted on autopsy) compared with females, whereas more females had primary electric disease (4% versus 2%; *P*=0.02) and nonischemic causes (53% versus 39%; *P*<0.01).

### Race and Ethnicity

- In the ARIC study, 215 of 3832 (5.61%) Black and 332 of 11 237 (2.95%) White participants experienced SCD during 27.4 years of follow-up.[129] The sex-adjusted HR for SCD comparing Black with White participants was 2.12 (95% CI, 1.79–2.51), and the fully adjusted HR was 1.38 (95% CI, 1.11–1.71).
- In a prospective postmortem study in San Francisco County, all incident presumed SCDs in individuals 18 to 90 years of age were autopsied through active surveillance of consecutive out-of-hospital deaths between February 1, 2011, and March 1, 2014.[128] Among 525 autopsied presumed SCDs in San Francisco County, sudden arrhythmic death was defined as deaths for which no extracardiac cause or acute HF was noted on autopsy. After adjustment for age, Black females had higher incidence of sudden arrhythmic death than White females (IRR, 2.55 [95% CI, 1.38–4.71]; *P*<0.01), Asian males had a lower incidence than White males (IRR, 0.51 [95% CI, 0.36–0.73]; *P*<0.01), and Hispanic males had a lower incidence than White males (IRR, 0.51 [95% CI, 0.31–0.85]; *P*<0.01). Among autopsy-proven sudden arrhythmic deaths, MI with nonobstructive coronary arteries was more common in Asian individuals than in White individuals (7% versus 1%; *P*<0.05).

### HD, Cardiac Risk Factors, and Other Comorbidities

- Incidence of SCD was 0.10 per 100 patient-years (95% CI, 0.07–0.14) in a cohort of 3242 untreated patients with hypertension without evidence of coronary or cerebrovascular disease at entry who were followed up for an average of 10.3 years.[130] The prevalence of electrocardiographic LVH was 13.9%. For patients with electrocardiographic signs of LVH, the rate of SCD was 0.37 per 100 patient-years versus 0.05 per 100 patient-years for patients without electrocardiographic LVH (aHR, 2.99 [95% CI, 1.47–6.09], adjusted for age, sex, diabetes, and 24-hour ambulatory pulse pressure).
- In a cohort of 233 970 patients from the United Kingdom, resting heart rate >90 bpm was associated with an increased hazard of SCD or cardiac arrest as initial presentation of HD (aHR, 2.71 [95% CI, 1.90–3.83]).[131]
- Among 7011 patients admitted to the hospital with acute HF, the 30-day rate of SCD, SCA, or VT/VF was 1.8% (n=121).[132] Events were associated with male sex (aOR, 1.73 [95% CI, 1.07–2.49]), history of VT (aOR, 2.11 [95% CI, 1.30–3.42]), chronic obstructive pulmonary disease (aOR, 1.63 [95% CI, 1.07–2.49]), or prolonged QRS interval (aOR, 1.10 [95% CI, 1.03–1.17] per 10% increase from baseline).
- Analysis of 76 009 patients including 8401 with AF from 21 studies between 1991 and 2017 found that patients with AF had a higher risk of incident SCD/SCA or VF/VT (RR, 2.04 [95% CI, 1.77–2.35]).[133]

- Among 21 105 patients with AF followed up for a median of 2.8 years, SCD accounted for 31.7% of all deaths, with an incidence of 12.9 per 1000 patient-years.[134]
- Risk of SCD in the general population ≥45 years of age who were initially free of CVD when recruited in 1987 to 1993 and followed up for a subsequent 10 years was associated with male sex, Black race, diabetes, current smoking, and SBP.[135]
- A logistical model incorporating age, sex, race, current smoking, SBP, use of antihypertensive medication, diabetes, serum potassium, serum albumin, HDL-C, eGFR, and QTc interval, derived in 13 677 adults, correctly stratified 10-year risk of SCD in a separate cohort of 4207 adults (C statistic, 0.820 in ARIC and 0.745 in the CHS).[135]
- In a registry of 2119 SCAs in Portland, OR, from 2002 to 2015, prior syncope was present in 6.8% of cases, and history of syncope was associated with increased risk of SCA relative to 746 geographically matched control subjects (OR, 2.8 [95% CI, 1.68–4.85]).[136]
- In a cohort of 5211 Finnish people >30 years of age in 2000 to 2001 who were followed up for a median of 13.2 years, high baseline thyroid-stimulating hormone was independently associated with greater risk of SCD (HR, 2.28 [95% CI, 1.13–4.60]).[137]
- In a meta-analysis that included 17 studies with 118 954 subjects, presence of depression or depressive symptoms was associated with increased risk of SCD (HR, 1.62 [95% CI, 1.37–1.92]), specifically for VT/VF (HR, 1.47 [95% CI, 1.23–1.76]).[138]
- The interaction among CHD, PA, and SCD is complex. Analysis from a Finnish registry of 1946 patients with angiographically documented CHD found that risk of SCD was increased in patients with more advanced angina (Canadian Cardiovascular Society angina grade ≥2) and both active (HR, 7.46 [95% CI, 2.32–23.9]; $P<0.001$) and inactive (HR, 3.64 [95% CI, 1.16–11.5]; $P<0.05$) lifestyles, whereas risk of SCD was decreased in active patients with lesser grades of angina (Canadian Cardiovascular Society angina grade 1; HR, ≈0.5).[139]

### Electrocardiographic Abnormalities

- Age- and sex-adjusted prevalence of electrocardiographic abnormalities associated with SCD was 0.6% to 1.1% in a sample of 7889 Spanish citizens ≥40 years of age, including Brugada syndrome in 0.13%, QTc <340 milliseconds in 0.18%, and QTc ≥480 milliseconds in 0.42%.[140]
- Among 12 241 ARIC study participants, of whom 346 had SCD during a median follow-up of 23.6 years, prolongation of the QT interval at baseline was associated with risk of SCD (HR, 1.49 [95% CI, 1.01–2.18]), and this association was driven specifically by the T-wave onset to T-peak component of the total interval.[141]
- Among 20 177 participants in the ARIC study followed up for 14 years (median), the incidence of SCD was 1.86 per 1000 person-years. Five global markers of electric heterogeneity measured on a standard 12-lead ECG at baseline and during follow-up demonstrated an independent predictor of risk for SCD.[142]
- In a cohort of 4176 individuals with no known HD, 687 (16.5%) had early repolarization with terminal J wave, but this pattern had no association with cardiac deaths (0.8%) over 6 years of follow-up compared with matched controls.[143]

### Social Determinants of Health/Health Equity

- In the ARIC study, 215 of 3832 (5.61%) Black and 332 of 11 237 (2.95%) White participants experienced SCD during 27.4 years of follow-up.[129] The sex-adjusted HR for SCD comparing Black with White participants was 2.12 (95% CI, 1.79–2.51), and the fully-adjusted HR was 1.38 (95% CI, 1.11–1.71).
- Survival and neurological recovery after cardiac arrest are worse in White Hispanic, Black, and Asian individuals compared with White individuals.[144] In this single-center, retrospective study of patients receiving targeted temperature management after cardiac arrest, survival and neurological recovery were worse in individuals from underrepresented racial and ethnic groups (self-identified or identified by family as being Black, Asian, or White Hispanic compared with NH White). White people had a higher chance of a good outcome than people from underrepresented racial and ethnic groups (34.4% versus 21.7%; $P=0.015$). The observed disparities were explained in part by delays in onset of medical care: White people were brought to medical attention more quickly, and individuals from underrepresented races and ethnicities were more likely to have anoxic brain injury on early CT scans or highly malignant electroencephalograms during the first 24 hours. People from underrepresented racial and ethnic groups were more likely to have early severe electroencephalogram/CT anoxic changes (25.0% versus 15.8%; $P=0.03$). There were no statistically significant differences in the number of invasive procedures.

### Mortality (See Table 19-6)

- In 2021, primary-cause SCD mortality was 20 114, and any-mention SCD mortality in the United States was 446 757 (Table 19-6). The any-mention age-adjusted annual rate was 111.2 (95% CI, 110.9–111.5) SCDs per 100 000 population (unpublished NHLBI tabulation).[145]

- Of 1 452 death certificates from 1999 to 2015 for US residents 1 to 34 years of age, 31 492 listed SCD (2%) as the cause of death, for an SCD rate of 1.32 per 100 000 individuals.[146]
  - SCD rate varied by age, from 0.49 per 100 000 (1–10 years of age) to 2.76 per 100 000 (26–34 years of age).
  - The rate of SCD declined from 1999 to 2015, from 1.48 to 1.13 per 100 000 individuals.

### Complications

- Survivors of cardiac arrest experience multiple medical problems related to critical illness, including impaired consciousness and cognitive deficit. Functional impairments are associated with reduced function, reduced quality of life, and shortened life span.[147,148]
- Serial testing in a cohort of 141 people who survived hospitalization after SCA revealed severe cognitive deficits in 14 (13%), anxiety and depression in 16 (15%), posttraumatic stress symptoms in 29 (28%), and severe fatigue in 55 (52%).[149] Subjective symptoms declined over time after SCA, although 10% to 22% had cognitive impairments at 12 months, with executive functioning being most affected.[150]
- Of 141 individuals who survived hospitalization after SCA, 41 (72%) returned to work by 12 months.[149]
- In a meta-analysis of 35 studies including 7186 survivors, the incidence of first recurrence of cardiac arrest was 15.24% (95% CI, 11.01%–19.95%; mean follow-up time, 41.3±29.3 months) and second recurrence was 35.03% (95% CI, 19.65%–51.93%; mean follow-up, 161.1± 54.3 months).[151] Shockable initial rhythm increased the incidence of first recurrence of cardiac arrest ($P$=0.01).

### Special Circumstances

#### Opioid-Associated Cardiac Arrest

- The incidence of opioid-associated OHCA has been increasing with the overall rise in prevalence of synthetic opioids in the United States since 2013.[152]
- Most estimates are based on EMS-treated events and do not account for those individuals who were left untreated by EMS after opiate overdose.[152] One study estimates that <35% of opioid deaths are treated by EMS; therefore, estimations of incidence are most likely gross underestimations of the magnitude of this problem.[153]
- Two publications from large North American data sets estimate the incidence of opioid-associated OHCA at 2% of the total OHCA population; however, recent smaller studies with the benefit of greater depth of chart review estimate that this incidence is closer to 6% to 15% of all OHCAs.[122,154,155]

#### Sports-Related Cardiac Arrest

- Sports-related SCA accounted for 39% of SCAs among those ≤18 years of age, 13% among those 19 to 25 years of age, and 7% among those 25 to 34 years of age in a prospective registry of 3775 SCAs in Portland, OR, between 2002 and 2015 that included 186 SCAs in young people (5–34 years of age).[156]
- Incidence of SCA or SCD was 1 per 44 832 athlete-years for males and 1 per 237 510 athlete-years for females according to a 2007 to 2013 registry of 104 cases of SCA and SCD in high school athletes.[157]
- Incidence of SCA during competitive sports in people 12 to 45 years of age was 0.76 per 100 000 athlete-years in a population-based registry of all paramedic responses in Toronto, ON, Canada, from 2009 to 2014.[158]
- Incidence of SCD, estimated from LexisNexis and public media reports, during youth sport participation, estimated by the Sport and Fitness Industry Association, from 2007 to 2015 was 1.83 deaths per 10 million athlete-years.[159]
- Studies that included >14 million participants in long-distance or marathon running events from 1976 to 2009 reported race-related incidence of SCA or SCD ranging from 0.6 to 1.9 per 100 000 runners with various methods used to ascertain events.[160] Only 2 deaths were reported among 1 156 271 participants in half-marathons or full marathons in Sweden from 2007 to 2016, yielding an estimated SCD incidence of 0.24 (95% CI, 0.04–0.79) per 100 000 runners.[161]
- In a 2007 to 2013 registry of 104 cases of SCA and SCD in high school athletes, adjudication revealed a cause of death in 50 cases (73%): idiopathic LVH or possible cardiomyopathy (26%), autopsy-negative sudden unexplained death (18%), HCM (14%), and myocarditis (14%).[157]
- Adjudication of cause of death in 179 cases of SCA in middle school, high school, college, and professional athletes from 2014 to 2016 identified a cause in 117 (65.4%): HCM (16.2%), coronary artery anomalies (13.7%), idiopathic cardiomyopathy (11.1%), autopsy-negative sudden unexplained death (6.8%), WPW syndrome (6.8%), and LQTS (6.0%).[162]
- Among 55 patients admitted to 8 Spanish hospitals with SCA during or within 1 hour of vigorous sport activities between 2007 and 2016, 90.9% were male, mean age was 47 years (SD, 15 years), and 96.4% presented with shockable rhythm. The cause of SCA varied by age: 25% cardiomyopathy, 63% idiopathic VF, and 13% AMI for those <35 years of age; and 9% cardiomyopathy, 18% idiopathic VF, 67% AMI, and 7% unknown for those ≥35 years of age.[163]
- Preparticipation screening of 5169 middle and high school students (mean age, 13.06 years [SD,

1.78 years]) from 2010 to 2017 revealed high-risk cardiovascular conditions in 1.47%.[164] Anatomic findings included DCM (n=11), nonobstructive HCM (n=3), and anomalous coronary artery origins (n=23). Electrocardiographic findings included WPW syndrome (n=4), prolonged QT intervals (n=34), and Brugada pattern (n=1).
- In a population-based registry of all paramedic responses for SCA from 2009 to 2014, 43.8% of athletes with SCA during competitive sports survived to hospital discharge.[158]

### *Maternal Cardiac Arrest*

- Incidence of maternal cardiovascular collapse requiring CPR during childbirth was 10 in 250 719 (4.0 per 100 000 births) in a registry of births in New York.[165]

## Specific Ventricular Arrhythmias and Inherited Channelopathies

### *Genetics and Family History Associated With SCD*

- Exome sequencing in younger (<51 years of age) decedents who had sudden unexplained death or suspected arrhythmic death revealed likely pathogenic variants in channelopathy- or cardiomyopathy-related genes for 29% to 34% of cases.[166–168]
- Screening of SCA survivors by targeted exome sequencing for 185 clinically relevant cardiac genes revealed a pathogenic variant in 45% of patients, with a 28% yield in patients without any clear cardiac phenotype.[169]
- Multiple studies have attempted to quantify the yield of genetic screening in probands and their family members:
  - Screening of 398 first-degree relatives of 186 probands with unexplained SCA and 212 probands with unexplained SCD revealed cardiac abnormalities in 30.2%: LQTS (13%), CPVT (4%), ARVC (4%), and Brugada syndrome (3%).[170]
  - In a registry of families of probands with unexplained SCD before 45 years of age from 2009 to 2014, screening of 230 people from 64 families revealed a presumptive diagnosis in 25% of families: Brugada syndrome in 11%, LQTS in 7.8%, DCM in 3.1%, and HCM in 3.1%.[171]
  - Screening of 292 relatives of 56 probands with SCD revealed a diagnosis in 47 relatives (16.1%): LQTS in 12.7%, CPVT in 0.3%, DCM in 0.7%, ARVC in 0.3%, and thoracic aortic dilation in 0.3%. Among relatives completing follow-up, 3.3% had a cardiac event within 3 years, and 7.2% had a cardiac event within 5 years.[172]
- Prevalence of genetic HD is reported to decline with increasing age among survivors of SCA according to a report on 180 patients from a genetic heart rhythm clinic from 1999 to 2017.[173] Among 127 adults, diagnoses included idiopathic VF (44.1%), arrhythmogenic bileaflet mitral valve (14.2%), acquired LQTS (9.4%), LQTS (7.9%), and J-wave syndromes such as Brugada (3.9%). Among 53 children, diagnoses included LQTS (28.3%), CPVT (20.8%), idiopathic VF (20.8%), HCM (5.7%), and triadin knockout syndrome (5.7%).

### *Genome-Wide Association Studies*

- GWASs on cases of arrhythmic death attempt to identify previously unidentified common genetic variants and biological pathways associated with potentially lethal ventricular arrhythmias and risk of sudden death. Limitations of these studies are the small number of samples available for analysis and the heterogeneity of case definition. The number of loci uniquely associated with SCD is much smaller than for other complex diseases. For example, a GWAS of 3939 cases with SCA found no variants associated with SCD at genome-wide significance, which suggests that common genetic variations may not portend a significant risk factor for SCD.[174] However, the oligogenic nature of genetic determinants of SCA requires further evaluation.
- Although SCA GWASs are limited, investigations have been conducted with multiple electrocardiographic traits used as a phenotype (ie, QRS, QT duration), which have identified novel genetic variants associated with these traits that are also associated with cardiac conduction, arrhythmias, and other cardiovascular end points.[175]
- A GWAS of T-peak-to-T-end interval on ECG, a predictor of increased arrhythmic risk, in the UK Biobank identified 32 genomic loci for resting T-peak-to-T-end interval, 3 for T-peak-to-T-end response to exercise, and 3 for T-peak-to-T-end response to recovery, but a GRS of these variants was not associated with arrhythmic risk.[176]

### *Long QT Syndrome*

- Hereditary LQTS is a genetic channelopathy characterized by prolongation of the QT interval (QTc typically >460 milliseconds) and susceptibility to ventricular tachyarrhythmias that lead to syncope and SCD. Investigators have identified rare variants in 15 genes leading to 17 different subtypes of LQTS phenotype.[177,178] There is variability in presentation, therapeutic approach, and prognosis by subtype.
- Approximately 5% of sudden infant death syndrome cases and some cases of intrauterine fetal death could be attributable to LQTS.[179]
- Ancestry-specific LQTS variants exist: The S1103Y polymorphism in *SCN5A* is found in 13% of Black individuals and has been linked to lethal arrhythmias and SCD in Black individuals with HF.[180,181]

- Acquired prolongation of the QT interval is common. Prevalence of prolonged QTc was 115 of 412 (27.9%) among adults admitted to an ICU from 2014 to 2016 in Brazil.[182] At least 1 drug known to prolong QT interval was present in 70.4% of these cases.
- Prevalence of prolonged QTc interval was 50 of 712 patients (7%) admitted to a short-stay medical unit in the United Kingdom.[183]
- Prevalence of prolonged QTc interval was 95 of 7522 patients (1.9%) with ECG in the ED from 2010 to 2011, and these prolongations were attributable individually or in combination to electrolyte disturbances (51%), QT-prolonging medical conditions (56%), or QT-prolonging medications (77%).[184]
- Among 65 654 patients on hemodialysis, initiation of a selective serotonin reuptake inhibitor with higher (47.1% of patients) versus lower (52.9% of patients) QT-prolonging potential was associated with higher risk of SCD (aHR, 1.18 [95% CI, 1.05–1.31]).[185]
- Genetic testing for LQTS among 281 families had a diagnostic yield for genetic variants of 47%.[186] Nearly a third of patients with acquired LQTS are reported to carry pathogenic congenital LQTS variants.[187]
- However, some studies have called into question whether previously identified LQTS genes are truly causative.[188,189] The ClinGen Channelopathy Clinical Domain Working Group, leveraging large publicly available genetic databases, has shown that only 3 genes (*KCNQ1*, *KCNH2*, *SCN5A*) have definitive gene-disease association for typical LQTS, with another 4 (*CALM1*, *CALM2*, *CALM3*, *TRDN*) having definitive evidence for association with disease onset in childhood. That group has found that *KCNE1* and *KCNE2*, which are commonly clinically tested, had limited or disputed evidence for typical LQTS but showed strong evidence for association with acquired LQTS. Several induced pluripotent stem cell–cardiomyocytes models are now being used to assess the significance of novel variants and to understand mechanisms of action of modifier genes.[190]
- GWASs have identified additional rare and common variants in genes associated with QT interval,[188] suggesting that individuals with long QT who are variant negative could have a polygenic inheritance.
- Common genetic variants may explain ≈15% of the susceptibility to LQTS. A 68-SNP PRS for the QT interval had a higher score in genotype-negative (no disease-causing rare variant identified) patients compared with genotype-positive patients, supporting a polygenic basis for LQTS in genotype-negative patients. In genotype-negative patients, the third (OR, 3.74; $P=4.2\times10^{-6}$) and fourth (OR, 6.13; $P=4.8\times10^{-11}$) quartiles of the PRS score were associated with a higher odds of LQTS compared with the first quartile.[191]
- A randomized controlled multicenter trial of 665 patients with COVID-19 in Brazil treated with standard care, hydroxychloroquine alone or in combination with azithromycin, found a 14.6% incidence of QT interval prolongation >480 milliseconds in patients in the 2 active treatment groups versus 1.7% in the standard care group. No patient developed TdP.[192]
- A prospective survey of 119 patients with COVID-19 treated in 3 New York hospitals who received both chloroquine or hydroxychloroquine and azithromycin and 82 patients treated with chloroquine or hydroxychloroquine alone revealed significant increases in QTc.[193] Patients receiving both drugs demonstrated significantly greater increases in QTc than patients receiving monotherapy. A peak QTc >500 milliseconds was observed in 8.6% of patients receiving a single drug and 9.2% of patients receiving 2 drugs. There was no difference in QT prolongation according to sex. No patients in this series developed TdP.
- A retrospective analysis of 91 hospitalized patients with COVID-19 in Connecticut treated with hydroxychloroquine and azithromycin found QTC prolongation >500 milliseconds in 14% on treatment.[194] Almost half the patients with marked QTc prolongation were receiving other agents known to prolong the QT interval, most often propofol. Two patients developed VT: TdP in 1 patient and polymorphic VT leading to VF in the other.
- A retrospective analysis of 415 hospitalized patients with COVID-19 infection treated with hydroxychloroquine and azithromycin found QTc prolongation >500 milliseconds in 21%, but no TdP was observed.[195]
- A retrospective cohort analysis of 170 patients in Wuhan, China, hospitalized with COVID-19 infection and evidence of myocarditis (elevated cardiac troponin I) found 6 patients with VT/VF, all of whom died.[196] Patients treated with QT-prolonging agents had significantly longer QTc, but the increase in QTc was not associated with mortality independently.
- A common ion channel genetic variant, p.Ser1103Tyr-SCN5A, which predisposes to QT prolongation and increased risk of TdP, is found almost exclusively in the Black population with a prevalence of 8%. This variant not only increases risk for drug-induced TdP but also has the ability to increase the risk for TdP in the presence of hypoxemia and acidemia resulting from an increase in the late Na current. This may explain part of the increased risk of OHCA in Black individuals and their increased mortality in the face of COVID infection.[197]

- Reappraisal of the 17 LQTS genes led to the classification of 3 genes (*KCNQ1*, *KCNH2*, *SCN5A*) as definitive genes causing LQTS and 4 genes (*CALM1*, *CALM2*, *CALM3*, *TRDN*) as having definitive or strong evidence for causality in LQTS with atypical features; 1 gene (*CACNA1C*) had moderate evidence for causing LQTS, and the other genes had limited evidence for causing LQTS.[198]

### Short QT Syndrome

#### Prevalence and Incidence

- Short QT syndrome is an inherited mendelian condition characterized by shortening of the QT interval (typically QT <320 milliseconds) and predisposition to AF, ventricular tachyarrhythmias, and sudden death. Variants in 5 ion channel genes (*SQT1*–*SQT5*) have been described.[199]
- Prevalence of a QTc interval <320 milliseconds in a population of 41 767 young, predominantly male Swiss conscripts was 0.02%,[200] which was identical to the prevalence in a Portugal sudden death registry.[201]
- Prevalence of QT interval ≤340 milliseconds in 99 380 unique patients ≤21 years of age at the Cincinnati Children's Hospital between 1993 and 2013 was 0.05%.[202] Of these children, 15 of 45 (33%) were symptomatic.

#### Genetics

- The genes that have been associated with short QT syndrome are many of the same ones involved in LQTS but with opposite effects on channel function and include potassium channel genes and calcium channel genes. The yield of genetic testing in short QT syndrome is only 23% of 53 probands.[203]

### Brugada Syndrome

#### Prevalence and Incidence

- Brugada syndrome is an acquired or inherited channelopathy characterized by persistent ST-segment elevation in the right precordial leads ($V_1$ and $V_2$), either at rest or with provocative testing, and susceptibility to ventricular arrhythmias and SCD.[204] Brugada syndrome is associated with variants in at least 12 ion channel–related genes.
- In a meta-analysis of 24 studies, prevalence was estimated at 0.4% worldwide, with regional prevalence of 0.9%, 0.3%, and 0.2% in Asia, Europe, and North America, respectively.[205] Prevalence was higher in males (0.9%) than in females (0.1%).[206]
- Among 678 patients with Brugada syndrome from 23 centers in 14 countries, patients whose first documented arrhythmic event was SCA had a mean age of 39 years (SD, 15 years), whereas age at the first documented arrhythmic event in patients with prophylactic defibrillator implantation was 46 years (SD, 13 years).[207]
- In a multicenter retrospective study of 770 patients with Brugada syndrome, 177 (23%) were female.[208] At initial presentation, 85% were asymptomatic. Females were less likely to have a type 1 electrocardiographic pattern (31% versus 55%), but females were more likely to have a family history of SCD (49.7% versus 29.8%). Genetic testing was positive in 19% of females versus 13.5% of males ($P$=0.06). During a mean follow-up of 122 months, 2.8% of females versus 7.1% of males ($P$=0.04) experienced appropriate ICD therapy or SCD. Two factors independently predicted arrhythmic events: a positive genetic test (OR, 18.71 [95% CI, 1.82–192.53]) and AF (OR, 21.12 [95% CI, 1.27–350.85]).
- Family history of SCD has not been helpful in risk prediction of patients with Brugada syndrome. However, a meta-analysis of 22 studies involving 3386 patients found that history of SCD in family members <40 years of age doubled the risk for a major arrhythmic event.[209]

#### Genetics

- Brugada syndrome is considered primarily a monogenic mendelian disease with autosomal dominant inheritance and incomplete phenotypic penetrance. However, other forms of inheritance (X-linked) have also been suggested.[210]
- Rare genetic variants in *SCN5A* account for disease in 20% of patients with Brugada syndrome. Variants in additional genes have been reported but remain unclear.[211]
- Variants in the *PKP2* gene that causes ARVC have been reported to cause an arrhythmogenic phenotype in the absence of overt structural disease[212] and may be implicated in Brugada syndrome.[213]
- Apart from identifying 10 new loci, a GWAS meta-analysis for Brugada syndrome supported by functional studies has elucidated the causal role of *MAPRE2* in the pathogenesis of Brugada syndrome.[214]
- The large proportion of sporadic cases and variable penetrance in *SCN5A* carriers has suggested a more complex pattern of penetrance. PRS-based analysis for Brugada syndrome supports that the disease threshold varies between individuals depending on the contributions of rare variants of *SCN5A*, common risk alleles, and exposure to sodium channel blockade.[214]
- A reappraisal of 21 genes associated with Brugada syndrome for clinical validity led to the classification of only *SCN5A* as definitive evidence for causing Brugada syndrome, and the other 20 were classified as limited evidence for causing Brugada syndrome.[215]

### Catecholaminergic Polymorphic VT

#### Prevalence and Incidence

- CPVT is a familial condition characterized by adrenergically induced polymorphic ventricular

arrhythmias associated with syncope and sudden death. Arrhythmias include frequent ectopy, bidirectional VT, and polymorphic VT with exercise or catecholaminergic stimulation (such as emotion or medicines such as isoproterenol). Most patients present in childhood or adolescence. Variants in genes encoding RYR2 (*CPVT1*) are found in the majority of patients and result in an autosomal dominant pattern of inheritance.[216] Variants in genes encoding CASQ2 (*CPVT2*) are found in a small minority and result in an autosomal recessive pattern of inheritance. Other less common variants have also been described in *TRDN* and *TECRL* (autosomal recessive), as well as *CALM1*, *CALM2*, and *CALM3* (autosomal dominant).

- Analysis of 171 probands with CPVT who were <19 years of age and 65 adult relatives described clinical presentations and prevalence of genotypes.[217] The presenting symptom was cardiac arrest for 28% of cases and syncope/seizure in 58%. Genetic testing of 194 individuals identified variants in *RYR2* (60%), *CASQ2* (5%), and >1 gene in 17 cases (9%). For 23 cases (12%), no genetic variant was identified.

### *Complications*

- In a cohort of 34 patients with CPVT, 20.6% developed fatal cardiac events during 7.4 years of follow-up.[218]
- Incidence of SCA in children with ≥2 CPVT gene variants was 11 of 15 (73%).[219] VT or exertional syncope occurred in 3 of the children (20%), and only 1 (7%) was asymptomatic.

### *Arrhythmogenic RV Dysplasia/ARVC*

- Arrhythmogenic RV dysplasia or ARVC is a form of genetically inherited structural HD that presents with fibrofatty replacement of the myocardium, which increases risk for palpitations, syncope, and sudden death attributable to VT.[220]
- Twelve ARVC loci have been described (*ARVC1–ARVC12*).[221]
- Clinical Genomics Resource reappraisal of 26 candidate ARVC genes found 6 to have strong definitive evidence and 2 to have moderate evidence supporting their role in ARVC.[222]
- Although the original descriptions localized the disease to the RV, more recent work has demonstrated that LV involvement may occur early in the course of the disease.[223]

### *Complications*

- In a cohort of 301 patients with ARVC from a single center in Italy, the probability of a first life-threatening arrhythmic event was 14% at 5 years, 23% at 10 years, and 30% at 15 years.[224]
- In a pooled analysis examining 5485 patients, rates of SCD were 0.65 per 1000 (95% CI, 0.00–6.43; $I^2$=0.00%) in those with an ICD placed and 7.21 (95% CI, 2.38–13.79; $I^2$=0.0%) in the non-ICD cohort.[225] Patient characteristics identified individuals at a higher risk of life-threatening arrhythmia: age at presentation (aHR, 0.98 [95% CI, 0.97–0.99]), male sex (2.08 [95% CI, 1.29–3.36]), RV dysfunction (6.99 [95% CI, 2.17–22.49]), QRS fragmentation (6.55 [95% CI, 3.33–12.90]), T-wave inversion (1.12 [95% CI, 1.02–1.24]), syncope at presentation (2.83 [95% CI, 2.40–4.08]), and previous nonsustained ventricular tachyarrhythmia (2.53 [95% CI, 1.44–4.45]).
- In a cohort of 502 patients with ARVC, younger patients (<50 years versus >50 years of age) were more likely to present with SCA (5% versus 2%) or SCD (7% versus 6%).[226]

## Hypertrophic Cardiomyopathy

(Please refer to Chapter 22 [Cardiomyopathy and Heart Failure] for statistics on the general epidemiology of HCM.)

### *Complications*

- SCA rates were 2.7%/y in a retrospective cohort of 106 patients with HCM treated medically and followed up for a mean of 7.7 years.[227]
- Among 1436 SCA cases in individuals 5 to 59 years of age between 2002 and 2015, HCM was present in 3.2% of those 5 to 34 years of age and 2.2% of those 35 to 59 years of age. This study noted the difficulty in distinguishing HCM from secondary LVH in older patients, who were excluded from the analysis.[228]
- In a pooled analysis of 98 studies and N=70 510 patients (431 407 patient-years), contemporary SCD rates from 2015 to present were 0.32%/y and significantly lower compared with 2000 or earlier (incidence rate, 0.32% [95% CI, 0.20%–0.52%] versus incidence rate, 0.73% [95% CI, 0.53%–1.02%], respectively).[229] Reported SCD rates for HCM were lowest in North America (incidence rate, 0.28% [95% CI, 0.18%–0.43%]) and highest in Asia (incidence rate, 0.67% [95% CI, 0.54%–0.84%]).

### *Early Repolarization Syndrome*

#### *Prevalence and Incidence*

- There had been no single electrocardiographic definition or set of criteria for ERP until recently. Studies have used a range of criteria, including ST-segment elevation, terminal QRS slurring, terminal QRS notching, J-point elevation, J waves, and other variations. Although the Brugada electrocardiographic pattern is considered an early repolarization

variant, it is generally not included in epidemiological assessments of ERP or early repolarization syndrome.[230] The problem with older definitions of ERP is the high prevalence of this electrocardiographic finding in the general population. Currently, the existence of the electrocardiographic pattern of early repolarization in asymptomatic people is called ERP, whereas early repolarization in patients with arrhythmic syncope or cardiac arrest is called early repolarization syndrome.[231]

- ERP was observed in 4% to 19% of the population (more commonly in young males and in athletes) and conventionally has been considered a benign finding.[230]
- Among 11 956 residents of rural Liaoning Province, China, who were ≥35 years of age, 1.3% had ERP, with a higher prevalence in males (2.6%) than females (0.2%).[232]
- In an Italian public health screening project, 24% of 13 016 students 16 to 19 years of age had at least 1 of the following electrocardiographic abnormalities: ventricular ectopic beats, atrioventricular block, Brugada-like electrocardiographic pattern, left anterior/posterior fascicular block, LVH/RV hypertrophy, long/short QT interval, left atrial enlargement, right atrial enlargement, short PQ interval, and ventricular preexcitation WPW syndrome.[233]

### *Complications*

- Early repolarization had been considered a benign normal electrocardiographic variant until reports linked early repolarization in the inferior and lateral leads with idiopathic VF.[234]
- The consensus panel[231] and others have identified certain electrocardiographic characteristics associated with increased risk for VF: ERP in the inferior and lateral ECG leads and J waves associated with horizontal or downsloping ST segments (as opposed to rapidly ascending ST segments).[235]
- ERP was associated with increased age- and sex-adjusted hazard of SCD among people 30 to 50 years of age in the Mini-Finland Health Survey (HR, 1.72 [95% CI, 1.05–2.80]).[236]
- Shocks from an automatic ICD occur more often and earlier in survivors of idiopathic VF with inferolateral early repolarization syndrome (HR, 3.9 [95% CI, 1.4–11.0]; $P$=0.01).[237]

## *Premature Ventricular Contractions*

- In a study of 1139 older adults in the CHS without HF or systolic dysfunction studied by Holter monitor (median duration, 22.2 hours), 0.011% of all heartbeats were premature ventricular contractions, and 5.5% of participants had nonsustained VT. Over follow-up, the highest quartile of ambulatory electrocardiographic premature ventricular contraction burden was associated with an adjusted odds of decreased LVEF (OR, 1.13 [95% CI, 1.05–1.21]) and incident HF (HR, 1.06 [95% CI, 1.02–1.09]) and death (HR, 1.04 [95% CI, 1.02–1.06]).[238] Although premature ventricular contraction ablation has been shown to improve cardiomyopathy, the association with death may be complex, representing both a potential cause and a noncausal marker for coronary or structural HD.

## *Tetralogy of Fallot*

- Patients with repaired TOF are known to be at risk for ventricular arrhythmias and SCD. However, the true incidence is not clear. Prevalence estimates from multicenter studies range from 1% to 14%.[239–241]

## *Cardiac Sarcoidosis*

- Cardiac involvement in sarcoidosis is increasingly recognized as a cardiomyopathy with relatively high risk for sudden death attributable to ventricular tachyarrhythmias. Estimates of the prevalence of cardiac involvement in sarcoidosis vary widely, depending on the method of diagnosis, ranging from 3.7% to 54.9%.[242]
- A review of the NIS from 2012 to 2014 identified 46 289 patients with a diagnosis of sarcoidosis. VT was recognized in 2.29% of all patients with sarcoidosis compared with 1.22% of control patients ($P$<0.001). VF also was recognized significantly more frequently in patients with sarcoidosis: 0.25% versus 0.21% ($P$<0.001). Prevalence of cardiac arrest in patients with sarcoidosis was 0.72%.[243]

## *Monomorphic VT*

### *Prevalence and Incidence*

- Incidence of monomorphic VT in hospitalized patients with AMI decreased from 14.6% in 1986 to 1988 to 10.5% in 2009 to 2011.[244]
- Prevalence of sustained VT in patients with LV aneurysm after MI is reported at 10%.[245]
- Incidence of late (>48 hours) monomorphic VT after AMI in the GISSI-3 database was 1% by 6 weeks.[246] Presence of VT was associated with significantly increased total mortality attributed primarily to in-hospital pump failure and refractory VF.
- Monomorphic VT occurred in 9 of 342 patients (2.6%) at a median of 1 day (IQR, 0.25–4.75 days) after PCI for chronic total occlusion of a coronary artery.[247]
- During a mean follow-up period of 85 months, sustained VT was observed in 13 of 250 patients (5.2%) and monomorphic VT in 9 of 250 patients (3.6%) with congenital LV aneurysms or diverticula.[248]

## Polymorphic VT/VF

### Prevalence and Incidence

- In the setting of AMI, the prevalence of polymorphic VT was 4.4%.[249]
- Incidence of VF in hospitalized patients with AMI decreased from 8.2% in 1986 to 1988 to 1.7% in 2009 to 2011.[244]

### Complications

- In the setting of AMI, polymorphic VT is associated with increased mortality (17.8%).[249]

## Torsade de Pointes

### Prevalence and Incidence

- Among 14 756 patients exposed to QT-prolonging drugs in 36 studies, 6.3% developed QT prolongation, and 0.33% developed TdP.[250]

### Risk Factors

- An up-to-date list of drugs with the potential to cause TdP is available at a website maintained by the University of Arizona Center for Education and Research on Therapeutics.[251]

**Table 19-1. Differences in Bystander Interventions and Survival After OHCA by Race, Ethnicity, Sex, and Neighborhood Characteristics, CARES, United States, 2022**

| | Nontraumatic pathogenesis survival rates | Bystander intervention rates | |
|---|---|---|---|
| | Overall survival to hospital discharge | CPR | Public AED use |
| Total | 13 794/147 736 (9.3%) | 45 044/112 591 (40.0%) | 2149/18 994 (11.3%) |
| Race and ethnicity | | | |
| American Indian/Alaska Native | 51/577 (8.8%) | 194/466 (41.6%) | 9/93 (9.7%) |
| Asian | 353/3811 (9.3%) | 1212/3024 (40.1%) | 56/394 (14.2%) |
| Black/African American | 2574/31 303 (8.2%) | 7498/22 746 (33.0%) | 326/3647 (8.9%) |
| Hispanic/Latino | 1060/12 193 (8.7%) | 3748/9741 (38.5%) | 161/1838 (8.8%) |
| Native Hawaiian/Pacific Islander | 56/677 (8.3%) | 243/547 (44.4%) | 6/98 (6.1%) |
| White | 7428/74 687 (9.9%) | 23 925/56 847 (42.1%) | 1195/9558 (12.5%) |
| Unknown | 2272/24 488 (9.3%) | 8224/19 220 (42.8%) | 396/3366 (11.8%) |
| Sex | | | |
| Male | 9093/92 606 (9.8%) | 29 123/72 627 (40.1%) | 1747/14 876 (11.7%) |
| Female | 4696/55 091 (8.5%) | 15 910/39 932 (39.8%) | 402/4113 (9.8%) |
| Neighborhood racial composition | | | |
| ≥70% White | 6854/68 742 (10.0%) | 22 969/53 110 (43.2%) | 1021/8501 (12.0%) |
| ≥40% Black | 1723/22 194 (7.8%) | 5273/16 811 (31.4%) | 209/2516 (8.3%) |
| Integrated | 5129/56 540 (9.1%) | 16 662/42 443 (39.3%) | 833/7777 (10.7%) |
| Neighborhood median household income | | | |
| <$40 000 annually | 2034/22 515 (9.0%) | 5331/17 145 (31.1%) | 243/3157 (7.7%) |
| $40 000–$80 000 annually | 7079/77 856 (9.1%) | 23 560/59 207 (39.8%) | 1009/9755 (10.3%) |
| >$80 000 annually | 4484/46 274 (9.7%) | 15 700/35 351 (44.4%) | 704/5584 (12.6%) |

Bystander CPR rate excludes 9-1-1 responder–witnessed, nursing home, and health care facility arrests. Public AED use rate excludes 9-1-1 responder–witnessed, home/residence, nursing home, and health care facility arrests. Sex was missing for 38 cases. Race is unknown for 16.2% of CARES cases in the 2022 data set because a number of communities do not collect this information.

AED indicates automated external defibrillator; CARES, Cardiac Arrest Registry to Enhance Survival; CPR, cardiopulmonary resuscitation; and OHCA, out-of-hospital cardiac arrest.

Source: Data derived from CARES.[3]

**Table 19-2. Variation in EMS-Treated OHCA in Selected States, United States, 2022**

| | OHCA incidence | | | Nontraumatic pathogenesis survival rates | | Bystander intervention rates | |
|---|---|---|---|---|---|---|---|
| | EMS-treated OHCA cases reported to CARES, n | Percent of population reporting data, % | Incidence rate per 100 000 people | Overall survival to hospital discharge, % | Utstein survival, % | CPR, % | Public AED use, % |
| National | 147 736 | 50.1 | 88.8 | 9.3 | 30.7 | 40 | 11.3 |
| State | | | | | | | |
| Alaska | 542 | 83.0 | 89.1 | 12.7 | 42.5 | 73.2 | 18.8 |
| California | 26 403 | 83.8 | 80.3 | 7.8 | 28.6 | 41 | 9.6 |
| Colorado | 3711 | 78.8 | 81 | 11.6 | 35.2 | 38.8 | 13.9 |
| Connecticut | 2480 | 73.7 | 93.3 | 9.5 | 34 | 22.8 | 6 |
| Delaware | 1317 | 100.0 | 131.3 | 10.6 | 41.5 | 37 | 9 |
| Hawaii | 1693 | 100.0 | 117.4 | 10.9 | 38.2 | 37.4 | 10.4 |
| Maine | 1363 | 100.0 | 99.3 | 7.6 | 20.1 | 52.2 | 14.6 |
| Michigan | 9275 | 87.3 | 105.7 | 8.1 | 25.2 | 35.6 | 9.1 |
| Minnesota | 3293 | 82.4 | 70.1 | 10.1 | 33.3 | 37.9 | 11.4 |
| Mississippi | 1695 | 63.9 | 89.9 | 6.3 | 23.8 | 38.7 | 9.9 |
| Missouri | 3134 | 52.3 | 97.1 | 10 | 35.9 | 40 | 15.4 |
| Montana | 660 | 88.5 | 67.5 | 11.2 | 26 | 50 | 6.1 |
| Nebraska | 701 | 56.1 | 63.7 | 15.4 | 37.4 | 50.1 | 12 |
| North Carolina | 9117 | 87.4 | 98.8 | 10.8 | 29.3 | 38.8 | 11.1 |
| Oregon | 2940 | 84.1 | 82.3 | 14.6 | 40.6 | 56.9 | 12.9 |
| Utah | 1666 | 100.0 | 49.9 | 10.2 | 32.5 | 37.2 | 9.2 |
| Vermont | 547 | 100.0 | 84.7 | 5.5 | 20 | 48.7 | 14.6 |
| Washington | 5342 | 98.0 | 70.5 | 12.6 | 35.8 | 51.7 | 11.3 |
| Wisconsin | 3482 | 65.5 | 90.1 | 10.5 | 36.5 | 38.8 | 11.8 |
| District of Columbia | 917 | 100.0 | 137 | 7.1 | 37.7 | 28.9 | 12.7 |

Criteria for reporting: at least 50% population catchment in state; voluntarily reporting data. Utstein: witnessed by bystander and found in shockable rhythm. Bystander CPR rate excludes 9-1-1 responder–witnessed, nursing home, and health care facility arrests.

Public AED use rate excludes 9-1-1 responder–witnessed, home/residence, nursing home, and health care facility arrests.

AED indicates automated external defibrillator; CARES, Cardiac Arrest Registry to Enhance Survival; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; and OHCA, out-of-hospital cardiac arrest.

Source: Data derived from CARES.[3]

**Table 19-3. Characteristics of and Outcomes for OHCA (CARES) and IHCA (GWTG-R), United States, 2022**

| | OHCA* | | | IHCA | | |
|---|---|---|---|---|---|---|
| | Adults (>18 y) | Children (1–18 y) | Infants (<1 y)† | Adults (>18 y) | Children (1–18 y) | Infants (<1 y) |
| Females | 37.2 | 39.0 | 41.9 | 40.79 | 47.42 | 43.95 |
| Males | 62.8 | 61.0 | 58.1 | 59.21 | 52.58 | 56.05 |
| Survival to hospital discharge | 9.3 | 15.8 | 6.6 | 21.32 | 43.94 | 44.53 |
| Good functional status at hospital discharge | 7.5 | 13.3 | 5.5 | 79.92 | 73.01 | 83.87 |
| Initial rhythm | | | | | | |
| VF/VT/shockable | 17.3 | 9.5 | 2.6 | 13.36 | 3.97 | 2.03 |
| PEA | 22.2 | 15.3 | 11.3 | 53.06 | 43.48 | 23.47 |
| Asystole | 52.2 | 64.5 | 79.1 | 22.67 | 22.42 | 15.58 |
| Unknown | … | … | … | 7.33 | 7.58 | 7.49 |
| Public setting | 17.3 | 19.0 | 8.1 | … | … | … |
| Home | 72.1 | 80.5 | 91.9 | … | … | … |

(*Continued*)

**Table 19-3. Continued**

| | OHCA* | | | IHCA | | |
|---|---|---|---|---|---|---|
| | Adults (>18 y) | Children (1–18 y) | Infants (<1 y)† | Adults (>18 y) | Children (1–18 y) | Infants (<1 y) |
| Nursing home | 10.6 | 0.5 | 0.0 | … | … | … |
| Public AED use‡ | 11.3 | 17.2 | 1.9 | … | … | … |
| Arrest in ICU, operating room, or ED | … | … | … | 60.41 | 71.15 | 68.65 |
| Noncritical care area | … | … | … | 39.59 | 28.85 | 31.35 |

Values are percentages.

AED indicates automated external defibrillator; CARES, Cardiac Arrest Registry to Enhance Survival; ED, emergency department; ellipses (…), data not available; EMS, emergency medical services; GWTG-R, Get With The Guidelines–Resuscitation; ICU, intensive care unit; IHCA, in-hospital cardiac arrest; OHCA, out-of-hospital cardiac arrest; PEA, pulseless electric activity; VF, ventricular fibrillation; and VT, ventricular tachycardia.

*Inclusion criteria: an out-of-hospital cardiac arrest for which resuscitation is attempted by a 9-1-1 responder (CPR or defibrillation). This would also include patients who received an AED shock by a bystander before the arrival of 9-1-1 responders. Analysis excludes patients with missing hospital outcome (n=305).

†Stillborn neonates and perinatal newborns born without signs of life are not CARES cases and are not entered into the registry.

‡Inclusion criteria: an out-of-hospital cardiac arrest.

Source: OHCA data derived from CARES[3] and are based on 143 507 EMS-treated OHCA adult cases, 2105 EMS-treated OHCA pediatric cases (1–18 years of age), and 1687 EMS-treated OHCA infant cases (<1 year of age) in 2022. IHCA data are from GWTG-R (unpublished AHA tabulation) 2022 and are based on 39 896 adult IHCAs in 379 hospitals, 660 child (1–18 years of age) IHCAs in 118 hospitals, and 1027 infant (<1 year of age) IHCAs in 93 hospitals.

**Table 19-4. Outcomes of EMS-Treated Nontraumatic OHCA in Adults (>18 Years of Age), CARES, United States, 2022**

| Presenting characteristics (n) | Survival to hospital admission | Survival to hospital discharge | Survival with good neurological function (CPC 1 or 2) | In-hospital mortality* |
|---|---|---|---|---|
| All presentations (143 507) | 24.9 | 9.3 | 7.5 | 62.7 |
| Home/residence (103 447) | 23.5 | 7.9 | 6.2 | 66.5 |
| Nursing home (15 224) | 14.4 | 3.5 | 1.7 | 75.8 |
| Public setting (24 836) | 36.9 | 18.7 | 16.3 | 49.3 |
| Unwitnessed (72 899) | 15.7 | 4.0 | 2.9 | 74.4 |
| Bystander witnessed (53 794) | 32.9 | 14.0 | 11.6 | 57.5 |
| 9-1-1 Responder witnessed (16 810) | 38.8 | 17.0 | 13.9 | 56.1 |
| Shockable presenting rhythm (24 750) | 44.8 | 26.6 | 23.4 | 40.6 |
| Nonshockable presenting rhythm (118 728) | 20.7 | 5.7 | 4.1 | 72.7 |
| Layperson CPR† (43 228) | 26.8 | 11.2 | 9.5 | 58.2 |
| No layperson CPR† (65 489) | 22.1 | 7.0 | 5.4 | 68.3 |

Values are percentages.

Inclusion criteria: an OHCA for which resuscitation is attempted by a 9-1-1 responder (CPR or defibrillation). This would also include patients who received an AED shock by a bystander before the arrival of 9-1-1 responders. Analysis excludes patients with missing hospital outcome (n=291).

AED indicates automated external defibrillator; CARES, Cardiac Arrest Registry to Enhance Survival; CPC, Cerebral Performance Category; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; and OHCA, out-of-hospital cardiac arrest.

*Percentage of patients admitted to the hospital who died before hospital discharge.

†Excludes nursing home/health care facility events.

Source: Data derived from CARES.[3]

**Table 19-5. Outcomes of EMS-Treated Nontraumatic OHCA in Children and Infants, CARES, United States, 2022**

| Age group, y (n) | Survival to hospital admission | Survival to hospital discharge | Survival with good neurological function (CPC 1 or 2) | In-hospital mortality* |
|---|---|---|---|---|
| <1 (1687) | 18.7 | 6.6 | 5.5 | 64.6 |
| 1–12 (1207) | 32.9 | 14.7 | 11.2 | 55.4 |
| 13–18 (898) | 35.2 | 17.3 | 16.3 | 50.9 |

Values are percentages.

Inclusion criteria: an OHCA for which resuscitation is attempted by a 9-1-1 responder (CPR or defibrillation). This would also include patients who received an AED shock by a bystander before the arrival of 9-1-1 responders. Analysis excludes patients with missing hospital outcome (n=37). Stillborn neonates and perinatal newborns born without signs of life are not CARES cases and are not entered into the registry.

CARES indicates Cardiac Arrest Registry to Enhance Survival; CPC, Cerebral Performance Category; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; and OHCA, out-of-hospital cardiac arrest.

*Percentage of patients admitted to the hospital who died before hospital discharge.

Source: Data derived from CARES.[3]

**Table 19-6. SCA Mortality, United States, 2021 (*ICD-10* I46.0, I46.1, I46.9, I49.0)**

| Population group | No. of deaths as underlying cause, 2021, all ages |
|---|---|
| Both sexes | 20 114 |
| Males | 11 250 |
| Females | 8864 |
| NH White males | 8137 |
| NH White females | 6217 |
| NH Black males | 2069 |
| NH Black females | 1846 |
| Hispanic males | 690 |
| Hispanic females | 521 |
| NH Asian males | 225 |
| NH Asian females | 170 |
| NH American Indian/Alaska Native | 102 |
| NH Native Hawaiian or Pacific Islander | 31 |

Mortality for Hispanic, NH American Indian or Alaska Native, and NH Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting Hispanic origin or race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native, Asian, Pacific Islander, and Hispanic decedents, as well as undercounts of these groups in censuses.

*ICD-10* indicates *International Classification of Diseases, 10th Revision*; NH, non-Hispanic; and SCA, sudden cardiac arrest.

Sources: Any-mention cause and underlying cause data derived from Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research database.[145]

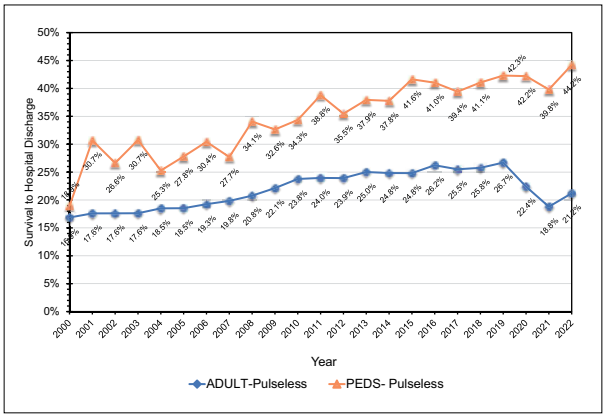



**Chart 19-1. Temporal trends in survival to hospital discharge after IHCA in adults and children in GWTG–Resuscitation from 2000 to 2022, United States.**

GWTG indicates Get With The Guidelines; IHCA, in-hospital cardiac arrest; and PEDS, pediatrics.

Source: GWTG–Resuscitation; unpublished American Heart Association data.

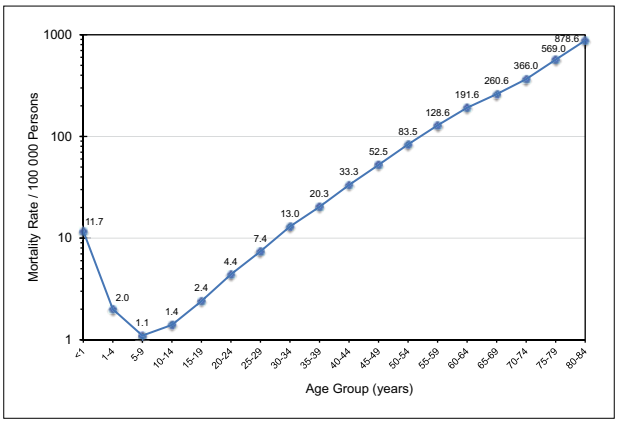



**Chart 19-2. Age-specific mortality rates for any mention of SCD, by age, United States, 2021.**

SCD indicates sudden cardiac death.

Source: Data derived from Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research database.[145]

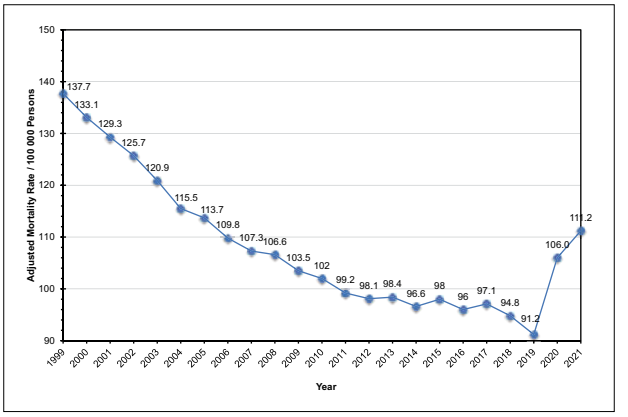



**Chart 19-3. Age-adjusted mortality rates for any mention of SCD, United States, 1999 to 2021.**

SCD indicates sudden cardiac death.

Source: Data derived from Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research.[145]

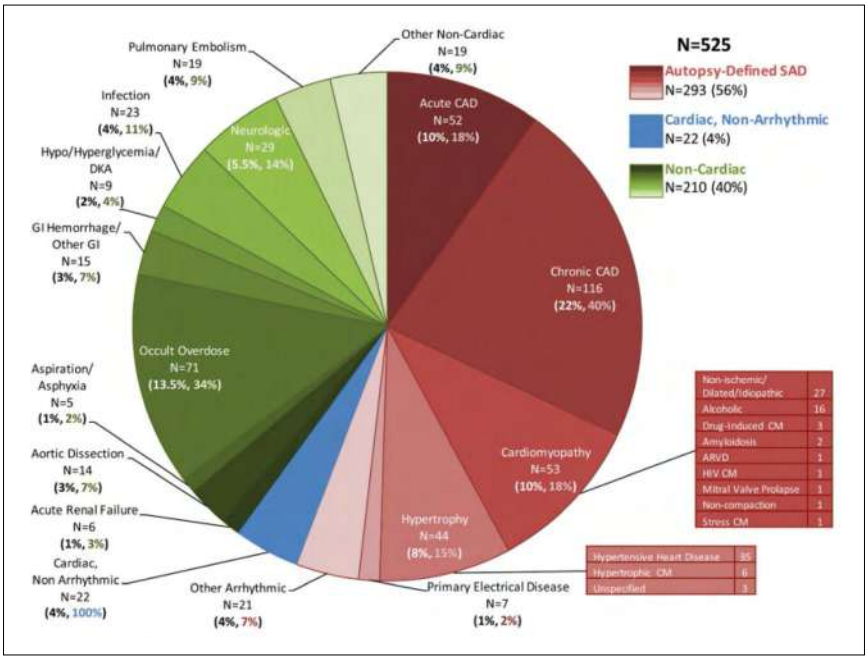
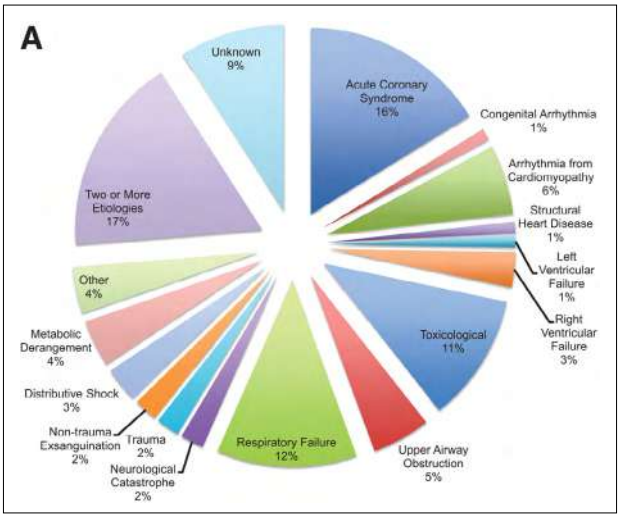



**Chart 19-4. Adjudicated causes of autopsied WHO-defined SCDs.**

Adjudicated causes of autopsied WHO-defined SCDs after review of comprehensive medical records, EMS records, complete autopsy, toxicology, and postmortem chemistries. Autopsy-defined SADs had no identifiable extracardiac (eg, PE, hemorrhage, lethal toxicology) or nonarrhythmic (tamponade, acute HF) cause of death. The first percent is of total WHO-defined SCDs; the second percent is of cause of death category. Overall, autopsy-defined SADs accounted for 56% of all WHO-defined SCDs; 4% were cardiac nonarrhythmic cause of death; and 40% were noncardiac cause of death.

ARVD indicates arrhythmogenic right ventricular dysplasia; CAD, coronary artery disease; CM, cardiomyopathy; DKA, diabetic ketoacidosis; EMS, emergency medical services; GI, gastrointestinal; HF, heart failure; PE, pulmonary embolism; SAD, sudden arrhythmic death; SCD, sudden cardiac death; and WHO, World Health Organization.

Source: Adapted with permission from Tseng et al.[121] Copyright © 2018 American Heart Association, Inc.



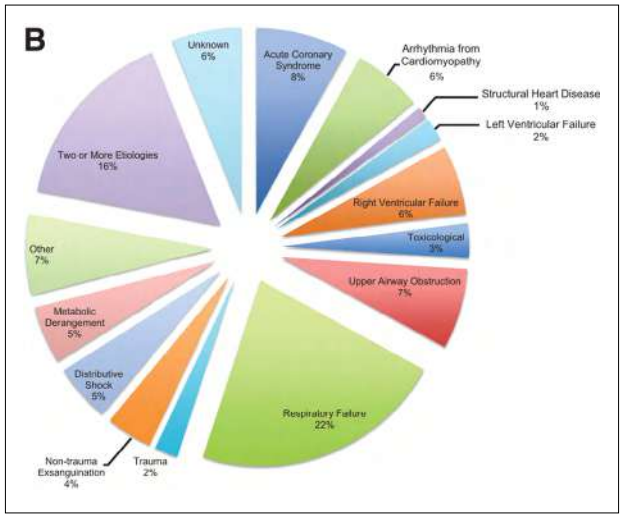




**Chart 19-5. Detailed causes of OHCA and IHCA in 1 US center.**

**A**, Proportion of hospitalized patients with each cause after OHCA.

**B**, Proportion of hospitalized patients with each cause after IHCA.

Pathogenesis based on testing and evaluation in the hospital. "Other" corresponds to all other causes.

IHCA indicates in-hospital cardiac arrest; and OHCA, out-of-hospital cardiac arrest.

Source: Data derived from Chen et al.[122]

(*Continued*)

**Chart 19-5 Continued.**

## REFERENCES


1. Jacobs I, Nadkarni V, Bahr J, Berg RA, Billi JE, Bossaert L, Cassan P, Coovadia A, D'Este K, Finn J, et al; International Liaison Committee on Resuscitation. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein templates for resuscitation registries: a statement for healthcare professionals from a task force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian Resuscitation Council, New Zealand Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Councils of Southern Africa). *Circulation*. 2004;110:3385–3397. doi: 10.1161/01.CIR.0000147236.85306.15
2. Perkins GD, Jacobs IG, Nadkarni VM, Berg RA, Bhanji F, Biarent D, Bossaert LL, Brett SJ, Chamberlain D, de Caen AR, et al; for the Utstein Collaborators. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update of the Utstein resuscitation registry templates for out-of-hospital cardiac arrest: a statement for healthcare professionals from a task force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian and New Zealand Council on Resuscitation, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa, Resuscitation Council of Asia); and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation [published correction appears in *Circulation*. 2015;132:e168–e160]. *Circulation*. 2015;132:1286–1300. doi: 10.1161/CIR.0000000000000144
3. Cardiac Arrest Registry to Enhance Survival. Accessed April 1, 2023. https://mycares.net
4. Allan KS, Morrison LJ, Pinter A, Tu JV, Dorian P; Rescu Investigators. Unexpected high prevalence of cardiovascular disease risk factors and psychiatric disease among young people with sudden cardiac arrest. *J Am Heart Assoc*. 2019;8:e010330. doi: 10.1161/JAHA.118.010330
5. Wittwer MR, Zeitz C, Beltrame JF, Arstall MA. Aetiology of resuscitated out-of-hospital cardiac arrest treated at hospital. *Resuscitation*. 2022;170:178–183. doi: 10.1016/j.resuscitation.2021.11.035
6. Lai PH, Lancet EA, Weiden MD, Webber MP, Zeig-Owens R, Hall CB, Prezant DJ. Characteristics associated with out-of-hospital cardiac arrestsand resuscitations during the novel coronavirus disease 2019 pandemic in New York City. *JAMA Cardiol*. 2020;5:1154–1163. doi: 10.1001/jamacardio.2020.2488
7. Chan PS, Girotra S, Tang Y, Al-Araji R, Nallamothu BK, McNally B. Outcomes for out-of-hospital cardiac arrest in the United States during the coronavirus disease 2019 pandemic. *JAMA Cardiol*. 2021;6:296–303. doi: 10.1001/jamacardio.2020.6210
8. Nickles AV, Oostema A, Allen J, O'Brien SL, Demel SL, Reeves MJ. Comparison of out-of-hospital cardiac arrests and fatalities in the metro detroit area during the COVID-19 pandemic with previous-year events. *JAMA Netw Open*. 2021;4:e2032331. doi: 10.1001/jamanetworkopen.2020.32331
9. Rollman JE, Kloner RA, Bosson N, Niemann JT, Gausche-Hill M, Williams M, Clare C, Tan W, Wang X, Shavelle DM, et al. Emergency medical services responses to out-of-hospital cardiac arrest and suspected ST-segment-elevation myocardial infarction during the COVID-19 pandemic in Los Angeles County. *J Am Heart Assoc*. 2021;10:e019635. doi: 10.1161/JAHA.120.019635
10. Lim ZJ, Ponnapa Reddy M, Afroz A, Billah B, Shekar K, Subramaniam A. Incidence and outcome of out-of-hospital cardiac arrests in the COVID-19 era: a systematic review and meta-analysis. *Resuscitation*. 2020;157:248–258. doi: 10.1016/j.resuscitation.2020.10.025
11. Perrin N, Iglesias JF, Rey F, Benzakour L, Cimci M, Noble S, Degrauwe S, Tessitore E, Mach F, Roffi M. Impact of the COVID-19 pandemic on acute coronary syndromes. *Swiss Med Wkly*. 2020;150:w20448. doi: 10.4414/smw.2020.20448
12. Pemberton K, Bosley E, Franklin RC, Watt K. Pre-hospital outcomes of adult out-of-hospital cardiac arrest of presumed cardiac aetiology in Queensland, Australia (2002-2014): Trends over time. *Emerg Med Australas*. 2019;31:813–820. doi: 10.1111/1742-6723.13353
13. Lee SY, Song KJ, Shin SD, Ro YS, Hong KJ, Kim YT, Hong SO, Park JH, Lee SC. A disparity in outcomes of out-of-hospital cardiac arrest by community socioeconomic status: a ten-year observational study. *Resuscitation*. 2018;126:130–136. doi: 10.1016/j.resuscitation.2018.02.025
14. Faxén J, Jernberg T, Hollenberg J, Gadler F, Herlitz J, Szummer K. Incidence and predictors of out-of-hospital cardiac arrest within 90 days after myocardial infarction. *J Am Coll Cardiol*. 2020;76:2926–2936. doi: 10.1016/j.jacc.2020.10.033
15. Kontos MC, Fordyce CB, Chen AY, Chiswell K, Enriquez JR, de Lemos J, Roe MT. Association of acute myocardial infarction cardiac arrest patient volume and in-hospital mortality in the United States: insights from the National Cardiovascular Data Registry Acute Coronary Treatment and Intervention Outcomes Network Registry. *Clin Cardiol*. 2019;42:352–357. doi: 10.1002/clc.23146
16. Shavelle DM, Bosson N, Thomas JL, Kaji AH, Sung G, French WJ, Niemann JT. Outcomes of ST elevation myocardial infarction complicated by out-of-hospital cardiac arrest (from the Los Angeles County regional system). *Am J Cardiol*. 2017;120:729–733. doi: 10.1016/j.amjcard.2017.06.010
17. Olgin JE, Pletcher MJ, Vittinghoff E, Wranicz J, Malik R, Morin DP, Zweibel S, Buxton AE, Elayi CS, Chung EH, et al; VEST Investigators. Wearable cardioverter-defibrillator after myocardial infarction. *N Engl J Med*. 2018;379:1205–1215. doi: 10.1056/NEJMoa1800781
18. Zhao B, Johnston FH, Salimi F, Kurabayashi M, Negishi K. Short-term exposure to ambient fine particulate matter and out-of-hospital cardiac arrest: a nationwide case-crossover study in Japan. *Lancet Planet Health*. 2020;4:e15–e23. doi: 10.1016/S2542-5196(19)30262-1
19. Kranc H, Novack V, Shtein A, Sonkin R, Jaffe E, Novack L. Ambient air pollution and out-of-hospital cardiac arrest: Israel nation wide assessment. *Atmos Environ*. 2021;261:118567. doi: 10.1016/j.atmosenv.2021.118567
20. Gentile FR, Primi R, Baldi E, Compagnoni S, Mare C, Contri E, Reali F, Bussi D, Facchin F, Currao A, et al; Lombardia CARe Researchers. Out-of-hospital cardiac arrest and ambient air pollution: a dose-effect relationship and an association with OHCA incidence. *PLoS One*. 2021;16:e0256526. doi: 10.1371/journal.pone.0256526
21. Bougouin W, Mustafic H, Marijon E, Murad MH, Dumas F, Barbouttis A, Jabre P, Beganton F, Empana JP, Celermajer DS, et al. Gender and survival after sudden cardiac arrest: a systematic review and meta-analysis. *Resuscitation*. 2015;94:55–60. doi: 10.1016/j.resuscitation.2015.06.018
22. Ng YY, Wah W, Liu N, Zhou SA, Ho AF, Pek PP, Shin SD, Tanaka H, Khunkhlai N, Lin CH, et al; PAROS Clinical Research Network. Associations between gender and cardiac arrest outcomes in Pan-Asian out-of-hospital cardiac arrest patients. *Resuscitation*. 2016;102:116–121. doi: 10.1016/j.resuscitation.2016.03.002
23. Dicker B, Conaglen K, Howie G. Gender and survival from out-of-hospital cardiac arrest: a New Zealand registry study. *Emerg Med J*. 2018;35:367–371. doi: 10.1136/emermed-2017-207176
24. Vogelsong MA, May T, Agarwal S, Cronberg T, Dankiewicz J, Dupont A, Friberg H, Hand R, McPherson J, Mlynash M, et al. Influence of sex on survival, neurologic outcomes, and neurodiagnostic testing after out-of-hospital cardiac arrest. *Resuscitation*. 2021;167:66–75. doi: 10.1016/j.resuscitation.2021.07.037
25. Rachoin JS, Olsen P, Gaughan J, Cerceo E. Racial differences in outcomes and utilization after cardiac arrest in the USA: a longitudinal study comparing different geographical regions in the USA from 2006-2018. *Resuscitation*. 2021;169:115–123. doi: 10.1016/j.resuscitation.2021.10.038
26. Monlezun DJ, Samura AT, Patel RS, Thannoun TE, Balan P. Racial and socioeconomic disparities in out-of-hospital cardiac arrest outcomes: artificial intelligence-augmented propensity score and geospatial cohort analysis of 3,952 patients. *Cardiol Res Pract*. 2021;2021:3180987. doi: 10.1155/2021/3180987
27. Office of the Assistant Secretary for Planning and Evaluation. Prior HHS poverty guidelines and Federal Register references. Accessed April 24, 2023. https://aspe.hhs.gov/topics/poverty-economic-mobility/poverty-guidelines/prior-hhs-poverty-guidelines-federal-register-references
28. Castra L, Genin M, Escutnaire J, Baert V, Agostinucci JM, Revaux F, Ursat C, Tazarourte K, Adnet F, Hubert H. Socioeconomic status and incidence of cardiac arrest: a spatial approach to social and territorial disparities. *Eur J Emerg Med*. 2019;26:180–187. doi: 10.1097/MEJ.0000000000000534
29. Goh CE, Mooney SJ, Siscovick DS, Lemaitre RN, Hurvitz P, Sotoodehnia N, Kaufman TK, Zulaika G, Lovasi GS. Medical facilities in the neighborhood and incidence of sudden cardiac arrest. *Resuscitation*. 2018;130:118–123. doi: 10.1016/j.resuscitation.2018.07.005
30. Hughes ZH, Shah NS, Tanaka Y, Hammond MM, Passman R, Khan SS. Rural-urban temporal trends for sudden cardiac death in the United States, 1999-2019. *JACC Clin Electrophysiol*. 2022;8:382–384. doi: 10.1016/j.jacep.2021.12.006
31. Anderson ML, Cox M, Al-Khatib SM, Nichol G, Thomas KL, Chan PS, Saha-Chaudhuri P, Fosbol EL, Eigel B, Clendenen B, et al. Rates of cardiopulmonary resuscitation training in the United States. *JAMA Intern Med*. 2014;174:194–201. doi: 10.1001/jamainternmed.2013.11320

32. Blewer A, Ibrahim S, Leary M, Dutwin D, McNally B, Anderson M, Morrison L, Aufderheide T, Day M, Idris A, et al. Cardiopulmonary resuscitation training disparities in the United States. *J Am Heart Assoc*. 2017;6:e006124. doi: 10.1161/JAHA.117.006124
33. Bakke HK, Steinvik T, Angell J, Wisborg T. A nationwide survey of first aid training and encounters in Norway. *BMC Emerg Med*. 2017;17:6. doi: 10.1186/s12873-017-0116-7
34. Bray JE, Smith K, Case R, Cartledge S, Straney L, Finn J. Public cardiopulmonary resuscitation training rates and awareness of hands-only cardiopulmonary resuscitation: a cross-sectional survey of Victorians. *Emerg Med Australas*. 2017;29:158–164. doi: 10.1111/1742-6723.12720
35. Brooks B, Chan S, Lander P, Adamson R, Hodgetts GA, Deakin CD. Public knowledge and confidence in the use of public access defibrillation. *Heart*. 2015;101:967–971. doi: 10.1136/heartjnl-2015-307624
36. Lee MJ, Hwang SO, Cha KC, Cho GC, Yang HJ, Rho TH. Influence of nationwide policy on citizens' awareness and willingness to perform bystander cardiopulmonary resuscitation. *Resuscitation*. 2013;84:889–894. doi: 10.1016/j.resuscitation.2013.01.009
37. Cartledge S, Saxton D, Finn J, Bray JE. Australia's awareness of cardiac arrest and rates of CPR training: results from the Heart Foundation's HeartWatch survey. *BMJ Open*. 2020;10:e033722. doi: 10.1136/bmjopen-2019-033722
38. Gonzalez M, Leary M, Blewer AL, Cinousis M, Sheak K, Ward M, Merchant RM, Becker LB, Abella BS. Public knowledge of automatic external defibrillators in a large U.S. urban community. *Resuscitation*. 2015;92:101–106. doi: 10.1016/j.resuscitation.2015.04.022
39. Duber HC, McNellan CR, Wollum A, Phillips B, Allen K, Brown JC, Bryant M, Guptam RB, Li Y, Majumdar P, et al. Public knowledge of cardiovascular disease and response to acute cardiac events in three cities in China and India. *Heart*. 2018;104:67–72. doi: 10.1136/heartjnl-2017-311388
40. Krammel M, Schnaubelt S, Weidenauer D, Winnisch M, Steininger M, Eichelter J, Hamp T, van Tulder R, Sulzgruber P. Gender and age-specific aspects of awareness and knowledge in basic life support. *PLoS One*. 2018;13:e0198918. doi: 10.1371/journal.pone.0198918
41. Ong ME, Shin SD, De Souza NN, Tanaka H, Nishiuchi T, Song KJ, Ko PC, Leong BS, Khunkhlai N, Naroo GY, et al; PAROS Clinical Research Network. Outcomes for out-of-hospital cardiac arrests across 7 countries in Asia: the Pan Asian Resuscitation Outcomes Study (PAROS). *Resuscitation*. 2015;96:100–108. doi: 10.1016/j.resuscitation.2015.07.026
42. Okubo M, Matsuyama T, Gibo K, Komukai S, Izawa J, Kiyohara K, Nishiyama C, Kiguchi T, Callaway CW, Iwami T, et al. Sex differences in receiving layperson cardiopulmonary resuscitation in pediatric out-of-hospital cardiac arrest: a nationwide cohort study in Japan. *J Am Heart Assoc*. 2019;8:e010324. doi: 10.1161/JAHA.118.010324
43. Sasson C, Magid DJ, Chan P, Root ED, McNally BF, Kellermann AL, Haukoos JS; CARES Surveillance Group. Association of neighborhood characteristics with bystander-initiated CPR. *N Engl J Med*. 2012;367:1607–1615. doi: 10.1056/NEJMoa1110700
44. Moon S, Bobrow BJ, Vadeboncoeur TF, Kortuem W, Kisakye M, Sasson C, Stolz U, Spaite DW. Disparities in bystander CPR provision and survival from out-of-hospital cardiac arrest according to neighborhood ethnicity. *Am J Emerg Med*. 2014;32:1041–1045. doi: 10.1016/j.ajem.2014.06.019
45. Garcia RA, Spertus JA, Girotra S, Nallamothu BK, Kennedy KF, McNally BF, Breathett K, Del Rios M, Sasson C, Chan PS. Racial and ethnic differences in bystander CPR for witnessed cardiac arrest. *N Engl J Med*. 2022;387:1569–1578. doi: 10.1056/NEJMoa2200798
46. Shekhar A, Narula J. Globally, GDP per capita correlates strongly with rates of bystander CPR. *Ann Glob Health*. 2022;88:36. doi: 10.5334/aogh.3624
47. Albaeni A, Beydoun MA, Beydoun HA, Akinyele B, RaghavaKurup L, Chandra-Strobos N, Eid SM. Regional variation in outcomes of hospitalized patients having out-of-hospital cardiac arrest. *Am J Cardiol*. 2017;120:421–427. doi: 10.1016/j.amjcard.2017.04.045
48. Andrew E, Nehme Z, Wolfe R, Bernard S, Smith K. Long-term survival following out-of-hospital cardiac arrest. *Heart*. 2017;103:1104–1110. doi: 10.1136/heartjnl-2016-310485
49. Pape M, Rajan S, Hansen SM, Mortensen RN, Ridersholm S, Folke F, Karlsson L, Lippert F, Kober L, Gislason G, et al. Survival after out-of-hospital cardiac arrest in nursing homes: a nationwide study. *Resuscitation*. 2018;125:90–98. doi: 10.1016/j.resuscitation.2018.02.004
50. Branch KRH, Strote J, Gunn M, Maynard C, Kudenchuk PJ, Brusen R, Petek BJ, Sayre MR, Edwards R, Carlbom D, et al. Early head-to-pelvis computed tomography in out-of-hospital circulatory arrest without obvious etiology. *Acad Emerg Med*. 2021;28:394–403. doi: 10.1111/acem.14228
51. Amacher SA, Bohren C, Blatter R, Becker C, Beck K, Mueller J, Loretz N, Gross S, Tisljar K, Sutter R, et al. Long-term survival after out-of-hospital cardiac arrest: a systematic review and meta-analysis. *JAMA Cardiol*. 2022;7:633–643. doi: 10.1001/jamacardio.2022.0795
52. Elfwén L, Lagedal R, Rubertsson S, James S, Oldgren J, Olsson J, Hollenberg J, Jensen U, Ringh M, Svensson L, et al. Post-resuscitation myocardial dysfunction in out-of-hospital cardiac arrest patients randomized to immediate coronary angiography versus standard of care. *IJC Heart and Vasculature*. 2020;27:100483. doi: 10.1016/j.ijcha.2020.100483
53. Song H, Kim HJ, Park KN, Kim SH, Kim WY, Lee BK, Cho IS, Lee JH, Youn CS; Korean Hypothermia Network Investigators. Which out-of-hospital cardiac arrest patients without ST-segment elevation benefit from early coronary angiography? Results from the Korean Hypothermia Network prospective registry. *J Clin Med*. 2021;10:439. doi: 10.3390/jcm10030439
54. Desch S, Freund A, Akin I, Behnes M, Preusch MR, Zelniker TA, Skurk C, Landmesser U, Graf T, Eitel I, et al; TOMAHAWK Investigators. Angiography after out-of-hospital cardiac arrest without ST-segment elevation. *N Engl J Med*. 2021;385:2544–2553. doi: 10.1056/NEJMoa2101909
55. Herzog N, Laager R, Thommen E, Widmer M, Vincent AM, Keller A, Becker C, Beck K, Perrig S, Bernasconi L, et al. Association of taurine with in-hospital mortality in patients after out-of-hospital cardiac arrest: results from the prospective, observational communicate study. *J Clin Med*. 2020;9:1405. doi: 10.3390/jcm9051405
56. Rafecas A, Bañeras J, Sans-Roselló J, Ortiz-Pérez JT, Rueda-Sobella F, Santamarina E, Milà L, Sionis A, Gaig C, García-García C, et al. Change in neuron specific enolase levels in out-of-hospital cardiopulmonary arrest survivors as a simple and useful tool to predict neurological prognosis. *Rev Esp Cardiol (Engl Ed)*. 2020;73:232–240. doi: 10.1016/j.rec.2019.01.007
57. Ryoo SM, Kim YJ, Sohn CH, Ahn S, Seo DW, Kim WY. Prognostic abilities of serial neuron-specific enolase and lactate and their combination in cardiac arrest survivors during targeted temperature management. *J Clin Med*. 2020;9:159. doi: 10.3390/jcm9010159
58. Lascarrou JB, Miailhe AF, le Gouge A, Cariou A, Dequin PF, Reignier J, Coupez E, Quenot JP, Legriel S, Pichon N, et al. NSE as a predictor of death or poor neurological outcome after non-shockable cardiac arrest due to any cause: ancillary study of HYPERION trial data. *Resuscitation*. 2021;158:193–200. doi: 10.1016/j.resuscitation.2020.11.035
59. Panchal AR, Bartos JA, Cabanas JG, Donnino MW, Drennan IR, Hirsch KG, Kudenchuk PJ, Kurz MC, Lavonas EJ, Morley PT, et al; on behalf of the Advanced Life Support Writing Group. Part 3: adult basic and advanced life support: 2020 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2020;142(suppl 2):S366–S468. doi: 10.1161/CIR.0000000000000916
60. Dankiewicz J, Cronberg T, Lilja G, Jakobsen JC, Levin H, Ullén S, Rylander C, Wise MP, Oddo M, Cariou A, et al; TTM2 Trial Investigators. Hypothermia versus normothermia after out-of-hospital cardiac arrest. *N Engl J Med*. 2021;384:2283–2294. doi: 10.1056/NEJMoa2100591
61. Osman M, Munir MB, Regner S, Osman K, Benjamin MM, Kheiri B, Agrawal P, McCarthy P, Balla S, Bianco CM. Induced hypothermia in patients with cardiac arrest and a non-shockable rhythm: meta-analysis and trial sequential analysis. *Neurocrit Care*. 2021;34:279–286. doi: 10.1007/s12028-020-01034-x
62. Sandroni C, Natalini D, Nolan JP. Temperature control after cardiac arrest. *Crit Care*. 2022;26:361. doi: 10.1186/s13054-022-04238-z
63. Meyer MAS, Wiberg S, Grand J, Meyer ASP, Obling LER, Frydland M, Thomsen JH, Josiassen J, Møller JE, Kjaergaard J, et al. Treatment effects of interleukin-6 receptor antibodies for modulating the systemic inflammatory response after out-of-hospital cardiac arrest (the IMICA trial): a double-blinded, placebo-controlled, single-center, randomized, clinical trial. *Circulation*. 2021;143:1841–1851. doi: 10.1161/CIRCULATIONAHA.120.053318
64. Kjaergaard J, Møller JE, Schmidt H, Grand J, Mølstrøm S, Borregaard B, Venø S, Sarkisian L, Mamaev D, Jensen LO, et al. Blood-pressure targets in comatose survivors of cardiac arrest. *N Engl J Med*. 2022;387:1456–1466. doi: 10.1056/NEJMoa2208687
65. Schmidt H, Kjaergaard J, Hassager C, Molstrom S, Grand J, Borregaard B, Roelsgaard Obling LE, Veno S, Sarkisian L, Mamaev D, et al. Oxygen targets in comatose survivors of cardiac arrest. *N Engl J Med*. 2022;387:1467–1476. doi: 10.1056/NEJMoa2208686
66. Belohlavek J, Smalcova J, Rob D, Franek O, Smid O, Pokorna M, Horak J, Mrazek V, Kovarnik T, Zemanek D, et al. Effect of intra-arrest transport, extracorporeal cardiopulmonary resuscitation, and immediate invasive assessment and treatment on functional neurologic outcome in refractory out-of-hospital cardiac arrest: a randomized clinical trial. *JAMA*. 2022;327:737–747. doi: 10.1001/jama.2022.1025
67. Silverstein FS, Slomine BS, Christensen J, Holubkov R, Page K, Dean JM, Moler FW; Therapeutic Hypothermia to Improve Survival After Cardiac Arrest Trial Group. Functional outcome trajectories after out-of-hospital

pediatric cardiac arrest. *Crit Care Med*. 2016;44:e1165–e1174. doi: 10.1097/CCM.0000000000002003
68. Tong JT, Eyngorn I, Mlynash M, Albers GW, Hirsch KG. Functional neurologic outcomes change over the first 6 months after cardiac arrest. *Crit Care Med*. 2016;44:e1202–e1207. doi: 10.1097/CCM.0000000000001963
69. Lilja G, Nielsen N, Bro-Jeppesen J, Dunford H, Friberg H, Hofgren C, Horn J, Insorsi A, Kjaergaard J, Nilsson F, et al. Return to work and participation in society after out-of-hospital cardiac arrest. *Circ Cardiovasc Qual Outcomes*. 2018;11:e003566. doi: 10.1161/CIRCOUTCOMES.117.003566
70. Descatha A, Dumas F, Bougouin W, Cariou A, Geri G. Work factors associated with return to work in out-of-hospital cardiac arrest survivors. *Resuscitation*. 2018;128:170–174. doi: 10.1016/j.resuscitation.2018.05.021
71. Tiainen M, Vaahersalo J, Skrifvars MB, Hastbacka J, Gronlund J, Pettila V. Surviving out-of-hospital cardiac arrest: the neurological and functional outcome and health-related quality of life one year later. *Resuscitation*. 2018;129:19–23. doi: 10.1016/j.resuscitation.2018.05.011
72. van Wijnen HG, Rasquin SM, van Heugten CM, Verbunt JA, Moulaert VR. The impact of cardiac arrest on the long-term wellbeing and caregiver burden of family caregivers: a prospective cohort study. *Clin Rehabil*. 2017;31:1267–1275. doi: 10.1177/0269215516686155
73. Yaow CYL, Teoh SE, Lim WS, Wang RSQ, Han MX, Pek PP, Tan BY, Ong MEH, Ng QX, Ho AFW. Prevalence of anxiety, depression, and post-traumatic stress disorder after cardiac arrest: a systematic review and meta-analysis. *Resuscitation*. 2022;170:82–91. doi: 10.1016/j.resuscitation.2021.11.023
74. Hsu Chen C, Chang CY, Yang MC, Wu JH, Liao CH, Su CP, Chen YC, Ho SY, Huang CC, Lee TH, et al. The impact of emergency interventions and patient characteristics on the risk of heart failure in patients with nontraumatic OHCA. *Emerg Med Int*. 2019;2019:6218389. doi: 10.1155/2019/6218389
75. Nishiyama C, Brown SP, May S, Iwami T, Koster RW, Beesems SG, Kuisma M, Salo A, Jacobs I, Finn J, et al. Apples to apples or apples to oranges? International variation in reporting of process and outcome of care for out-of-hospital cardiac arrest. *Resuscitation*. 2014;85:1599–1609. doi: 10.1016/j.resuscitation.2014.06.031
76. Grasner JT, Lefering R, Koster RW, Masterson S, Bottiger BW, Herlitz J, Wnent J, Tjelmeland IB, Ortiz FR, Maurer H, et al; EuReCa ONE Collaborators. EuReCa ONE-27 Nations, ONE Europe, ONE Registry: a prospective one month analysis of out-of-hospital cardiac arrest outcomes in 27 countries in Europe. *Resuscitation*. 2016;105:188–195. doi: 10.1016/j.resuscitation.2016.06.004
77. Gowens P, Smith K, Clegg G, Williams B, Nehme Z. Global variation in the incidence and outcome of emergency medical services witnessed out-of-hospital cardiac arrest: a systematic review and meta-analysis. *Resuscitation*. 2022;175:120–132. doi: 10.1016/j.resuscitation.2022.03.026
78. Holmberg MJ, Ross CE, Fitzmaurice GM, Chan PS, Duval-Arnould J, Grossestreuer AV, Yankama T, Donnino MW, Andersen LW; American Heart Association's Get With The Guidelines–Resuscitation Investigators. Annual incidence of adult and pediatric in-hospital cardiac arrest in the United States. *Circ Cardiovasc Qual Outcomes*. 2019;12:e005580.
79. Andersen LW, Holmberg MJ, Berg KM, Donnino MW, Granfeldt A. In-hospital cardiac arrest: a review. *JAMA*. 2019;321:1200–1210. doi: 10.1001/jama.2019.1696
80. Australia and New Zealand Cardiac Arrest Outcome and Determinants of ECMO Investigators. The epidemiology of in-hospital cardiac arrests in Australia: a prospective multicentre observational study. *Crit Care Resusc*. 2019;21:180–187.
81. Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project (HCUP). Accessed April 1, 2023. http://hcupnet.ahrq.gov/
82. Hessulf F, Karlsson T, Lundgren P, Aune S, Stromsoe A, Sodersved Kallestedt ML, Djarv T, Herlitz J, Engdahl J. Factors of importance to 30-day survival after in-hospital cardiac arrest in Sweden: a population-based register study of more than 18000 cases. *Int J Cardiol*. 2018;255:237–242. doi: 10.1016/j.ijcard.2017.12.068
83. Rasmussen TP, Riley DJ, Sarazin MV, Chan PS, Girotra S. Variation across hospitals in in-hospital cardiac arrest incidence among Medicare beneficiaries. *JAMA Netw Open*. 2022;5:e2148485. doi: 10.1001/jamanetworkopen.2021.48485
84. Costa YC, Rafaelli A, Mauro V, Charask A, Tajer C, Gagliardi J; Investigators of the ARGEN–IAM-ST Registry. Cardiac arrest within the first 24 hours after hospital admission in ST-segment elevation acute coronary syndromes:. the ARGEN-IAM-ST registry. *Rev Argent Cardiol*. 2019;87:227–229.
85. Abe T, Olanipekun T, Igwe J, Ndausung U, Amah C, Chang A, Effoe V, Egbuche O, Ogunbayo G, Onwuanyi A. Incidence and predictors of sudden cardiac arrest in the immediate post-percutaneous coronary intervention period for ST-elevation myocardial infarction: a single-center study. *Coron Artery Dis*. 2022;33:261–268. doi: 10.1097/MCA.0000000000001119
86. Li H, Wu TT, Liu PC, Liu XS, Mu Y, Guo YS, Chen Y, Xiao LP, Huang JF. Characteristics and outcomes of in-hospital cardiac arrest in adults hospitalized with acute coronary syndrome in China. *Am J Emerg Med*. 2019;37:1301–1306. doi: 10.1016/j.ajem.2018.10.003
87. Fielding-Singh V, Willingham MD, Fischer MA, Grogan T, Benharash P, Neelankavil JP. A population-based analysis of intraoperative cardiac arrest in the United States. *Anesth Analg*. 2020;130:627–634. doi: 10.1213/ANE.0000000000004477
88. Heller AR, Mees ST, Lauterwald B, Reeps C, Koch T, Weitz J. Detection of deteriorating patients on surgical wards outside the ICU by an automated MEWS-based early warning system with paging functionality. *Ann Surg*. 2020;271:100–105. doi: 10.1097/SLA.0000000000002830
89. Hogan H, Hutchings A, Wulff J, Carver C, Holdsworth E, Nolan J, Welch J, Harrison D, Black N. Type of Track and Trigger system and incidence of in-hospital cardiac arrest: an observational registry-based study. *BMC Health Serv Res*. 2020;20:885. doi: 10.1186/s12913-020-05721-5
90. Ko BS, Lim TH, Oh J, Lee Y, Yun I, Yang MS, Ahn C, Kang H. The effectiveness of a focused rapid response team on reducing the incidence of cardiac arrest in the general ward. *Medicine (Baltimore)*. 2020;99:e19032. doi: 10.1097/MD.0000000000019032
91. Mankidy B, Howard C, Morgan CK, Valluri KA, Giacomino B, Marfil E, Voore P, Ababio Y, Razjouyan J, Naik AD, et al. Reduction of in-hospital cardiac arrest with sequential deployment of rapid response team and medical emergency team to the emergency department and acute care wards. *PLoS One*. 2020;15:e0241816. doi: 10.1371/journal.pone.0241816
92. Parikh PB, Malhotra A, Qadeer A, Patel JK. Impact of sex on survival and neurologic outcomes in adults with in-hospital cardiac arrest. *Am J Cardiol*. 2020;125:309–312. doi: 10.1016/j.amjcard.2019.10.039
93. Hayek SS, Brenner SK, Azam TU, Shadid HR, Anderson E, Berlin H, Pan M, Meloche C, Feroz R, O'Hayer P, et al; STOP-COVID Investigators. In-hospital cardiac arrest in critically ill patients with covid-19: multicenter cohort study. *BMJ*. 2020;371:m3513. doi: 10.1136/bmj.m3513
94. Edwards JM, Nolan JP, Soar J, Smith GB, Reynolds E, Carnall J, Rowan KM, Harrison DA, Doidge JC. Impact of the COVID-19 pandemic on in-hospital cardiac arrests in the UK. *Resuscitation*. 2022;173:4–11. doi: 10.1016/j.resuscitation.2022.02.007
95. Andersen LW, Kim WY, Chase M, Berg KM, Mortensen SJ, Moskowitz A, Novack V, Cocchi MN, Donnino MW; American Heart Association's Get With the Guidelines–Resuscitation Investigators. The prevalence and significance of abnormal vital signs prior to in-hospital cardiac arrest. *Resuscitation*. 2016;98:112–117. doi: 10.1016/j.resuscitation.2015.08.016
96. Smith GB, Prytherch DR, Jarvis S, Kovacs C, Meredith P, Schmidt PE, Briggs J. A comparison of the ability of the physiologic components of medical emergency team criteria and the U.K. national early warning score to discriminate patients at risk of a range of adverse clinical outcomes. *Crit Care Med*. 2016;44:2171–2181. doi: 10.1097/CCM.0000000000002000
97. Green M, Lander H, Snyder A, Hudson P, Churpek M, Edelson D. Comparison of the between the flags calling criteria to the MEWS, NEWS and the electronic Cardiac Arrest Risk Triage (eCART) score for the identification of deteriorating ward patients. *Resuscitation*. 2018;123:86–91. doi: 10.1016/j.resuscitation.2017.10.028
98. Kim M, Li G. Postoperative complications affecting survival after cardiac arrest in general surgery patients. *Anesth Analg*. 2018;126:858–864. doi: 10.1213/ANE.0000000000002460
99. Nolan JP, Soar J, Smith GB, Gwinnutt C, Parrott F, Power S, Harrison DA, Nixon E, Rowan K; National Cardiac Arrest Audit. Incidence and outcome of in-hospital cardiac arrest in the United Kingdom National Cardiac Arrest Audit. *Resuscitation*. 2014;85:987–992. doi: 10.1016/j.resuscitation.2014.04.002
100. Al-Dury N, Rawshani A, Israelsson J, Stromsoe A, Aune S, Agerstrom J, Karlsson T, Ravn-Fischer A, Herlitz J. Characteristics and outcome among 14,933 adult cases of in-hospital cardiac arrest: a nationwide study with the emphasis on gender and age. *Am J Emerg Med*. 2017;35:1839–1844. doi: 10.1016/j.ajem.2017.06.012
101. Dolmatova EV, Moazzami K, Klapholz M, Kothari N, Feurdean M, Waller AH. Impact of hospital teaching status on mortality, length of stay and cost among patients with cardiac arrest in the United States. *Am J Cardiol*. 2016;118:668–672. doi: 10.1016/j.amjcard.2016.05.062
102. Evans E, Swanson MB, Mohr N, Boulos N, Vaughan-Sarrazin M, Chan PS, Girotra S; American Heart Association's Get With The Guidelines-Resuscitation Investigators. Epinephrine before defibrillation in patients

with shockable in-hospital cardiac arrest: propensity matched analysis. *BMJ*. 2021;375:e066534. doi: 10.1136/bmj-2021-066534
103. Andersen LW, Isbye D, Kjærgaard J, Kristensen CM, Darling S, Zwisler ST, Fisker S, Schmidt JC, Kirkegaard H, Grejs AM, et al. Effect of vasopressin and methylprednisolone vs placebo on return of spontaneous circulation in patients with in-hospital cardiac arrest: a randomized clinical trial. *JAMA*. 2021;326:1586–1594.
104. Bucy RA, Hanisko KA, Kamphuis LA, Nallamothu BK, Iwashyna TJ, Pfeiffer PN. Suicide risk management protocol in post-cardiac arrest survivors: development, feasibility, and outcomes. *Ann Am Thorac Soc*. 2017;14:363–367. doi: 10.1513/AnnalsATS.201609-694BC
105. Doherty ZB, Fletcher JA, Fuzzard KL, Leach MJ, O'Sullivan BG, Panozzo LE, Pound GM, Saka E, Kippen RJ. Functional outcomes following an in-hospital cardiac arrest: a retrospective cohort study. *Aust Crit Care*. 2022;35:424–429. doi: 10.1016/j.aucc.2021.07.002
106. Shao F, Li CS, Liang LR, Qin J, Ding N, Fu Y, Yang K, Zhang GQ, Zhao L, Zhao B, et al. Incidence and outcome of adult in-hospital cardiac arrest in Beijing, China. *Resuscitation*. 2016;102:51–56. doi: 10.1016/j.resuscitation.2016.02.002
107. Ngunga LM, Yonga G, Wachira B, Ezekowitz JA. Initial rhythm and resuscitation outcomes for patients developing cardiac arrest in hospital: data from low-middle income country. *Glob Heart*. 2018;13:255–260. doi: 10.1016/j.gheart.2018.07.001
108. Inoue M, Tohira H, Williams T, Bailey P, Borland M, McKenzie N, Brink D, Finn J. Incidence, characteristics and survival outcomes of out-of-hospital cardiac arrest in children and adolescents between 1997 and 2014 in Perth, Western Australia. *Emerg Med Australas*. 2017;29:69–76. doi: 10.1111/1742-6723.12657
109. Nehme Z, Namachivayam S, Forrest A, Butt W, Bernard S, Smith K. Trends in the incidence and outcome of paediatric out-of-hospital cardiac arrest: a 17-year observational study. *Resuscitation*. 2018;128:43–50. doi: 10.1016/j.resuscitation.2018.04.030
110. Albargi H, Mallett S, Berhane S, Booth S, Hawkes C, Perkins GD, Norton M, Foster T, Scholefield B. Bystander cardiopulmonary resuscitation for paediatric out-of-hospital cardiac arrest in England: an observational registry cohort study. *Resuscitation*. 2022;170:17–25. doi: 10.1016/j.resuscitation.2021.10.042
111. Tham LP, Wah W, Phillips R, Shahidah N, Ng YY, Shin SD, Nishiuchi T, Wong KD, Ko PC, Khunklai N, et al. Epidemiology and outcome of paediatric out-of-hospital cardiac arrests: a paediatric sub-study of the Pan-Asian Resuscitation Outcomes Study (PAROS). *Resuscitation*. 2018;125:111–117. doi: 10.1016/j.resuscitation.2018.01.040
112. Albrecht M, de Jonge RCJ, Nadkarni VM, de Hoog M, Hunfeld M, Kammeraad JAE, Moors XRJ, van Zellem L, Buysse CMP. Association between shockable rhythms and long-term outcome after pediatric out-of-hospital cardiac arrest in Rotterdam, the Netherlands: an 18-year observational study. *Resuscitation*. 2021;166:110–120. doi: 10.1016/j.resuscitation.2021.05.015
113. Berg RA, Nadkarni VM, Clark AE, Moler F, Meert K, Harrison RE, Newth CJ, Sutton RM, Wessel DL, Berger JT, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network. Incidence and outcomes of cardiopulmonary resuscitation in PICUs. *Crit Care Med*. 2016;44:798–808. doi: 10.1097/CCM.0000000000001484
114. Alten JA, Klugman D, Raymond TT, Cooper DS, Donohue JE, Zhang W, Pasquali SK, Gaies MG. Epidemiology and outcomes of cardiac arrest in pediatric cardiac ICUs. *Pediatr Crit Care Med*. 2017;18:935–943. doi: 10.1097/PCC.0000000000001273
115. Esangbedo ID, Byrnes J, Brandewie K, Ebraheem M, Yu P, Zhang S, Raymond T. Risk factors for peri-intubation cardiac arrest in pediatric cardiac intensive care patients: a multicenter study. *Pediatr Crit Care Med*. 2020;21:e1126–e1133. doi: 10.1097/PCC.0000000000002472
116. Holmberg MJ, Wiberg S, Ross CE, Kleinman M, Hoeyer-Nielsen AK, Donnino M, Andersen LW; American Heart Association's Get With The Guidelines–Resuscitation Investigators. Trends in survival after pediatric in-hospital cardiac arrest in the United States. *Circulation*. 2019;140:1398–1408.
117. Morgan RW, Wolfe HA, Reeder RW, Alvey JS, Frazier AH, Friess SH, Maa T, McQuillen PS, Meert KL, Nadkarni VM, et al. The temporal association of the COVID-19 pandemic and pediatric cardiopulmonary resuscitation quality and outcomes. *Pediatr Crit Care Med*. 2022;23:908–918. doi: 10.1097/PCC.0000000000003073
118. Abate SM, Nega S, Basu B, Tamrat K. Global mortality of children after perioperative cardiac arrest: a systematic review, meta-analysis, and meta-regression. *Ann Med Surg (Lond)*. 2022;74:103285. doi: 10.1016/j.amsu.2022.103285
119. Fernandez-Vazquez D, Ferrero-Gregori A, Alvarez-Garcia J, Gomez-Otero I, Vazquez R, Delgado Jimenez J, Worner Diz F, Bardaji A, Garcia-Pavia P, Bayes-Genis A, et al. Changes in causes of death and influence of therapeutic improvement over time in patients with heart failure and reduced ejection fraction. *Rev Esp Cardiol (Engl Ed)*. 2020;73:561–568. doi: 10.1016/j.rec.2019.09.030
120. Pouleur AC, Barkoudah E, Uno H, Skali H, Finn PV, Zelenkofske SL, Belenkov YN, Mareev V, Velazquez EJ, Rouleau JL, et al; VALIANT Investigators. Pathogenesis of sudden unexpected death in a clinical trial of patients with myocardial infarction and left ventricular dysfunction, heart failure, or both. *Circulation*. 2010;122:597–602. doi: 10.1161/CIRCULATIONAHA.110.940619
121. Tseng ZH, Olgin JE, Vittinghoff E, Ursell PC, Kim AS, Sporer K, Yeh C, Colburn B, Clark NM, Khan R, et al. Prospective countywide surveillance and autopsy characterization of sudden cardiac death: POST SCD study. *Circulation*. 2018;137:2689–2700. doi: 10.1161/CIRCULATIONAHA.117.033427
122. Chen N, Callaway CW, Guyette FX, Rittenberger JC, Doshi AA, Dezfulian C, Elmer J; Pittsburgh Post-Cardiac Arrest Service. Arrest etiology among patients resuscitated from cardiac arrest. *Resuscitation*. 2018;130:33–40. doi: 10.1016/j.resuscitation.2018.06.024
123. Merlo M, Gentile P, Artico J, Cannata A, Paldino A, De Angelis G, Barbati G, Alonge M, Gigli M, Pinamonti B, et al. Arrhythmic risk stratification in patients with dilated cardiomyopathy and intermediate left ventricular dysfunction. *J Cardiovasc Med (Hagerstown)*. 2019;20:343–350. doi: 10.2459/JCM.0000000000000792
124. Boas R, Thune JJ, Pehrson S, Kober L, Nielsen JC, Videbaek L, Haarbo J, Korup E, Bruun NE, Brandes A, et al. Prevalence and prognostic association of ventricular arrhythmia in non-ischaemic heart failure patients: results from the DANISH trial. *Europace*. 2021;23:587–595. doi: 10.1093/europace/euaa341
125. Haukilahti MAE, Holmstrom L, Vahatalo J, Kentta T, Tikkanen J, Pakanen L, Kortelainen ML, Perkiomaki J, Huikuri H, Myerburg RJ, et al. Sudden cardiac death in women. *Circulation*. 2019;139:1012–1021. doi: 10.1161/CIRCULATIONAHA.118.037702
126. Cunningham JW, Vaduganathan M, Claggett BL, John JE, Desai AS, Lewis EF, Zile MR, Carson P, Jhund PS, Kober L, et al. Myocardial infarction in heart failure with preserved ejection fraction: pooled analysis of 3 clinical trials. *JACC Heart Fail*. 2020;8:618–626. doi: 10.1016/j.jchf.2020.02.007
127. Tu SJ, Gallagher C, Elliott AD, Linz D, Pitman BM, Hendriks JML, Lau DH, Sanders P, Wong CX. Alcohol consumption and risk of ventricular arrhythmias and sudden cardiac death: an observational study of 408,712 individuals. *Heart Rhythm*. 2022;19:177–184. doi: 10.1016/j.hrthm.2021.09.040
128. Tseng ZH, Ramakrishna S, Salazar JW, Vittinghoff E, Olgin JE, Moffatt E. Sex and racial differences in autopsy-defined causes of presumed sudden cardiac death. *Circ Arrhythm Electrophysiol*. 2021;14:e009393. doi: 10.1161/CIRCEP.120.009393
129. Zhao D, Post WS, Blasco-Colmenares E, Cheng A, Zhang Y, Deo R, Pastor-Barriuso R, Michos ED, Sotoodehnia N, Guallar E. Racial differences in sudden cardiac death. *Circulation*. 2019;139:1688–1697. doi: 10.1161/CIRCULATIONAHA.118.036553
130. Verdecchia P, Angeli F, Cavallini C, Aita A, Turturiello D, De Fano M, Reboldi G. Sudden cardiac death in hypertensive patients. *Hypertension*. 2019;73:1071–1078. doi: 10.1161/HYPERTENSIONAHA.119.12684
131. Archangelidi O, Pujades-Rodriguez M, Timmis A, Jouven X, Denaxas S, Hemingway H. Clinically recorded heart rate and incidence of 12 coronary, cardiac, cerebrovascular and peripheral arterial diseases in 233,970 men and women: a linked electronic health record study. *Eur J Prev Cardiol*. 2018;25:1485–1495. doi: 10.1177/2047487318785228
132. Pokorney SD, Al-Khatib SM, Sun JL, Schulte P, O'Connor CM, Teerlink JR, Armstrong PW, Ezekowitz JA, Starling RC, Voors AA, et al. Sudden cardiac death after acute heart failure hospital admission: insights from ASCEND-HF. *Eur J Heart Fail*. 2018;20:525–532. doi: 10.1002/ejhf.1078
133. Rattanawong P, Upala S, Riangwiwat T, Jaruvongvanich V, Sanguankeo A, Vutthikraivit W, Chung EH. Atrial fibrillation is associated with sudden cardiac death: a systematic review and meta-analysis. *J Interv Card Electrophysiol*. 2018;51:91–104. doi: 10.1007/s10840-017-0308-9
134. Eisen A, Ruff CT, Braunwald E, Nordio F, Corbalan R, Dalby A, Dorobantu M, Mercuri M, Lanz H, Rutman H, et al. sudden cardiac death in patients with atrial fibrillation: insights from the ENGAGE AF-TIMI 48 Trial. *J Am Heart Assoc*. 2016;5:e003735. doi: 10.1161/JAHA.116.003735
135. Deo R, Norby FL, Katz R, Sotoodehnia N, Adabag S, DeFilippi CR, Kestenbaum B, Chen LY, Heckbert SR, Folsom AR, et al.

Development and validation of a sudden cardiac death prediction model for the general population. *Circulation*. 2016;134:806–816. doi: 10.1161/CIRCULATIONAHA.116.023042
136. Aro AL, Rusinaru C, Uy-Evanado A, Reinier K, Phan D, Gunson K, Jui J, Chugh SS. Syncope and risk of sudden cardiac arrest in coronary artery disease. *Int J Cardiol*. 2017;231:26–30. doi: 10.1016/j.ijcard.2016.12.021
137. Langen VL, Niiranen TJ, Puukka P, Lehtonen AO, Hernesniemi JA, Sundvall J, Salomaa V, Jula AM. Thyroid-stimulating hormone and risk of sudden cardiac death, total mortality and cardiovascular morbidity. *Clin Endocrinol (Oxf)*. 2018;88:105–113. doi: 10.1111/cen.13472
138. Shi S, Liu T, Liang J, Hu D, Yang B. Depression and risk of sudden cardiac death and arrhythmias: a meta-analysis. *Psychosom Med*. 2017;79:153–161. doi: 10.1097/PSY.0000000000000382
139. Tulppo MP, Kiviniemi AM, Lahtinen M, Ukkola O, Toukola T, Perkiömäki J, Junttila MJ, Huikuri HV. Physical activity and the risk for sudden cardiac death in patients with coronary artery disease. *Circ Arrhythm Electrophysiol*. 2020;13:e007908. doi: 10.1161/CIRCEP.119.007908
140. Awamleh Garcia P, Alonso Martin JJ, Graupner Abad C, Jimenez Hernandez RM, Curcio Ruigomez A, Talavera Calle P, Cristobal Varela C, Serrano Antolin J, Muniz J, Gomez Doblas JJ, et al; Investigators of the OFRECE study. Prevalence of electrocardiographic patterns associated with sudden cardiac death in the Spanish population aged 40 years or older: results of the OFRECE study. *Rev Esp Cardiol (Engl Ed)*. 2017;70:801–807. doi: 10.1016/j.rec.2016.11.039
141. O'Neal WT, Singleton MJ, Roberts JD, Tereshchenko LG, Sotoodehnia N, Chen LY, Marcus GM, Soliman EZ. Association between QT-interval components and sudden cardiac death: the ARIC study (Atherosclerosis Risk in Communities). *Circ Arrhythm Electrophysiol*. 2017;10:e005485. doi: 10.1161/CIRCEP.117.005485
142. Waks JW, Sitlani CM, Soliman EZ, Kabir M, Ghafoori E, Biggs ML, Henrikson CA, Sotoodehnia N, Biering-Sørensen T, Agarwal SK, et al. Global electric heterogeneity risk score for prediction of sudden cardiac death in the general population: the Atherosclerosis Risk in Communities (ARIC) and Cardiovascular Health (CHS) studies. *Circulation*. 2016;133:2222–2234. doi: 10.1161/CIRCULATIONAHA.116.021306
143. Lanza GA, Argiro A, Mollo R, De Vita A, Spera F, Golino M, Rota E, Filice M, Crea F. Six-year outcome of subjects without overt heart disease with an early repolarization/J wave electrocardiographic pattern. *Am J Cardiol*. 2017;120:2073–2077. doi: 10.1016/j.amjcard.2017.08.028
144. Jacobs CS, Beers L, Park S, Scirica B, Henderson GV, Hsu L, Bevers M, Dworetzky BA, Lee JW. Racial and ethnic disparities in postcardiac arrest targeted temperature management outcomes. *Crit Care Med*. 2020;48:56–63. doi: 10.1097/CCM.0000000000004001
145. Centers for Disease Control and Prevention and National Center for Health Statistics. Multiple cause of death, CDC WONDER online database. Accessed April 1, 2023. https://wonder.cdc.gov/mcd-icd10.html
146. El-Assaad I, Al-Kindi SG, Aziz PF. Trends of out-of-hospital sudden cardiac death among children and young adults. *Pediatrics*. 2017;140:e20171438. doi: 10.1542/peds.2017-1438
147. Geri G, Dumas F, Bonnetain F, Bougouin W, Champigneulle B, Arnaout M, Carli P, Marijon E, Varenne O, Mira JP, et al. Predictors of long-term functional outcome and health-related quality of life after out-of-hospital cardiac arrest. *Resuscitation*. 2017;113:77–82. doi: 10.1016/j.resuscitation.2017.01.028
148. Elmer J, Rittenberger JC, Coppler PJ, Guyette FX, Doshi AA, Callaway CW; Pittsburgh Post-Cardiac Arrest Service. Long-term survival benefit from treatment at a specialty center after cardiac arrest. *Resuscitation*. 2016;108:48–53. doi: 10.1016/j.resuscitation.2016.09.008
149. Moulaert VRM, van Heugten CM, Gorgels TPM, Wade DT, Verbunt JA. Long-term outcome after survival of a cardiac arrest: a prospective longitudinal cohort study. *Neurorehabil Neural Repair*. 2017;31:530–539. doi: 10.1177/1545968317697032
150. Steinbusch CVM, van Heugten CM, Rasquin SMC, Verbunt JA, Moulaert VRM. Cognitive impairments and subjective cognitive complaints after survival of cardiac arrest: a prospective longitudinal cohort study. *Resuscitation*. 2017;120:132–137. doi: 10.1016/j.resuscitation.2017.08.007
151. Lam TJR, Yang J, Poh JE, Ong MEH, Liu N, Yeo JW, Gräsner JT, Masuda Y, Ho AFW. Long term risk of recurrence among survivors of sudden cardiac arrest: a systematic review and meta-analysis. *Resuscitation*. 2022;176:30–41. doi: 10.1016/j.resuscitation.2022.04.027
152. Dezfulian C, Orkin AM, Maron BA, Elmer J, Girotra S, Gladwin MT, Merchant RM, Panchal AR, Perman SM, Starks MA, et al; on behalf of the American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular and Stroke Nursing; Council on Quality of Care and Outcomes Research; and Council on Clinical Cardiology. Opioid-associated out-of-hospital cardiac arrest: distinctive clinical features and implications for health care and public responses: a scientific statement from the American Heart Association. *Circulation*. 2021;143:e836–e870. doi: 10.1161/CIR.0000000000000958
153. Paredes VL, Rea TD, Eisenberg MS, Cobb LA, Copass MK, Cagle A, Martin TG. Out-of-hospital care of critical drug overdoses involving cardiac arrest. *Acad Emerg Med*. 2004;11:71–74. doi: 10.1197/j.aem.2003.08.014
154. Smith G, Beger S, Vadeboncoeur T, Chikani V, Walter F, Spaite DW, Bobrow B. Trends in overdose-related out-of-hospital cardiac arrest in Arizona. *Resuscitation*. 2019;134:122–126. doi: 10.1016/j.resuscitation.2018.10.019
155. Elmer J, Lynch MJ, Kristan J, Morgan P, Gerstel SJ, Callaway CW, Rittenberger JC; Pittsburgh Post-Cardiac Arrest Service. Recreational drug overdose-related cardiac arrests: break on through to the other side. *Resuscitation*. 2015;89:177–181. doi: 10.1016/j.resuscitation.2015.01.028
156. Jayaraman R, Reinier K, Nair S, Aro AL, Uy-Evanado A, Rusinaru C, Stecker EC, Gunson K, Jui J, Chugh SS. Risk factors of sudden cardiac death in the young: multiple-year community-wide assessment. *Circulation*. 2018;137:1561–1570. doi: 10.1161/CIRCULATIONAHA.117.031262
157. Harmon KG, Asif IM, Maleszewski JJ, Owens DS, Prutkin JM, Salerno JC, Zigman ML, Ellenbogen R, Rao AL, Ackerman MJ, et al. Incidence and etiology of sudden cardiac arrest and death in high school athletes in the United States. *Mayo Clin Proc*. 2016;91:1493–1502. doi: 10.1016/j.mayocp.2016.07.021
158. Landry CH, Allan KS, Connelly KA, Cunningham K, Morrison LJ, Dorian P; Rescu Investigators. Sudden cardiac arrest during participation in competitive sports. *N Engl J Med*. 2017;377:1943–1953. doi: 10.1056/NEJMoa1615710
159. Endres BD, Kerr ZY, Stearns RL, Adams WM, Hosokawa Y, Huggins RA, Kucera KL, Casa DJ. Epidemiology of sudden death in organized youth sports in the United States, 2007-2015. *J Athl Train*. 2019;54:349–355. doi: 10.4085/1062-6050-358-18
160. Waite O, Smith A, Madge L, Spring H, Noret N. Sudden cardiac death in marathons: a systematic review. *Phys Sportsmed*. 2016;44:79–84. doi: 10.1080/00913847.2016.1135036
161. Nilson F, Borjesson M. Mortality in long-distance running races in Sweden: 2007-2016. *PLoS One*. 2018;13:e0195626. doi: 10.1371/journal.pone.0195626
162. Peterson DF, Siebert DM, Kucera KL, Thomas LC, Maleszewski JJ, Lopez-Anderson M, Suchsland MZ, Harmon KG, Drezner JA. Etiology of sudden cardiac arrest and death in US competitive athletes: a 2-year prospective surveillance study. *Clin J Sport Med*. 2020;30:305–314. doi: 10.1097/JSM.0000000000000598
163. Vicent L, Ariza-Sole A, Gonzalez-Juanatey JR, Uribarri A, Ortiz J, Lopez de Sa E, Sans-Rosello J, Querol CT, Codina P, Sousa-Casasnovas I, et al; Cardiac Arrest and Myocardial Infarction Notified After Marathon or Similar Effort (CAMINAMOS) Registry. Exercise-related severe cardiac events. *Scand J Med Sci Sports*. 2018;28:1404–1411. doi: 10.1111/sms.13037
164. Angelini P, Cheong BY, Lenge De Rosen VV, Lopez A, Uribe C, Masso AH, Ali SW, Davis BR, Muthupillai R, Willerson JT. High-risk cardiovascular conditions in sports-related sudden death: prevalence in 5,169 schoolchildren screened via cardiac magnetic resonance. *Tex Heart Inst J*. 2018;45:205–213. doi: 10.14503/THIJ-18-6645
165. Goffman D, Ananth CV, Fleischer A, D'Alton M, Lavery JA, Smiley R, Zielinski K, Chazotte C; Safe Motherhood Initiative Obstetric Hemorrhage Work Group. The New York State Safe Motherhood Initiative: early impact of obstetric hemorrhage bundle implementation. *Am J Perinatol*. 2019;36:1344–1350. doi: 10.1055/s-0038-1676976
166. Bagnall RD, Weintraub RG, Ingles J, Duflou J, Yeates L, Lam L, Davis AM, Thompson T, Connell V, Wallace J, et al. A prospective study of sudden cardiac death among children and young adults. *N Engl J Med*. 2016;374:2441–2452. doi: 10.1056/NEJMoa1510687
167. Christiansen SL, Hertz CL, Ferrero-Miliani L, Dahl M, Weeke PE, LuCamp, Ottesen GL, Frank-Hansen R, Bundgaard H, Morling N. Genetic investigation of 100 heart genes in sudden unexplained death victims in a forensic setting. *Eur J Hum Genet*. 2016;24:1797–1802. doi: 10.1038/ejhg.2016.118
168. Nunn LM, Lopes LR, Syrris P, Murphy C, Plagnol V, Firman E, Dalageorgou C, Zorio E, Domingo D, Murday V, et al. Diagnostic yield of molecular autopsy in patients with sudden arrhythmic death syndrome using targeted exome sequencing. *Europace*. 2016;18:888–896. doi: 10.1093/europace/euv285
169. Asatryan B, Schaller A, Seiler J, Servatius H, Noti F, Baldinger SH, Tanner H, Roten L, Dillier R, Lam A, et al. Usefulness of genetic testing in sudden cardiac arrest survivors with or without previous

clinical evidence of heart disease. *Am J Cardiol*. 2019;123:2031–2038. doi: 10.1016/j.amjcard.2019.02.061
170. Steinberg C, Padfield GJ, Champagne J, Sanatani S, Angaran P, Andrade JG, Roberts JD, Healey JS, Chauhan VS, Birnie DH, et al. Cardiac abnormalities in first-degree relatives of unexplained cardiac arrest victims: a report from the Cardiac Arrest Survivors With Preserved Ejection Fraction Registry. *Circ Arrhythm Electrophysiol*. 2016;9:e004274. doi: 10.1161/CIRCEP.115.004274
171. Quenin P, Kyndt F, Mabo P, Mansourati J, Babuty D, Thollet A, Guyomarch B, Redon R, Barc J, Schott JJ, et al. Clinical yield of familial screening after sudden death in young subjects: the French experience. *Circ Arrhythm Electrophysiol*. 2017;10:e005236. doi: 10.1161/CIRCEP.117.005236
172. Mullertz KM, Christiansen MK, Broendberg AK, Pedersen LN, Jensen HK. Outcome of clinical management in relatives of sudden cardiac death victims. *Int J Cardiol*. 2018;262:45–50. doi: 10.1016/j.ijcard.2018.03.022
173. Giudicessi JR, Ackerman MJ. Role of genetic heart disease in sentinel sudden cardiac arrest survivors across the age spectrum. *Int J Cardiol*. 2018;270:214–220. doi: 10.1016/j.ijcard.2018.05.100
174. Ashar FN, Mitchell RN, Albert CM, Newton-Cheh C, Brody JA, Muller-Nurasyid M, Moes A, Meitinger T, Mak A, Huikuri H, et al. A comprehensive evaluation of the genetic architecture of sudden cardiac arrest. *Eur Heart J*. 2018;39:3961–3969. doi: 10.1093/eurheartj/ehy474
175. Norland K, Sveinbjornsson G, Thorolfsdottir RB, Davidsson OB, Tragante V, Rajamani S, Helgadottir A, Gretarsdottir S, van Setten J, Asselbergs FW, et al. Sequence variants with large effects on cardiac electrophysiology and disease. *Nat Commun*. 2019;10:4803. doi: 10.1038/s41467-019-12682-9
176. Ramirez J, van Duijvenboden S, Young WJ, Orini M, Lambiase PD, Munroe PB, Tinker A. Common genetic variants modulate the electrocardiographic Tpeak-to-Tend interval. *Am J Hum Genet*. 2020;106:764–778. doi: 10.1016/j.ajhg.2020.04.009
177. Bezzina CR, Lahrouchi N, Priori SG. Genetics of sudden cardiac death. *Circ Res*. 2015;116:1919–1936. doi: 10.1161/CIRCRESAHA.116.304030
178. Nakano Y, Shimizu W. Genetics of long-QT syndrome. *J Hum Genet*. 2016;61:51–55. doi: 10.1038/jhg.2015.74
179. Tester DJ, Wong LCH, Chanana P, Jaye A, Evans JM, FitzPatrick DR, Evans MJ, Fleming P, Jeffrey I, Cohen MC, et al. Cardiac genetic predisposition in sudden infant death syndrome. *J Am Coll Cardiol*. 2018;71:1217–1227. doi: 10.1016/j.jacc.2018.01.030
180. Sun AY, Koontz JI, Shah SH, Piccini JP, Nilsson KR Jr, Craig D, Haynes C, Gregory SG, Hranitzky PM, Pitt GS. The S1103Y cardiac sodium channel variant is associated with implantable cardioverter-defibrillator events in blacks with heart failure and reduced ejection fraction. *Circ Cardiovasc Genet*. 2011;4:163–168. doi: 10.1161/CIRCGENETICS.110.958652
181. Splawski I, Timothy KW, Tateyama M, Clancy CE, Malhotra A, Beggs AH, Cappuccio FP, Sagnella GA, Kass RS, Keating MT. Variant of *SCN5A* sodium channel implicated in risk of cardiac arrhythmia. *Science*. 2002;297:1333–1336. doi: 10.1126/science.1073569
182. Fernandes FM, Silva EP, Martins RR, Oliveira AG. QTc interval prolongation in critically ill patients: prevalence, risk factors and associated medications. *PLoS One*. 2018;13:e0199028. doi: 10.1371/journal.pone.0199028
183. Mahmud R, Gray A, Nabeebaccus A, Whyte MB. Incidence and outcomes of long QTc in acute medical admissions. *Int J Clin Pract*. 2018;72:e13250. doi: 10.1111/ijcp.13250
184. Anderson HN, Bos JM, Haugaa KH, Morlan BW, Tarrell RF, Caraballo PJ, Ackerman MJ. Prevalence and outcome of high-risk QT prolongation recorded in the emergency department from an institution-wide QT alert system. *J Emerg Med*. 2018;54:8–15. doi: 10.1016/j.jemermed.2017.08.073
185. Assimon MM, Brookhart MA, Flythe JE. Comparative cardiac safety of selective serotonin reuptake inhibitors among individuals receiving maintenance hemodialysis. *J Am Soc Nephrol*. 2019;30:611–623. doi: 10.1681/ASN.2018101032
186. Hofman N, Tan HL, Alders M, Kolder I, de Haij S, Mannens MM, Lombardi MP, Dit Deprez RH, van Langen I, Wilde AA. Yield of molecular and clinical testing for arrhythmia syndromes: report of 15 years' experience. *Circulation*. 2013;128:1513–1521. doi: 10.1161/CIRCULATIONAHA.112.000091
187. Itoh H, Crotti L, Aiba T, Spazzolini C, Denjoy I, Fressart V, Hayashi K, Nakajima T, Ohno S, Makiyama T, et al. The genetics underlying acquired long QT syndrome: impact for genetic screening. *Eur Heart J*. 2016;37:1456–1464. doi: 10.1093/eurheartj/ehv695
188. Bihlmeyer NA, Brody JA, Smith AV, Warren HR, Lin H, Isaacs A, Liu CT, Marten J, Radmanesh F, Hall LM, et al. ExomeChip-wide analysis of 95 626 individuals identifies 10 novel loci associated with QT and JT intervals. *Circ Genom Precis Med*. 2018;11:e001758. doi: 10.1161/CIRCGEN.117.001758
189. Roberts JD, Asaki SY, Mazzanti A, Bos JM, Tuleta I, Muir AR, Crotti L, Krahn AD, Kutyifa V, Shoemaker MB, et al. An international multicenter evaluation of type 5 long QT syndrome: a low penetrant primary arrhythmic condition. *Circulation*. 2020;141:429–439. doi: 10.1161/CIRCULATIONAHA.119.043114
190. Schwartz PJ. 1970-2020: 50 Years of research on the long QT syndrome-from almost zero knowledge to precision medicine. *Eur Heart J*. 2021;42:1063–1072. doi: 10.1093/eurheartj/ehaa769
191. Lahrouchi N, Tadros R, Crotti L, Mizusawa Y, Postema PG, Beekman L, Walsh R, Hasegawa K, Barc J, Ernsting M, et al. Transethnic genome-wide association study provides insights in the genetic architecture and heritability of long QT syndrome. *Circulation*. 2020;142:324–338. doi: 10.1161/CIRCULATIONAHA.120.045956
192. Cavalcanti AB, Zampieri FG, Rosa RG, Azevedo LCP, Veiga VC, Avezum A, Damiani LP, Marcadenti A, Kawano-Dourado L, Lisboa T, et al. Hydroxychloroquine with or without azithromycin in mild-to-moderate Covid-19. *N Engl J Med*. 2020;383:2041–2052. doi: 10.1056/NEJMoa2019014
193. Saleh M, Gabriels J, Chang D, Kim BS, Mansoor A, Mahmood E, Makker P, Ismail H, Goldner B, Willner J, et al. Effect of chloroquine, hydroxychloroquine, and azithromycin on the corrected QT interval in patients with SARS-CoV-2 infection. *Circ Arrhythm Electrophysiol*. 2020;13:e008662. doi: 10.1161/CIRCEP.120.008662
194. Maraj I, Hummel JP, Taoutel R, Chamoun R, Workman V, Li C, Tran L, DelVecchio A, Howes C, Akar JG. Incidence and determinants of QT interval prolongation in COVID-19 patients treated with hydroxychloroquine and azithromycin. *J Cardiovasc Electrophysiol*. 2020;31:1904–1907. doi: 10.1111/jce.14594
195. O'Connell TF, Bradley CJ, Abbas AE, Williamson BD, Rusia A, Tawney AM, Gaines R, Schott J, Dmitrienko A, Haines DE. Hydroxychloroquine/azithromycin therapy and QT prolongation in hospitalized patients with COVID-19. *JACC Clin Electrophysiol*. 2021;7:16–25. doi: 10.1016/j.jacep.2020.07.016
196. Si D, Du B, Ni L, Yang B, Sun H, Jiang N, Liu G, Massé S, Jin L, Nanthakumar J, et al. Death, discharge and arrhythmias among patients with COVID-19 and cardiac injury. *CMAJ*. 2020;192:E791–E798. doi: 10.1503/cmaj.200879
197. Giudicessi JR, Roden DM, Wilde AAM, Ackerman MJ. Genetic susceptibility for COVID-19-associated sudden cardiac death in African Americans. *Heart Rhythm*. 2020;17:1487–1492. doi: 10.1016/j.hrthm.2020.04.045
198. Adler A, Novelli V, Amin AS, Abiusi E, Care M, Nannenberg EA, Feilotter H, Amenta S, Mazza D, Bikker H, et al. An International, multicentered, evidence-based reappraisal of genes reported to cause congenital long QT syndrome. *Circulation*. 2020;141:418–428. doi: 10.1161/CIRCULATIONAHA.119.043132
199. Cross B, Homoud M, Link M, Foote C, Garlitski AC, Weinstock J, Estes NAM 3rd. The short QT syndrome. *J Interv Card Electrophysiol*. 2011;31:25–31. doi: 10.1007/s10840-011-9566-0
200. Kobza R, Roos M, Niggli B, Abacherli R, Lupi GA, Frey F, Schmid JJ, Erne P. Prevalence of long and short QT in a young population of 41,767 predominantly male Swiss conscripts. *Heart Rhythm*. 2009;6:652–657. doi: 10.1016/j.hrthm.2009.01.009
201. Providencia R, Karim N, Srinivasan N, Honarbakhsh S, Vidigal Ferreira MJ, Goncalves L, Marijon E, Lambiase PD. Impact of QTc formulae in the prevalence of short corrected QT interval and impact on probability and diagnosis of short QT syndrome. *Heart*. 2018;104:502–508. doi: 10.1136/heartjnl-2017-311673
202. Guerrier K, Kwiatkowski D, Czosek RJ, Spar DS, Anderson JB, Knilans TK. Short QT interval prevalence and clinical outcomes in a pediatric population. *Circ Arrhythm Electrophysiol*. 2015;8:1460–1464. doi: 10.1161/CIRCEP.115.003256
203. Giustetto C, Schimpf R, Mazzanti A, Scrocco C, Maury P, Anttonen O, Probst V, Blanc JJ, Sbragia P, Dalmasso P, et al. Long-term follow-up of patients with short QT syndrome. *J Am Coll Cardiol*. 2011;58:587–595. doi: 10.1016/j.jacc.2011.03.038
204. Brugada J, Campuzano O, Arbelo E, Sarquella-Brugada G, Brugada R. Present status of Brugada syndrome: JACC state-of-the-art review. *J Am Coll Cardiol*. 2018;72:1046–1059. doi: 10.1016/j.jacc.2018.06.037
205. Quan XQ, Li S, Liu R, Zheng K, Wu XF, Tang Q. A meta-analytic review of prevalence for Brugada ECG patterns and the risk for death. *Medicine (Baltimore)*. 2016;95:e5643. doi: 10.1097/MD.0000000000005643
206. Benito B, Brugada J, Brugada R, Brugada P. Brugada syndrome. *Rev Esp Cardiol*. 2009;62:1297–1315. doi: 10.1016/s1885-5857(09)73357-2
207. Milman A, Andorin A, Gourraud JB, Postema PG, Sacher F, Mabo P, Kim SH, Juang JJM, Maeda S, Takahashi Y, et al. Profile of patients with Brugada syndrome presenting with their first documented arrhythmic event: data

from the Survey on Arrhythmic Events in BRUgada Syndrome (SABRUS). *Heart Rhythm*. 2018;15:716–724. doi: 10.1016/j.hrthm.2018.01.014
208. Rodríguez-Mañero M, Jordá P, Hernandez J, Muñoz C, Grima EZ, García-Fernández A, Cañadas-Godoy MV, Jiménez-Ramos V, Oloriz T, Basterra N, et al. Long-term prognosis of women with Brugada syndrome and electrophysiological study. *Heart Rhythm*. 2021;18:664–671. doi: 10.1016/j.hrthm.2020.12.020
209. Rattanawong P, Kewcharoen J, Kanitsoraphan C, Barry T, Shanbhag A, Ko Ko NL, Vutthikraivit W, Home M, Agasthi P, Ashraf H, et al. Does the age of sudden cardiac death in family members matter in Brugada syndrome? *J Am Heart Assoc*. 2021;10:e019788. doi: 10.1161/JAHA.120.019788
210. David JP, Lisewski U, Crump SM, Jepps TA, Bocksteins E, Wilck N, Lossie J, Roepke TK, Schmitt N, Abbott GW. Deletion in mice of X-linked, Brugada syndrome- and atrial fibrillation-associated *Kcne5* augments ventricular KV currents and predisposes to ventricular arrhythmia. *FASEB J*. 2019;33:2537–2552. doi: 10.1096/fj.201800502R
211. Offerhaus JA, Bezzina CR, Wilde AAM. Epidemiology of inherited arrhythmias. *Nat Rev Cardiol*. 2020;17:205–215. doi: 10.1038/s41569-019-0266-2
212. Ingles J, Bagnall RD, Yeates L, McGrady M, Berman Y, Whalley D, Duflou J, Semsarian C. Concealed arrhythmogenic right ventricular cardiomyopathy in sudden unexplained cardiac death events. *Circ Genom Precis Med*. 2018;11:e002355. doi: 10.1161/CIRCGEN.118.002355
213. Cerrone M, Lin X, Zhang M, Agullo-Pascual E, Pfenniger A, Chkourko Gusky H, Novelli V, Kim C, Tirasawadichai T, Judge DP, et al. Missense mutations in plakophilin-2 cause sodium current deficit and associate with a Brugada syndrome phenotype. *Circulation*. 2014;129:1092–1103. doi: 10.1161/CIRCULATIONAHA.113.003077
214. Barc J, Tadros R, Glinge C, Chiang DY, Jouni M, Simonet F, Jurgens SJ, Baudic M, Nicastro M, Potet F, et al, Nantes Referral Center for Inherited Cardiac Arrhythmia. Genome-wide association analyses identify new Brugada syndrome risk loci and highlight a new mechanism of sodium channel regulation in disease susceptibility. *Nat Genet*. 2022;54:232–239. doi: 10.1038/s41588-021-01007-6
215. Hosseini SM, Kim R, Udupa S, Costain G, Jobling R, Liston E, Jamal SM, Szybowska M, Morel CF, Bowdin S, et al; National Institutes of Health Clinical Genome Resource Consortium. Reappraisal of reported genes for sudden arrhythmic death: evidence-based evaluation of gene validity for Brugada syndrome. *Circulation*. 2018;138:1195–1205. doi: 10.1161/CIRCULATIONAHA.118.035070
216. Walsh R, Adler A, Amin AS, Abiusi E, Care M, Bikker H, Amenta S, Feilotter H, Nannenberg EA, Mazzarotto F, et al. Evaluation of gene validity for CPVT and short QT syndrome in sudden arrhythmic death. *Eur Heart J*. 2022;43:1500–1510. doi: 10.1093/eurheartj/ehab687
217. Roston TM, Yuchi Z, Kannankeril PJ, Hathaway J, Vinocur JM, Etheridge SP, Potts JE, Maginot KR, Salerno JC, Cohen MI, et al. The clinical and genetic spectrum of catecholaminergic polymorphic ventricular tachycardia: findings from an international multicentre registry. *Europace*. 2018;20:541–547. doi: 10.1093/europace/euw389
218. Kawata H, Ohno S, Aiba T, Sakaguchi H, Miyazaki A, Sumitomo N, Kamakura T, Nakajima I, Inoue YY, Miyamoto K, et al. Catecholaminergic polymorphic ventricular tachycardia (CPVT) associated with ryanodine receptor (RyR2) gene mutations: long-term prognosis after initiation of medical treatment. *Circ J*. 2016;80:1907–1915. doi: 10.1253/circj.CJ-16-0250
219. Roston TM, Haji-Ghassemi O, LaPage MJ, Batra AS, Bar-Cohen Y, Anderson C, Lau YR, Maginot K, Gebauer RA, Etheridge SP, et al. Catecholaminergic polymorphic ventricular tachycardia patients with multiple genetic variants in the PACES CPVT Registry. *PLoS One*. 2018;13:e0205925. doi: 10.1371/journal.pone.0205925
220. Marcus FI, McKenna WJ, Sherill D, Basso C, Bauce B, Bluemke DA, Calkins H, Corrado D, Cox MG, Daubert JP, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. *Circulation*. 2010;121:1533–1541.
221. Mattesi G, Zorzi A, Corrado D, Cipriani A. Natural history of arrhythmogenic cardiomyopathy. *J Clin Med*. 2020;9:878. doi: 10.3390/jcm9030878
222. James CA, Jongbloed JDH, Hershberger RE, Morales A, Judge DP, Syrris P, Pilichou K, Domingo AM, Murray B, Cadrin-Tourigny J, et al. International evidence based reappraisal of genes associated with arrhythmogenic right ventricular cardiomyopathy using the Clinical Genome Resource Framework. *Circ Genom Precis Med*. 2021;14:e003273. doi: 10.1161/CIRCGEN.120.003273
223. Miles C, Finocchiaro G, Papadakis M, Gray B, Westaby J, Ensam B, Basu J, Parry-Williams G, Papatheodorou E, Paterson C, et al. Sudden death and left ventricular involvement in arrhythmogenic cardiomyopathy. *Circulation*. 2019;139:1786–1797. doi: 10.1161/CIRCULATIONAHA.118.037230
224. Mazzanti A, Ng K, Faragli A, Maragna R, Chiodaroli E, Orphanou N, Monteforte N, Memmi M, Gambelli P, Novelli V, et al. Arrhythmogenic right ventricular cardiomyopathy: clinical course and predictors of arrhythmic risk. *J Am Coll Cardiol*. 2016;68:2540–2550. doi: 10.1016/j.jacc.2016.09.951
225. Agbaedeng TA, Roberts KA, Colley L, Noubiap JJ, Oxborough D. Incidence and predictors of sudden cardiac death in arrhythmogenic right ventricular cardiomyopathy: a pooled analysis. *Europace*. 2022;24:1665–1674. doi: 10.1093/europace/euac014
226. Bhonsale A, Te Riele ASJM, Sawant AC, Groeneweg JA, James CA, Murray B, Tichnell C, Mast TP, van der Pols MJ, Cramer MJM, et al. Cardiac phenotype and long-term prognosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia patients with late presentation. *Heart Rhythm*. 2017;14:883–891. doi: 10.1016/j.hrthm.2017.02.013
227. Hoedemakers S, Vandenberk B, Liebregts M, Bringmans T, Vriesendorp P, Willems R, Van Cleemput J. Long-term outcome of conservative and invasive treatment in patients with hypertrophic obstructive cardiomyopathy. *Acta Cardiol*. 2019;74:253–261. doi: 10.1080/00015385.2018.1491673
228. Aro AL, Nair SG, Reinier K, Jayaraman R, Stecker EC, Uy-Evanado A, Rusinaru C, Jui J, Chugh SS. Population burden of sudden death associated with hypertrophic cardiomyopathy. *Circulation*. 2017;136:1665–1667. doi: 10.1161/CIRCULATIONAHA.117.030616
229. Abdelfattah OM, Martinez M, Sayed A, ElRefaei M, Abushouk AI, Hassan A, Masri A, Winters SL, Kapadia SR, Maron BJ, et al. Temporal and global trends of the incidence of sudden cardiac death in hypertrophic cardiomyopathy. *JACC Clin Electrophysiol*. 2022;8:1417–1427. doi: 10.1016/j.jacep.2022.07.012
230. Patton KK, Ellinor PT, Ezekowitz M, Kowey P, Lubitz SA, Perez M, Piccini J, Turakhia M, Wang P, Viskin S; on behalf of the American Heart Association Electrocardiography and Arrhythmias Committee of the Council on Clinical Cardiology and Council on Functional Genomics and Translational Biology. Electrocardiographic early repolarization: a scientific statement from the American Heart Association. *Circulation*. 2016;133:1520–1529. doi: 10.1161/CIR.0000000000000388
231. Antzelevitch C, Yan GX, Ackerman MJ, Borggrefe M, Corrado D, Guo J, Gussak I, Hasdemir C, Horie M, Huikuri H, et al. J-Wave syndromes expert consensus conference report: emerging concepts and gaps in knowledge. *Europace*. 2017;19:665–694. doi: 10.1093/europace/euw235
232. Sun GZ, Ye N, Chen YT, Zhou Y, Li Z, Sun YX. Early repolarization pattern in the general population: prevalence and associated factors. *Int J Cardiol*. 2017;230:614–618. doi: 10.1016/j.ijcard.2016.12.045
233. De Lazzari C, Genuini I, Gatto MC, Cinque A, Mancone M, D'Ambrosi A, Silvetti E, Fusto A, Pisanelli DM, Fedele F. Screening high school students in Italy for sudden cardiac death prevention by using a telecardiology device: a retrospective observational study. *Cardiol Young*. 2017;27:74–81. doi: 10.1017/S1047951116000147
234. Haissaguerre M, Derval N, Sacher F, Jesel L, Deisenhofer I, de Roy L, Pasquie JL, Nogami A, Babuty D, Yli-Mayry S, et al. Sudden cardiac arrest associated with early repolarization. *N Engl J Med*. 2008;358:2016–2023. doi: 10.1056/NEJMoa071968
235. Rosso R, Glikson E, Belhassen B, Katz A, Halkin A, Steinvil A, Viskin S. Distinguishing "benign" from "malignant early repolarization": the value of the ST-segment morphology. *Heart Rhythm*. 2012;9:225–229. doi: 10.1016/j.hrthm.2011.09.012
236. Holkeri A, Eranti A, Haukilahti MAE, Kerola T, Kentta TV, Tikkanen JT, Rissanen H, Heliovaara M, Knekt P, Junttila MJ, et al. Impact of age and sex on the long-term prognosis associated with early repolarization in the general population. *Heart Rhythm*. 2020;17:621–628. doi: 10.1016/j.hrthm.2019.10.026
237. Siebermair J, Sinner MF, Beckmann BM, Laubender RP, Martens E, Sattler S, Fichtner S, Estner HL, Kaab S, Wakili R. Early repolarization pattern is the strongest predictor of arrhythmia recurrence in patients with idiopathic ventricular fibrillation: results from a single centre long-term follow-up over 20 years. *Europace*. 2016;18:718–725. doi: 10.1093/europace/euv301
238. Dukes JW, Dewland TA, Vittinghoff E, Mandyam MC, Heckbert SR, Siscovick DS, Stein PK, Psaty BM, Sotoodehnia N, Gottdiener JS, et al. Ventricular ectopy as a predictor of heart failure and death. *J Am Coll Cardiol*. 2015;66:101–109. doi: 10.1016/j.jacc.2015.04.062
239. Khairy P, Aboulhosn J, Gurvitz MZ, Opotowsky AR, Mongeon FP, Kay J, Valente AM, Earing MG, Lui G, Gersony DR, et al; Alliance for Adult Research in Congenital Cardiology (AARCC). Arrhythmia burden in adults with surgically repaired tetralogy of Fallot: a multi-institutional study. *Circulation*. 2010;122:868–875. doi: 10.1161/CIRCULATIONAHA.109.928481
240. Valente AM, Gauvreau K, Assenza GE, Babu-Narayan SV, Schreier J, Gatzoulis MA, Groenink M, Inuzuka R, Kilner PJ, Koyak Z, et al. Contemporary predictors of death and sustained

ventricular tachycardia in patients with repaired tetralogy of Fallot enrolled in the INDICATOR cohort. *Heart*. 2014;100:247–253. doi: 10.1136/heartjnl-2013-304958
241. Gatzoulis MA, Balaji S, Webber SA, Siu SC, Hokanson JS, Poile C, Rosenthal M, Nakazawa M, Moller JH, Gillette PC, et al. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. *Lancet*. 2000;356:975–981. doi: 10.1016/S0140-6736(00)02714-8
242. Birnie DH, Sauer WH, Bogun F, Cooper JM, Culver DA, Duvernoy CS, Judson MA, Kron J, Mehta D, Cosedis Nielsen J, et al. HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. *Heart Rhythm*. 2014;11:1305–1323. doi: 10.1016/j.hrthm.2014.03.043
243. Salama A, Abdullah A, Wahab A, Eigbire G, Hoefen R, Alweis R. Cardiac sarcoidosis and ventricular arrhythmias: a rare association of a rare disease: a retrospective cohort study from the National Inpatient Sample and current evidence for management. *Cardiol J*. 2020;27:272–277. doi: 10.5603/CJ.a2018.0104
244. Tran HV, Ash AS, Gore JM, Darling CE, Kiefe CI, Goldberg RJ. Twenty-five year trends (1986-2011) in hospital incidence and case-fatality rates of ventricular tachycardia and ventricular fibrillation complicating acute myocardial infarction. *Am Heart J*. 2019;208:1–10. doi: 10.1016/j.ahj.2018.10.007
245. Ning X, Ye X, Si Y, Yang Z, Zhao Y, Sun Q, Chen R, Tang M, Chen K, Zhang X, et al. Prevalence and prognosis of ventricular tachycardia/ventricular fibrillation in patients with post-infarction left ventricular aneurysm: analysis of 575 cases. *J Electrocardiol*. 2018;51:742–746. doi: 10.1016/j.jelectrocard.2018.03.010
246. Volpi A, Cavalli A, Turato R, Barlera S, Santoro E, Negri E. Incidence and short-term prognosis of late sustained ventricular tachycardia after myocardial infarction: results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-3) data base. *Am Heart J*. 2001;142:87–92. doi: 10.1067/mhj.2001.115791
247. Konig S, Boudriot E, Arya A, Lurz JA, Sandri M, Erbs S, Thiele H, Hindricks G, Dinov B. Incidence and characteristics of ventricular tachycardia in patients after percutaneous coronary revascularization of chronic total occlusions. *PLoS One*. 2019;14:e0225580. doi: 10.1371/journal.pone.0225580
248. Haegeli LM, Ercin E, Steffel J, Wolber T, Tanner FC, Jenni R, Gamperli O, Saguner AM, Luscher TF, Brunckhorst C, et al. Incidence and prognosis of ventricular arrhythmias in patients with congenital left ventricular aneurysms or diverticula. *Am J Med*. 2015;128:653.e1–653.e6. doi: 10.1016/j.amjmed.2015.01.001
249. Hai JJ, Un KC, Wong CK, Wong KL, Zhang ZY, Chan PH, Lau CP, Siu CW, Tse HF. Prognostic implications of early monomorphic and non-monomorphic tachyarrhythmias in patients discharged with acute coronary syndrome. *Heart Rhythm*. 2018;15:822–829. doi: 10.1016/j.hrthm.2018.02.016
250. Arunachalam K, Lakshmanan S, Maan A, Kumar N, Dominic P. Impact of drug induced long QT syndrome: a systematic review. *J Clin Med Res*. 2018;10:384–390. doi: 10.14740/jocmr3338w
251. Arizona Center for Education and Research on Therapeutics. Credible Meds: QTDrugs list. Accessed April 15, 2023. https://crediblemeds.org/healthcare-providers/

# 20. SUBCLINICAL ATHEROSCLEROSIS

*See Table 20-1 and Charts 20-1 through 20-4*

Click here to return to the Table of Contents
Click here to return to the Abbreviations

Multiple complementary imaging modalities allow the detection and quantification of atherosclerosis through its stages in different vascular beds. Early identification of subclinical atherosclerosis can guide preventive care, including lifestyle modifications and medical treatment (eg, aspirin, antihypertensives, lipid-lowering therapy) to prevent clinical manifestations of atherosclerosis such as MI, stroke, or PAD. Several modalities can be used for imaging atherosclerosis, including noncontrast chest CT for evaluation of CAC, CCTA, B-mode ultrasound of the neck for evaluation of carotid artery IMT or plaque, brachial artery reactivity testing, aortic and carotid MRI, and tonometric methods of measuring vascular compliance or microvascular reactivity.

Among these modalities, the role of CAC in cardiovascular risk assessment is particularly well defined. According to the 2018 Cholesterol Clinical Practice Guideline[1] and the 2019 CVD Primary Prevention Clinical Practice Guidelines,[2] in intermediate-risk or selected borderline-risk adults, if the decision about statin therapy remains uncertain after 10-year ASCVD risk estimation and after accounting for risk enhancers, it is reasonable to use a CAC score in the decision to withhold, postpone, or initiate statin therapy. Other professional organizations such as the National Lipid Association[3] also recommend the use of CAC to guide preventive strategies for ASCVD risk reduction. In addition, in 2021 guidelines from the AHA, ACC, and multiple additional collaborating organizations, CCTA has received a Class IA recommendation for evaluation of chest pain in individuals with no history of CAD.[4]

This chapter begins with a focus on CAC and coronary atherosclerosis, followed by statistics on carotid IMT and carotid atherosclerosis, and includes statistics on other subclinical atherosclerosis imaging studies. The chapter prioritizes discussion of social determinants of health and health equity in relation to coronary and carotid atherosclerosis. Furthermore, the last section of the chapter provides statistics on subclinical atherosclerosis in relation to healthy lifestyle behaviors and preventive medications.

The 2024 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2024. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

## CAC and Coronary Atherosclerosis

### Background

- CAC measures atherosclerotic burden in the coronary arteries by noncontrast CT and captures calcified plaques. CAC is classically reported as an Agatston score based on the total area of calcium deposits and the density of coronary calcium.
- CCTA is a contrasted CT scan that can visualize calcified plaques and other components of coronary atherosclerotic plaque (including cholesterol-rich components) and assesses for coronary artery lumen narrowing.

### Prevalence and Risk Factors

#### (See Charts 20-1 and 20-2)

- The NHLBI's MESA, a study of White, Black, Chinese, and Hispanic adults, measured CAC in 6814 participants 45 to 84 years of age (mean, 63 years), including White (n=2619), Black (n=1898), Hispanic (n=1494), and Chinese (n=803) males and females.[5]
  - The overall prevalence of CAC in these 4 ethnic groups was 70.4%, 52.1%, 56.5%, and 59.2%, respectively, among males and 44.6%, 36.5%, 34.9%, and 41.9%, respectively, among females.
  - The prevalence and 75th percentile levels of CAC were highest in White males and lowest in Black and Hispanic females. Ethnic differences persisted after adjustment for risk factors, with a CAC prevalence that was 22% lower in Black people, 15% lower in Hispanic people, and 8% lower in Chinese people than in White people.
- Illustrating the variability of CAC by population and habits, a forager-horticulturalist population of 705 individuals living in the Bolivian Amazon had the lowest reported levels of CAC of any population recorded to date.[6]
  - Overall, in the population (mean age, 58 years; 50% female), 85% of individuals were free of any CAC, and even in individuals >75 years of age, 65% remained free of CAC. These unique data indicate that coronary atherosclerosis typically can be avoided by maintaining a low lifetime burden of CAD risk factors.[6]
- In US adults who are free of CAC at baseline, subsequent development of CAC is common. In 3116 MESA participants (58±9 years of age; 63% female) who had no detectable CAC at baseline and were followed up over 10 years, 53%, 36%, and 8% of individuals had CAC >0, CAC >10, and

CAC >100, respectively, at 10 years.[7] A rescanning interval of 3 to 7 years was suggested on the basis of age, sex, race and ethnicity, and diabetes.

- The duration of risk factor exposure is associated with CAC, as exemplified in an analysis of exposure to diabetes and prediabetes in 3628 participants in CARDIA.[8]
  - For each additional 5 years of exposure to diabetes and prediabetes, the aHR for CAC was 1.15 (95% CI, 1.06–1.25) and 1.07 (95% CI, 1.01–1.13), respectively.
- In 2359 asymptomatic adults (including 47% Hispanic) of the Miami Heart Study who underwent CCTA, 49% of participants had coronary plaque, 6% had stenosis ≥50%, and 7% had plaques with high-risk features (Chart 20-1).
- Beyond traditional cardiovascular risk factors, studies have identified APO, obesity, elevated lipoprotein(a), and HIV as being associated with calcified or noncalcified coronary atherosclerosis:
  - Among 10528 females in Sweden with ≥1 deliveries in 1973 or later who later participated in an imaging study at a median of 57.3 years of age in 2013 to 2018, atherosclerosis was present by CCTA in 32.1% (95% CI, 30.0%–34.2%) of females with a history of any APO.[9] This prevalence was higher compared with females without any history of APO (prevalence difference, 3.8% [95% CI, 1.6%–6.1%]; PR, 1.14 [95% CI, 1.06–1.22]).
  - Of 1585 participants free of CHD and free of MetS, those who were obese had a higher prevalence of CAC than individuals with a normal weight, with a PR of 1.59 (95% CI, 1.38–1.84).[10]
  - In 937 apparently healthy asymptomatic family members of individuals with premature ASCVD, high lipoprotein(a) levels were associated with CAC ≥100 (OR, 1.79 [95% CI, 1.13–2.83]).[11]
  - In a study-level meta-analysis involving 10867 participants (6699 living with HIV, 4168 not living with HIV; mean age, 52 years; 86% male; 32% Black), the prevalence of noncalcified plaque was 49% (95% CI, 47%–52%) in individuals living with HIV versus 20% (95% CI, 17%–23%) in individuals not living with HIV (OR, 1.23 [95% CI, 1.08–1.38]).[12]
- In a harmonized data set analysis of 19725 Black and White individuals 30 to 45 years of age from CARDIA, the CAC Consortium, and the Walter Reed Cohort, the prevalence of CAC>0 among White males, Black males, White females, and Black females was 26%, 16%, 10%, and 7%, respectively (Chart 20-2).[13]
- The 10-year trends in CAC among individuals without clinical CVD in MESA were assessed (Chart 20-3).
  - The mean age at the baseline examination was 67 years; 47.4% were male. Detectable CAC was evaluated in White, Black, Hispanic, and Chinese participants, with >50% prevalence at baseline.
  - Ten-year trends in CAC prevalence among the 4 racial and ethnic groups revealed a significant trend toward increased prevalence of CAC in Black participants but not in any other group (Chart 20-3). Among Black participants, the CAC PR (year 10 versus baseline) was 1.27 ($P_{trend}$<0.001).[14]
  - CAC severity was also evaluated at baseline and 10 years. After adjustment for age, sex, ethnicity, and type of CT scanner, the proportion of participants with no CAC decreased over time from 40.7% to 32.6% (*P*=0.007). The proportions increased from 29.9% to 37.0% (*P*=0.01) for those with CAC 1 to 99 and from 14.7% to 17.7% (*P*=0.14) for those with CAC 100 to 399, whereas the proportion with CAC ≥400 decreased from 9.1% to 7.2% (*P*=0.11).

### *CAC and Incidence of ASCVD Events (CHD and Stroke)*

#### *(See Chart 20-4)*

- The NHLBI's MESA reported the association of CAC with first CHD events over a median follow-up of 3.9 years among a population-based sample of 6722 individuals (39% White, 27% Black, 22% Hispanic, and 12% Chinese participants).[15]
  - Chart 20-4 shows the HRs associated with CAC scores of 1 to 100, 101 to 300, and >300 compared with CAC=0 after adjustment for standard risk factors. People with CAC 1 to 100 had ≈4 times greater risk, and those with CAC scores >100 were 7 to 10 times more likely to experience a CHD event than those without CAC.
  - CAC provided similar predictive value for CHD events in White, Chinese, Black, and Hispanic individuals (HRs ranging from 1.15–1.39 for each doubling of CAC).
- In 13397 low-risk younger adults 30 to 49 years of age of the Walter Reed Cohort, a CAC score >100 was associated with an HR of 5.16 (95% CI, 3.29–8.10) for MI, 3.14 (95% CI, 2.26–4.36) for MACEs (MI, stroke, or CVD death), 1.73 (95% CI, 1.01–2.97) for stroke, and 2.08 (95% CI, 1.13–3.82) for all-cause mortality.[16]
- A very high CAC score ≥1000 is associated with a MACE rate of 3.4 per 100 person-years, which is similar to that in a stable secondary prevention population.[17] After adjustment for age, sex, and traditional cardiovascular risk factors, individuals with CAC ≥1000 had a 5-fold greater risk of CVD mortality compared with those with CAC=0.[18]

- During 13.2 years of follow-up in asymptomatic individuals from the MESA study (n=4512; 61.9 years of age; 52.5% female; 36.8% White, 29.3% Black, 22.2% Hispanic, and 11.7% Chinese), an independent association with ASCVD risk was observed for elevated lipoprotein(a) levels (HR, 1.29 [95% CI, 1.04–1.61]) and elevated CAC scores (score of ≥100 versus 0: HR, 2.66 [95% CI, 2.07–3.43]).[19] No lipoprotein(a)-by-CAC interaction was observed. Similar findings were noted in the Dallas Heart Study.

### *CAC Progression and Risk*

- In MESA, 6778 participants showed annual CAC progression averaging 25±65 Agatston units. Among those without CAC at baseline, a 5-unit annual change in CAC was associated with HRs of 1.4 and 1.5 for total and hard CHD events, respectively.[20]
- In a MESA study of 2759 postmenopausal females, despite no association between sex hormones and prevalent CAC, an association emerged between sex hormones and CAC progression over a median of 4.7 years.[21]

### *Social Determinants of Health/Health Equity in CAC and Coronary Atherosclerosis*

In addition to the differences by race and ethnicity detailed previously, differences in CAC or associations with CAC have been described by factors such as sex, unemployment, and exposure to air pollution:

- In 1125 Black participants in the CARDIA study, exposure to a low versus high level of neighborhood-level racial residential segregation in young adulthood was associated with a lower risk of developing midlife CAC (rate ratio, 0.52 [95% CI, 0.28–0.98]).[22] This association was attenuated and lost significance after adjustment for cardiovascular risk factor burden (rate ratio, 0.56, [95% CI, 0.29–1.09]).
- In 1429 participants from the MESA study, insomnia symptoms were independently associated with an 18% higher prevalence of CAC (PR, 1.18 [95% CI, 1.04–1.33]) among females but not males (PR, 1.00 [95% CI, 0.91–1.08]).[23]
- In 312 females (mean age, 50.8 years), after adjustment for potential confounders, depression, health behaviors, and CVD risk factors, psychosocial well-being was not significantly associated with CAC progression.[24] However, among the 134 females with baseline CAC >0, well-being was associated with less CAC progression (RR, 0.921 [95% CI, 0.852–0.995]; $P=0.037$).
- In 3000 patients from rural central Appalachia, age (RR, 1.07; $P\leq0.0001$), being male (RR, 5.33; $P\leq0.0001$), having hypertension (RR, 2.37; $P\leq0.05$), and zip code–level unemployment (RR, 1.37; $P\leq0.05$) were associated with having diabetes and CAC score ≥1.[25]
- Among 606 asymptomatic adults in Australia (51% female; 56±7 years of age), exposure to higher PM2.5 was associated with greater odds of having CAC >100 (OR, 1.20 [95% CI, 1.02–1.43]) and >400 (OR, 1.55 [95% CI, 1.05–2.29]).[26] Similar associations were observed for $NO_2$.

## Carotid IMT and Carotid Atherosclerosis

### *Background*

- Carotid IMT measures the thickness of 2 layers (the intima and media) of the wall of the carotid arteries, the largest conduits of blood going to the brain. Carotid IMT is thought to be an earlier manifestation of atherosclerosis than CAC because thickening precedes the development of frank atherosclerotic plaque. Carotid IMT methods may vary by part of the artery measured (common carotid, internal carotid, or bulb), measurement of near and far walls, and reporting of average (more common) or maximum thickness.
- Carotid IMT is greater with age and in males. Thus, high-risk levels of thickening might be considered to be those in the highest quartile or quintile for one's age and sex or ≥1 mm.
- Stroke risk is higher with greater degrees of asymptomatic carotid stenosis (OR, 2.5 for stenosis 80%–99% versus 50%–79% [95% CI, 1.8–3.5]; $P<0.0001$) in a large meta-analysis of 11 cohort studies.[27]

### *Prevalence and Risk Factors*

- Sex and race differences have been demonstrated in carotid IMT. In 518 healthy Black and White males and females in the Bogalusa Heart Study, males had significantly higher carotid IMT in all segments than females ($P<0.05$), and Black participants had higher common carotid and carotid bulb IMT than White participants ($P<0.001$).[28] In MESA and a large cross-continent cohort of individuals of African, Asian, White European, and Hispanic ancestry, Black people had the thickest carotid IMT (particularly common carotid, 0.91 mm) of all 4 ethnic groups.[29] Chinese participants had the lowest carotid IMT (0.83 mm), in particular in the internal carotid, of the 4 ethnic groups.
- In a meta-analysis of 7645 individuals, carotid IMT increased from 723±39 μm in participants with normal BP to 779±45 μm in those with prehypertension and 858±82 μm in individuals with hypertension.[30]
- Adverse risk factors in early childhood and young adulthood are implicated in the early development of atherosclerosis. In the Bogalusa Heart Study (mean age, 32±3 years), carotid IMT was

significantly and positively associated with WC, SBP, DBP, and LDL-C and inversely correlated with HDL-C levels. Participants with greater numbers of adverse risk factors (0, 1, 2, 3, or more) had stepwise increases in mean carotid IMT levels.[28] Higher BMI and LDL-C levels measured at 4 to 7 years of age were associated with increased risk for carotid IMT >75th percentile in young adulthood.[30] Higher SBP and LDL-C and lower HDL-C in young adulthood also were associated with high carotid IMT. A large Finnish cohort study showed similar findings.[31] Increased trajectory of lipids from 5 to 45 years of age measured in 1201 individuals in the Bogalusa Heart Study was also associated with mid-life IMT compared with stable low lipid levels.[32]

- In 9388 US and Finnish individuals with longitudinal measurement of CVD risk factors and carotid IMT, CVH declined from childhood to adulthood and was associated with IMT thickening.[33]
- In the Cardiovascular Risk in Young Finns Study, childhood oral infections, including periodontal disease or caries, were associated with greater carotid IMT, particularly in males (third tertile of number of childhood oral infections versus tertiles 1 and 2: RR, 1.87 [95% CI, 1.25–2.79]).[34]
- Sleep patterns and duration, which are associated with CVD, are associated with subclinical atherosclerosis.[35] In nearly 4000 asymptomatic middle-aged individuals in the PESA study, individuals who slept <6 h/night had a 1.27 greater odds of noncoronary atherosclerosis defined by carotid and femoral ultrasound imaging, even with adjustment for conventional risk factors.[35]
- In individuals without diabetes or CVD, higher HbA1c was associated with the extent of subclinical atherosclerosis assessed by IMT and atherosclerotic plaque of the carotids, abdominal aorta, and iliofemoral arteries, as well as CAC (OR, 1.05, 1.27, 1.27, 1.36, 1.80, 1.87, and 2.47 for HbA1c 4.9%–5.0%, 5.1%–5.2%, 5.3%–5.4%, 5.5%–5.6%, 5.7%–5.8%, 5.9%–6.0%, and 6.1%–6.4%, respectively; reference, HbA1c ≤4.8%; $P<0.001$).[36]
- Low levels of exposure were not associated with carotid IMT after adjustment for CVD risk factors and SES in 6103 participants in the Malmö Diet and Cancer study.[37]
- Analyses from 15 cohorts across Africa, Asia, Europe, and North America encompassing 34 025 adults demonstrated that the association between CVD risk factors and IMT differs between different ethnic groups.[38]

### Social Determinants of Health/Health Equity in Carotid IMT and Vascular Disease

- In the FAMILIA trial of 436 socioeconomically challenged young adults who underwent carotid and femoral vascular ultrasound, subclinical atherosclerosis was present in 12.6% of NH Black versus 6.6% of Hispanic individuals, with higher risk for prevalent disease (OR, 3.45 [95% CI, 1.44–8.29]; $P=0.006$) and multivascular disease ($P=0.026$) in analyses adjusted for CVD risk factors, as well as lifestyle and SES factors.[39]
- In the biracial HANDLS study of 2270 adults, interaction analyses demonstrated a race-by-SES effect whereby individuals who self-identified as Black race with high (rather than low) SES had higher carotid IMT (0.71 versus 0.67 in White individuals) and aortic stiffness than other groups, suggesting a group with greater subclinical CVD.[40]
- In 2903 participants of the Cardiovascular Risk in Young Finns Study of individuals initially examined in youth, in adulthood, urban-dwelling (compared with rural-dwelling) residents had lower cardiovascular risk factors and lower IMT (−0.01 mm), lower vascular stiffness (PWV, −0.22 m/s), and higher carotid artery compliance (0.07%/10 mm Hg).[41]
- The IMPROVE study of 3703 European people assessed the relationship between SES and carotid IMT. Manual laborers had higher carotid IMT than white collar workers, a finding that was independent of sex, age groups, and education and was only partially mediated by risk factors (+7.7%, +5.3%, +4.6% for $IMT_{max}$, $IMT_{mean-max}$, and $IMT_{mean}$, respectively; all $P<0.0001$).[42]
- In the Cardiovascular Risk in Young Finns Study of 1813 adults 27 to 39 years of age followed up for >20 years, individuals with higher education had lower progression of IMT in follow-up ($P=0.002$).[43]
- Several studies from cohorts including ELSA-Brasil, Mexican-Teachers Cohort, and an urban US cohort suggest that psychosocial well-being is associated with lower IMT, whereas serious financial difficulty, psychosocial stress, and racial discrimination are associated with subclinical vascular disease, including elevated IMT.[44–46]

### Risk Prediction

No evidence or recommendation for screening asymptomatic individuals exists per the US Preventive Services Task Force.[47] However, several studies demonstrate the association of carotid atherosclerosis with CVD events:

- A study from 3 population-based cohorts (ARIC, N=13 907; MESA, N=6640; and the Rotterdam Study, N=5220) demonstrated that both a higher carotid IMT and the presence of carotid plaque were independently associated with an increased risk of incident AF.[48] In this study, a 1-SD increase in carotid IMT and the presence of carotid plaque were associated with a meta-analyzed HR for AF of 1.12 (95% CI, 1.08–1.16) and 1.30 (95% CI, 1.19–1.42), respectively.

- Carotid IMT has been associated with incident CVD in multiple large cohorts. In MESA, an IMT rate of change of 0.5 mm/y was associated with an HR of 1.23 (95% CI, 1.02–1.48) for incident stroke.[49] In MESA[49] and CHS participants,[50] the upper quartile and quintile were associated with 2- to 3-fold increased risks for CVD, respectively, including MI and stroke. Among >13 000 participants in ARIC, carotid IMT was associated with incident HF[51] and CHD and, with carotid plaque, was able to improve risk reclassification (0.742–0.755 [95% CI for difference in adjusted AUC, 0.008–0.017]).[52]
- Decrease in IMT has also been associated with reduced risk for CVD. In data from 100 667 patients from 119 RCTs followed up for an average of 3.7 years, each 10–µm/y decrease in IMT progression was associated with an RR of 0.91 (95% credible interval, 0.87–0.94).[53]
- Conflicting data have been reported on the contribution of carotid IMT alone to risk prediction. A consortium of 14 population-based cohorts consisting of 45 828 individuals followed up for a median of 11 years suggested that IMT did not add to FRS risk prediction of incident MI and stroke (95% CI, 2.7%–4.6%).[54]
- The ability of carotid IMT to predict incident CVD events also might depend on differential subgroup effects or ultrasound sensitivity. In MESA, combined IMT data from both the internal and common carotid arteries resulted in a significant improvement in the net reclassification improvement of 4.9% ($P$=0.024), with a particularly higher impact in individuals with an intermediate FRS, in whom the net reclassification improvement was 11.5%.[55] Both high and low IMT improved risk prediction in an analysis of registry patients and ARIC study participants at high risk for CVD: Maximum wall thickness >2.0 mm improved net reclassification index, integrated discrimination index, and C index ($P$<0.05); and maximum wall thickness <0.9 mm had a negative predictive value of 97% and 92% in the derivation and validation cohorts for CVD events.[56]

Advanced imaging methods may better identify risk:

- In the BioImage Study of 5808 asymptomatic US adults (mean age, 69 years; 56.5% female), increasing 3-dimensional carotid ultrasound plaque burden tertile was associated with an ≈2-fold risk for CVD (cardiovascular death, MI, and ischemic stroke; Table 20-1). Net reclassification improved significantly with carotid plaque burden (0.23).[57]
- In the Rotterdam Study of older adults, the presence of intraplaque hemorrhage (but not calcification or lipid-rich core) by high-resolution MRI demonstrated an association with incident stroke and CHD (HR, 2.42 [95% CI, 1.30–4.50] and 1.95 [95% CI, 1.20–3.14], respectively).[58]

## CAC, Carotid IMT, CT Angiography, and Risk Prediction

- In MESA, the investigators reported the follow-up of 6779 males and females in 4 ethnic groups over 9.5 years and compared the predictive utility of carotid IMT, carotid plaque, and CAC (presence and burden).[59]
  - For CVD and CHD prediction: Compared with traditional risk factors, C statistics for CVD (C=0.756) and CHD (C=0.752) increased the most by the addition of CAC presence (CVD, C=0.776; CHD, C=0.784; $P$<0.001), followed by carotid plaque presence (CVD, C=0.760; CHD, C=0.757; $P$<0.05). Mean IMT ≥75th percentile (for age, sex, and race) alone did not predict events.
  - For stroke/TIA prediction: Compared with risk factors (C=0.782), carotid plaque presence (C=0.787; $P$=0.045), but not CAC (C=0.785; $P$=0.438), added to risk prediction.
- In 4724 participants of the Suita study of middle to older adults with carotid ultrasound, 2722 of whom had follow-up ultrasounds, prevalent and incident common carotid artery plaque was associated with incident CVD (incident plaque HR, 1.95 [95% CI, 1.14–3.3]) for CVD and HR, 2.01 [95% CI, 1.01–3.99] for stroke].[60]
- Despite promise for examination of coronary anatomy, CT angiography has limited impact on the prediction of outcomes in asymptomatic individuals. Thus, guidelines have not recommended its use as a screening tool for the assessment of cardiovascular risk in asymptomatic individuals.[2] In the CONFIRM study, although CT angiography presence, extent, and severity of CAD improved risk prediction over traditional risk factors, no additional prognostic value for all-cause death was conferred once traditional risk factors and CAC scores were included in the model.[61]
- In 4184 young to middle-aged asymptomatic individuals in the PESA cohort in whom carotid ultrasound and CAC were performed, elastic net machine-learning models identified a score based on age, HbA1c, TC/HDL, leukocyte volume, and hemoglobin predicting prevalent and progression of subclinical atherosclerosis and CVD risk.[62] This score was externally validated in the AWHS of similarly aged males.

## Genetics and Family History

- Subclinical atherosclerosis is heritable. With the use of Vietnam Era Twin Registry data that included 98 middle-aged male twin pairs, carotid artery IMT heritability was estimated to be 59%.[63] Similarly,

44% of the variation in CAC quantity was attributable to genetic factors in a study of 698 adults from 302 families.[64] CAC progression also is heritable, although of smaller magnitude ($h^2$=14%).[65]

- There is evidence for genetic control of subclinical atherosclerosis, with several loci identified that are associated with CAC and carotid artery IMT in multiethnic and racial populations.[66–70] On the basis of the identified genes and variants, there are considerable shared genetic components to subclinical disease and other risk factors (such as blood lipids) and incident CVD.
- CHARGE Consortium investigators identified 8 unique genetic loci that contribute to carotid IMT in 71 128 individuals and 1 novel locus for carotid plaque in 48 434 individuals.[68] A parallel GWAS in the UK Biobank (N=45 185) identified 7 novel loci for carotid IMT (*ZNF385D*, *ADAMTS9*, *EDNRA*, *HAND2*, *MYOCD*, *ITCH/EDEM2/MMP24*, and *MRTFA*).[70] When the CHARGE Consortium and UK Biobank data were meta-analyzed, an additional 3 novel loci were identified at *APOB*, *FIP1L1*, and *LOXL4*.[70] Positive genetic correlations with CHD, PAD, SBP, and stroke and negative genetic correlations with HDL-C using linkage disequilibrium score regression analysis were observed. These observations suggest connections between genetic susceptibility to subclinical atherosclerosis with overt CVD and CVD risk factors.
- Ancestrally diverse populations can enable identification of novel subclinical atherosclerosis loci. In a study of N=7894 unrelated participants from sub-Saharan Africa, carotid IMT GWAS identified 2 novel loci for mean–maximum carotid IMT (*SIRPA* and *FBXL17*) and sex-specific loci at *SNX29*, *LARP6*, and *PROK1*.[71] These loci may influence macrophage activity (*SIRPA*), vascular endothelial growth (*PROK1*), and collagen synthesis (*LARP6*).
- A 48-SNP GRS for type 2 diabetes was associated with carotid plaque and ASCVD events in ≈160 000 individuals, suggesting a causal role between genetic predisposition to type 2 diabetes and ASCVD.[72]
- The combination of GWASs and proteomics has identified novel biomarkers of subclinical atherosclerosis, including circulating C-type lectin domain family 1 member B and platelet-derived growth factor receptor-β.[73]

## Measures of Vascular Function and Incident CVD Events

- Background BP and its variability are related to CVD events. In 1033 Japanese males and females, greater home BP variability was associated with higher carotid IMT >1.0 mm (fourth versus first quartile: RR, 1.71 [95% CI, 1.15–2.54]), prevalent aortic calcification (RR, 1.08 [95% CI, 1.02–1.15]), and ABI <1.1 (RR, 1.49 [95% CI, 1.12–1.97]).[74]
- Brachial FMD is a marker for nitric oxide release from the endothelium that can be measured by ultrasound. Impaired FMD is an early marker of CVD.
- Because of the absence of significant prospective data relating these measures to outcomes, guidelines do not recommend measuring either FMD or arterial stiffness for cardiovascular risk assessment in asymptomatic adults.[75]

### *Arterial Stiffness and CVD*

- Arterial stiffness, defined as pulse pressure ≥60 mm Hg, conferred a 27% greater odds of in-hospital mortality after multivariable adjustment for comorbidities among 12 170 patients hospitalized with SARS-CoV-2 in the SEMI-COVID-19 network in Spain.[76]
- A study from Denmark of 1678 individuals 40 to 70 years of age found that each 1-SD increment in aortic PWV (3.4 m/s) increased CVD risk by 16% to 20%.[77]
- In the FHS, higher PWV was associated with a 48% increased risk of incident CVD events, and PWV improved CVD risk prediction (integrated discrimination improvement, 0.7%; $P$<0.05).[78]
- In 440 Black participants in the JHS (mean age, 59±10 years; 60% female), natural log–transformed LV mass index measured by MRI was negatively correlated with reactive hyperemia index (coefficient, −0.114; $P$=0.02) after accounting for age, sex, BMI, diabetes, hypertension, ratio of TC to HDL-C, smoking, and history of CVD.[79]
- Evidence suggests that arterial stiffness has negative impacts on brain health across the life spectrum.
  - In 5853 children in the Generation R Study, DBP was related to nonverbal intelligence, and in 5187 adults in the Rotterdam Study, cognition was linearly related to SBP, PWV, and pulse pressure and nonlinearly related to DBP.[80]
  - In the ARIC–Neurocognitive and ARIC-PET studies, higher arterial stiffness measured by heart-carotid PWV was associated with greater β-amyloid deposition in the brain defined by positron emission tomography imaging, and carotid femoral PWV was associated with lower brain volumes and with higher WMH burden.[81]
  - FHS investigators also previously demonstrated arterial stiffness is related to brain aging, with structural brain abnormalities and progression of these abnormalities as occur in AD.[82–85]

### *FMD and CVD*

- In a meta-analysis of 13 studies involving 11 516 individuals without established CVD with a mean

follow-up duration of 2 to 7.2 years and adjusted for age, sex, and risk factors, a multivariate RR of 0.93 (95% CI, 0.90–0.96) for CVD per 1% increase in brachial FMD was observed.[86]

### *Comparison of Measures of Subclinical Atherosclerosis*

- CAC provides a particularly strong prognostic value in predicting CHD and CVD events among markers of subclinical atherosclerosis. In 1330 intermediate-risk individuals in MESA, CAC provided the highest incremental improvement over the FRS (0.784 for both CAC and FRS versus 0.623 for FRS alone), as well as the greatest net reclassification improvement (0.659) compared with other subclinical markers, including family history, ABI, IMT, and CRP.[87] Similar findings also were noted in the Rotterdam Study, in which addition of CAC score had the largest improvement in risk prediction among 12 CHD risk markers.[88]
  - In addition, in MESA, the values of 12 negative markers were compared for all and hard CHD and for all CVD events over the 10-year follow-up.[89] After accounting for CVD risk factors, absence of CAC had the strongest negative predictive value, with an adjusted mean diagnostic likelihood ratio of 0.41 (SD, 0.12) for all CHD and 0.54 (SD, 0.12) for CVD, followed by carotid IMT <25th percentile (diagnostic likelihood ratio, 0.65 [SD, 0.04] and 0.75 [SD, 0.04], respectively).

## Subclinical Atherosclerosis and Healthy Lifestyle/Preventive Medications

- CAC has been examined in multiple studies for its potential to identify those most likely and not likely to benefit from pharmacological treatment for the primary prevention of CVD.
  - CAC identifies those most likely to benefit from statin treatment across the spectrum of risk profiles with an appropriate $NNT_5$: The estimated $NNT_5$ for preventing 1 CVD event across dyslipidemia categories in the MESA cohort ranged from 23 to 30 in those with CAC ≥100.[90] A very high $NNT_5$ of 186 and 222 was estimated to prevent 1 CHD event in the absence of CAC among those with 10-year FRS of 11% to 20% and >20%, respectively. The respective estimated $NNT_5$ was as low as 36 and 50 with the presence of a very high CAC score (>300) among those with a 10-year FRS of 0% to 6% and 6% to 10%, respectively.[91]
  - Similarly, CAC testing has identified individuals who might derive the highest net benefit with aspirin therapy: In MESA, among aspirin-naive participants <70 years of age who were not at high risk for bleeding (n=3540), CAC ≥100 and CAC ≥400 identified individuals with an $NNT_5$ lower than the number needed to harm (for CAC ≥100, $NNT_5$=140 versus $NNH_5$=518).[92] In individuals with CAC=0, the $NNT_5$ of 1190 was much higher than the $NNH_5$ of 567. Similarly, in the Dallas Heart Study, among individuals at lower bleeding risk, CAC ≥100 identified individuals who would tend to have net benefit, but only if 10-year ASCVD risk was ≥5%.[93] In individuals at higher bleeding risk, net harm from aspirin was observed regardless of CAC and ASCVD risk.
  - In a microsimulation model of 1083 individuals with a family history of premature CAD, compared with traditional risk factor–based prediction alone, use of CAC scanning was more costly ($145) and more effective (0.0097 QALY) with an incremental cost-effective ratio of $15 014/QALY.[94] The incremental cost-effective ratio improved in the male, >60 years of age, and ≥7.5% 10-year risk subgroups, whereas CAC was not cost-effective in individuals with <5% 10-year risk or those 40 to 50 years of age.
- Optimal lifestyle habits in youth and adulthood are associated with lower subclinical atherosclerosis:
  - In overweight and obese children 6 to 13 years of age, greater nut consumption was independently associated with lower carotid IMT (β=0.135 mm; *P*=0.009).[95]
  - In a cohort of older females, a diet high in vegetables, particularly cruciferous vegetables, was associated with lower carotid IMT.[96] Consuming ≥3 servings of vegetables each day was associated with a ≈5% lower amount of carotid atherosclerosis compared with consuming <2 servings of vegetables.
  - In SWAN, healthier lifestyle, including self-reported abstinence from smoking, healthy diet, and PA, in females during midlife was associated with lower carotid IMT.[97] Similar results of lifestyle habits, including Mediterranean diet, abstinence from smoking, and moderate alcohol intake, were associated with lower subclinical atherosclerosis in nearly 2000 individuals in the Spanish AWHS.[98]
  - In the FHS, higher midlife-estimated cardiorespiratory fitness was associated with lower IMT (B=–0.12 mm [SE, 0.05 mm]) and aortic stiffness measured by carotid-femoral PWV (B=–11.13 ms/m [SE, 1.33 ms/m]).[99]

**Table 20-1. Association of Degree of CAC or Carotid Plaque With Incident CVD at the 3-Year Follow-Up in 5808 Asymptomatic Adults in the BioImage Study**

| | No CAC or tertile 1 | CAC tertile 2 | CAC tertile 3 |
|---|---|---|---|
| No carotid plaque or tertile 1 | 0.5 | 0.9 | 1.4 |
| Carotid plaque tertile 2 | 1.4 | 0.9 | 3.1 |
| Carotid plaque tertile 3 | 1.2 | 3 | 4.2 |

Numbers represent cumulative incidence (%) of CVD.

CAC indicates coronary artery calcification; and CVD, cardiovascular death, myocardial infarction, and ischemic stroke.

Source: Data derived from Baber et al.[57]

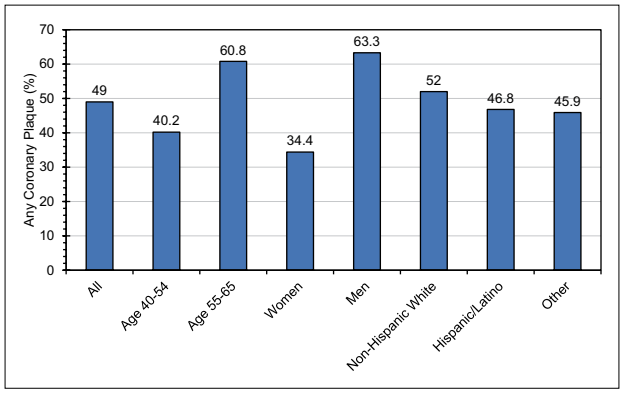



**Chart 20-1. Presence of any coronary plaque by CCTA in an asymptomatic US population of 2359 individuals in the Miami Heart Study at Baptist Health South Florida, 2015 to 2018.**

CCTA indicates coronary CT angiography.

Source: Data derived from Nasir et al.[100]

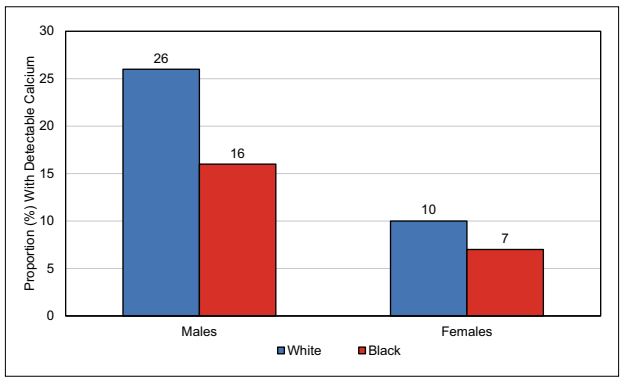



**Chart 20-2. Prevalence (percent) of detectable CAC by sex and race among 19 725 asymptomatic individuals 30 to 45 years of age without known ASCVD pooled from CARDIA (1995–2001), the CAC Consortium (1992–2011), and the Walter Reed Cohort (1997–2009).**

ASCVD indicates atherosclerotic cardiovascular disease; CAC, coronary artery calcification; and CARDIA, Coronary Artery Risk Development in Young Adults.

Source: Data derived from Javaid et al.[13]

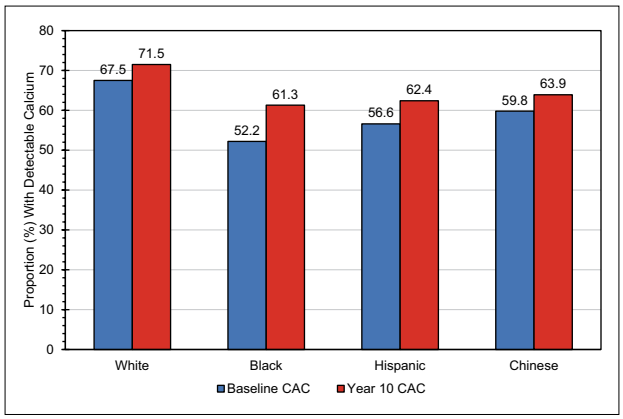



**Chart 20-3. Prevalence by ethnicity of detectable CAC at baseline (2000–2002) and year 10 (2010–2012) among US adults 55 to 84 years of age without CVD in MESA.**

CAC indicates coronary artery calcification; CVD, cardiovascular disease; and MESA, Multi-Ethnic Study of Atherosclerosis.

Source: Data derived from Bild et al.[5,14]

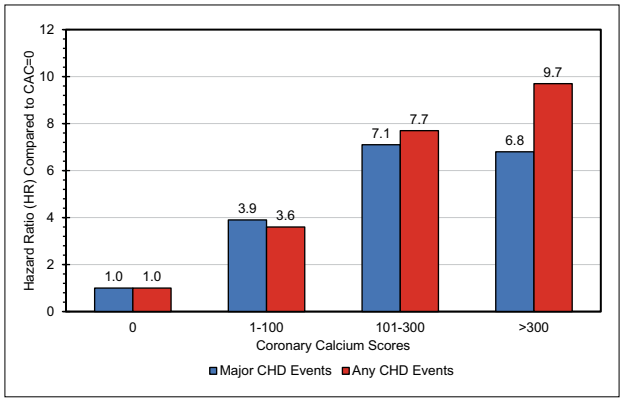



**Chart 20-4. HRs for CHD events associated with CAC scores: US adults 45 to 84 years of age (reference group, CAC=0) in MESA, baseline examination 2000 to 2002.**

Baseline examination in 2000 to 2002 with median of 3.9 years of follow-up (maximum, 5.3 years). All HRs, $P<0.0001$. Major CHD events included MI and death attributable to CHD; any CHD events included major CHD events plus definite angina or definite or probable angina followed by revascularization.

CAC indicates coronary artery calcification; CHD, coronary heart disease; HR, hazard ratio; MESA, Multi-Ethnic Study of Atherosclerosis; and MI, myocardial infarction.

Source: Data derived from Detrano et al.[15]

## REFERENCES


1. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published corrections appear in *Circulation*. 2019;139:e1182–e1186 and *Circulation*. 2023;148:e5]. *Circulation*. 2019;139:e1082–e1143. doi: 10.1161/CIR.0000000000000625
2. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published corrections appear in *Circulation*. 2019;140:e649–e650, *Circulation*. 2020;141:e60, and *Circulation*. 2020;141:e774]. *Circulation*. 2019;140:e596–e646. doi: 10.1161/CIR.0000000000000678
3. Orringer CE, Blaha MJ, Blankstein R, Budoff MJ, Goldberg RB, Gill EA, Maki KC, Mehta L, Jacobson TA. The National Lipid Association scientific statement on coronary artery calcium scoring to guide preventive strategies for ASCVD risk reduction. *J Clin Lipidol*. 2021;15:33–60. doi: 10.1016/j.jacl.2020.12.005
4. Gulati M, Levy PD, Mukherjee D, Amsterdam E, Bhatt DL, Birtcher KK, Blankstein R, Boyd J, Bullock-Palmer RP, Conejo T, et al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR guideline for the evaluation and diagnosis of chest pain: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2021;144:e368–e454. doi: 10.1161/CIR.0000000000001030
5. Bild DE, Detrano R, Peterson D, Guerci A, Liu K, Shahar E, Ouyang P, Jackson S, Saad MF. Ethnic differences in coronary calcification: the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation*. 2005;111:1313–1320. doi: 10.1161/01.CIR.0000157730.94423.4B
6. Kaplan H, Thompson RC, Trumble BC, Wann LS, Allam AH, Beheim B, Frohlich B, Sutherland ML, Sutherland JD, Stieglitz J, et al. Coronary atherosclerosis in indigenous South American Tsimane: a cross-sectional cohort study. *Lancet*. 2017;389:1730–1739. doi: 10.1016/S0140-6736(17)30752-3
7. Dzaye O, Razavi AC, Michos ED, Mortensen MB, Dardari ZA, Nasir K, Osei AD, Peng AW, Blankstein R, Page JH, et al. Coronary artery calcium scores indicating secondary prevention level risk: findings from the CAC Consortium and FOURIER trial. *Atherosclerosis*. 2022;347:70–76. doi: 10.1016/j.atherosclerosis.2022.02.006
8. Reis JP, Allen NB, Bancks MP, Carr JJ, Lewis CE, Lima JA, Rana JS, Gidding SS, Schreiner PJ. Duration of diabetes and prediabetes during adulthood and subclinical atherosclerosis and cardiac dysfunction in middle age: the CARDIA study. *Diabetes Care*. 2018;41:731–738. doi: 10.2337/dc17-2233
9. Sederholm Lawesson S, Swahn E, Pihlsgård M, Andersson T, Angerås O, Bacsovics Brolin E, Bergdahl E, Blomberg M, Christersson C, Gonçalves I, et al. Association between history of adverse pregnancy outcomes and coronary artery disease assessed by coronary computed tomography angiography. *JAMA*. 2023;329:393–404. doi: 10.1001/jama.2022.24093
10. Kowall B, Lehmann N, Mahabadi AA, Moebus S, Erbel R, Jockel KH, Stang A. Associations of metabolically healthy obesity with prevalence and progression of coronary artery calcification: results from the Heinz Nixdorf Recall Cohort Study. *Nutr Metab Cardiovasc Dis*. 2019;29:228–235. doi: 10.1016/j.numecd.2018.11.002
11. Verweij SL, de Ronde MWJ, Verbeek R, Boekholdt SM, Planken RN, Stroes ESG, Pinto-Sietsma SJ. Elevated lipoprotein(a) levels are associated with coronary artery calcium scores in asymptomatic individuals with a family history of premature atherosclerotic cardiovascular disease. *J Clin Lipidol*. 2018;12:597–603.e1. doi: 10.1016/j.jacl.2018.02.007
12. Soares C, Samara A, Yuyun MF, Echouffo-Tcheugui JB, Masri A, Samara A, Morrison AR, Lin N, Wu WC, Erqou S. Coronary artery calcification and plaque characteristics in people living with HIV: a systematic review and meta-analysis. *J Am Heart Assoc*. 2021;10:e019291. doi: 10.1161/JAHA.120.019291
13. Javaid A, Dardari ZA, Mitchell JD, Whelton SP, Dzaye O, Lima JAC, Lloyd-Jones DM, Budoff M, Nasir K, Berman DS, et al. Distribution of coronary artery calcium by age, sex, and race among patients 30-45 years old. *J Am Coll Cardiol*. 2022;79:1873–1886. doi: 10.1016/j.jacc.2022.02.051
14. Bild DE, McClelland R, Kaufman JD, Blumenthal R, Burke GL, Carr JJ, Post WS, Register TC, Shea S, Szklo M. Ten-year trends in coronary calcification in individuals without clinical cardiovascular disease in the multi-ethnic study of atherosclerosis. *PLoS One*. 2014;9:e94916. doi: 10.1371/journal.pone.0094916
15. Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR, Liu K, Shea S, Szklo M, Bluemke DA, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med*. 2008;358:1336–1345. doi: 10.1056/NEJMoa072100
16. Javaid A, Mitchell JD, Villines TC. Predictors of coronary artery calcium and long-term risks of death, myocardial infarction, and stroke in young adults. *J Am Heart Assoc*. 2021;10:e022513. doi: 10.1161/JAHA.121.022513
17. Peng AW, Dardari ZA, Blaha MJ. Response by Peng et al to letter regarding article, "very high coronary artery calcium (≥1000) and association with cardiovascular disease events, non-cardiovascular disease outcomes, and mortality: results from MESA." *Circulation*. 2021;144:e275–e276. doi: 10.1161/CIRCULATIONAHA.121.056534
18. Peng AW, Mirbolouk M, Orimoloye OA, Osei AD, Dardari Z, Dzaye O, Budoff MJ, Shaw L, Miedema MD, Rumberger J, et al. Long-term all-cause and cause-specific mortality in asymptomatic patients with CAC ≥ 1,000: results from the CAC Consortium. *JACC Cardiovasc Imaging*. 2020;13:83–93. doi: 10.1016/j.jcmg.2019.02.005
19. Mehta A, Vasquez N, Ayers CR, Patel J, Hooda A, Khera A, Blumenthal RS, Shapiro MD, Rodriguez CJ, Tsai MY, et al. Independent association of lipoprotein(a) and coronary artery calcification with atherosclerotic cardiovascular risk. *J Am Coll Cardiol*. 2022;79:757–768. doi: 10.1016/j.jacc.2021.11.058
20. Budoff MJ, Young R, Lopez VA, Kronmal RA, Nasir K, Blumenthal RS, Detrano RC, Bild DE, Guerci AD, Liu K, et al. Progression of coronary calcium and incident coronary heart disease events: MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol*. 2013;61:1231–1239. doi: 10.1016/j.jacc.2012.12.035
21. Subramanya V, Zhao D, Ouyang P, Ying W, Vaidya D, Ndumele CE, Heckbert SR, Budoff MJ, Post WS, Michos ED. Association of endogenous sex hormone levels with coronary artery calcium progression among post-menopausal women in the Multi-Ethnic Study of Atherosclerosis (MESA). *J Cardiovasc Comput Tomogr*. 2019;13:41–47. doi: 10.1016/j.jcct.2018.09.010
22. Reddy NM, Mayne SL, Pool LR, Gordon-Larsen P, Carr JJ, Terry JG, Kershaw KN. Exposure to neighborhood-level racial residential segregation in young adulthood to midlife and incident subclinical atherosclerosis in Black adults: the Coronary Artery Risk Development in Young Adults study. *Circ Cardiovasc Qual Outcomes*. 2022;15:e007986. doi: 10.1161/CIRCOUTCOMES.121.007986
23. Bertisch SM, Reid M, Lutsey PL, Kaufman JD, McClelland R, Patel SR, Redline S. Gender differences in the association of insomnia symptoms and coronary artery calcification in the Multi-Ethnic Study of Atherosclerosis. *Sleep*. 2021;44:zsab116. doi: 10.1093/sleep/zsab116
24. Janssen I, Powell LH, Everson-Rose SA, Hollenberg SM, El Khoudary SR, Matthews KA. Psychosocial well-being and progression of coronary artery calcification in midlife women. *J Am Heart Assoc*. 2022;11:e023937. doi: 10.1161/JAHA.121.023937
25. Mamudu HM, Jones A, Paul TK, Osedeme F, Stewart D, Alamian A, Wang L, Orimaye S, Bledsoe J, Poole A, et al. The co-existence of diabetes and subclinical atherosclerosis in rural central Appalachia: do residential characteristics matter? *J Diabetes Complications*. 2021;35:107851. doi: 10.1016/j.jdiacomp.2021.107851
26. Huynh Q, Marwick TH, Venkataraman P, Knibbs LD, Johnston FH, Negishi K. Long-term exposure to ambient air pollution is associated with coronary artery calcification among asymptomatic adults. *Eur Heart J Cardiovasc Imaging*. 2021;22:922–929. doi: 10.1093/ehjci/jeaa073
27. Howard DPJ, Gaziano L, Rothwell PM; Oxford Vascular Study. Risk of stroke in relation to degree of asymptomatic carotid stenosis: a population-based cohort study, systematic review, and meta-analysis. *Lancet Neurol*. 2021;20:193–202. doi: 10.1016/S1474-4422(20)30484-1
28. Urbina EM, Srinivasan SR, Tang R, Bond M, Kieltyka L, Berenson GS. Impact of multiple coronary risk factors on the intima-media thickness of different segments of carotid artery in healthy young adults (the Bogalusa Heart Study). *Am J Cardiol*. 2002;90:953–958. doi: 10.1016/s0002-9149(02)02660-7
29. Manolio TA, Arnold AM, Post W, Bertoni AG, Schreiner PJ, Sacco RL, Saad MF, Detrano RL, Szklo M. Ethnic differences in the relationship of carotid atherosclerosis to coronary calcification: the Multi-Ethnic Study of Atherosclerosis. *Atherosclerosis*. 2008;197:132–138. doi: 10.1016/j.atherosclerosis.2007.02.030
30. Li S, Chen W, Srinivasan SR, Bond MG, Tang R, Urbina EM, Berenson GS. Childhood cardiovascular risk factors and carotid vascular

changes in adulthood: the Bogalusa Heart Study [published correction appears in *JAMA*. 2003;290:2943]. *JAMA*. 2003;290:2271–2276. doi: 10.1001/jama.290.17.2271
31. Juonala M, Viikari JS, Kahonen M, Taittonen L, Laitinen T, Hutri-Kahonen N, Lehtimaki T, Jula A, Pietikainen M, Jokinen E, et al. Life-time risk factors and progression of carotid atherosclerosis in young adults: the Cardiovascular Risk in Young Finns Study. *Eur Heart J*. 2010;31:1745–1751. doi: 10.1093/eurheartj/ehq141
32. Yan Y, Li S, Liu Y, Guo Y, Fernandez C, Bazzano L, He J, Chen W. Associations between life-course lipid trajectories and subclinical atherosclerosis in midlife. *JAMA Netw Open*. 2022;5:e2234862. doi: 10.1001/jamanetworkopen.2022.34862
33. Allen NB, Krefman AE, Labarthe D, Greenland P, Juonala M, Kähönen M, Lehtimäki T, Day RS, Bazzano LA, Van Horn LV, et al. Cardiovascular health trajectories from childhood through middle age and their association with subclinical atherosclerosis. *JAMA Cardiol*. 2020;5:557–566. doi: 10.1001/jamacardio.2020.0140
34. Pussinen PJ, Paju S, Koponen J, Viikari JSA, Taittonen L, Laitinen T, Burgner DP, Kähönen M, Hutri-Kähönen N, Raitakari OT, et al. Association of childhood oral infections with cardiovascular risk factors and subclinical atherosclerosis in adulthood. *JAMA Netw Open*. 2019;2:e192523. doi: 10.1001/jamanetworkopen.2019.2523
35. Dominguez F, Fuster V, Fernandez-Alvira JM, Fernandez-Friera L, Lopez-Melgar B, Blanco-Rojo R, Fernandez-Ortiz A, Garcia-Pavia P, Sanz J, Mendiguren JM, et al. Association of sleep duration and quality with subclinical atherosclerosis. *J Am Coll Cardiol*. 2019;73:134–144. doi: 10.1016/j.jacc.2018.10.060
36. Rossello X, Raposeiras-Roubin S, Oliva B, Sánchez-Cabo F, García-Ruíz JM, Caimari F, Mendiguren JM, Lara-Pezzi E, Bueno H, Fernández-Friera L, et al. Glycated hemoglobin and subclinical atherosclerosis in people without diabetes. *J Am Coll Cardiol*. 2021;77:2777–2791. doi: 10.1016/j.jacc.2021.03.335
37. Hasslöf H, Molnár P, Andersson EM, Spanne M, Gustafsson S, Stroh E, Engström G, Stockfelt L. Long-term exposure to air pollution and atherosclerosis in the carotid arteries in the Malmö Diet and Cancer cohort. *Environ Res*. 2020;191:110095. doi: 10.1016/j.envres.2020.110095
38. Nonterah EA, Crowther NJ, Klipstein-Grobusch K, Oduro AR, Kavousi M, Agongo G, Anderson TJ, Asiki G, Boua PR, Choma SSR, et al; H3Africa AWI-Gen, USE-IMT Collaborative Study Group. Racial and ethnic differences in the association between classical cardiovascular risk factors and common carotid intima-media thickness: an individual participant data meta-analysis. *J Am Heart Assoc*. 2022;11:e023704. doi: 10.1161/JAHA.121.023704
39. Iglesies-Grau J, Fernandez-Jimenez R, Diaz-Munoz R, Jaslow R, de Cos-Gandoy A, Santos-Beneit G, Hill CA, Turco A, Kadian-Dodov D, Kovacic JC, et al. Subclinical atherosclerosis in young, socioeconomically vulnerable Hispanic and non-Hispanic Black adults. *J Am Coll Cardiol*. 2022;80:219–229. doi: 10.1016/j.jacc.2022.04.054
40. Wendell CR, Waldstein SR, Evans MK, Zonderman AB. Distributions of subclinical cardiovascular disease in a socioeconomically and racially diverse sample. *Stroke*. 2017;48:850–856. doi: 10.1161/STROKEAHA.116.015267
41. Nuotio J, Vahamurto L, Pahkala K, Magnussen CG, Hutri-Kahonen N, Kahonen M, Laitinen T, Taittonen L, Tossavainen P, Lehtimaki T, et al. CVD risk factors and surrogate markers: urban-rural differences. *Scand J Public Health*. 2020;48:752–761. doi: 10.1177/1403494819869816
42. Tedesco CC, Veglia F, de Faire U, Kurl S, Smit AJ, Rauramaa R, Giral P, Amato M, Bonomi A, Ravani A, et al; IMPROVE Study Group. Association of lifelong occupation and educational level with subclinical atherosclerosis in different European regions: results from the IMPROVE study. *Atherosclerosis*. 2018;269:129–137. doi: 10.1016/j.atherosclerosis.2017.12.023
43. Kestila P, Magnussen CG, Viikari JS, Kahonen M, Hutri-Kahonen N, Taittonen L, Jula A, Loo BM, Pietikainen M, Jokinen E, et al. Socioeconomic status, cardiovascular risk factors, and subclinical atherosclerosis in young adults: the Cardiovascular Risk in Young Finns Study. *Arterioscler Thromb Vasc Biol*. 2012;32:815–821. doi: 10.1161/ATVBAHA.111.241182
44. Cundiff JM, Kamarck TW, Muldoon MF, Marsland AL, Manuck SB. Expectations of respect and appreciation in daily life and associations with subclinical cardiovascular disease. *Health Psychol*. 2023;42:53–62. doi: 10.1037/hea0001255
45. Connors K, Flores-Torres MH, Cortés-Valencia A, Barrientos-Gutiérrez T, Cantú-Brito C, Rodriguez B, Lajous M, Valdimarsdóttir U, Catzin-Kuhlmann A. Serious financial difficulties, psychological stress, and subclinical cardiovascular disease in Mexican women. *Ann Epidemiol*. 2022;71:38–43. doi: 10.1016/j.annepidem.2022.03.001
46. Camelo LV, Machado AV, Chor D, Griep RH, Mill JG, Brant LCC, Barreto SM. Racial discrimination is associated with greater arterial stiffness and carotid intima-media thickness: the ELSA-Brasil study. *Ann Epidemiol*. 2022;72:40–47. doi: 10.1016/j.annepidem.2022.03.009
47. Guirguis-Blake JM, Webber EM, Coppola EL. Screening for asymptomatic carotid artery stenosis in the general population: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2021;325:487–489. doi: 10.1001/jama.2020.20364
48. Chen LY, Leening MJ, Norby FL, Roetker NS, Hofman A, Franco OH, Pan W, Polak JF, Witteman JC, Kronmal RA, et al. Carotid intima-media thickness and arterial stiffness and the risk of atrial fibrillation: the Atherosclerosis Risk in Communities (ARIC) Study, Multi-Ethnic Study of Atherosclerosis (MESA), and the Rotterdam Study. *J Am Heart Assoc*. 2016;5:e002907. doi: 10.1161/JAHA.115.002907
49. Polak JF, Pencina MJ, O'Leary DH, D'Agostino RB. Common carotid artery intima-media thickness progression as a predictor of stroke in Multi-Ethnic Study of Atherosclerosis. *Stroke*. 2011;42:3017–3021. doi: 10.1161/STROKEAHA.111.625186
50. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. *N Engl J Med*. 1999;340:14–22. doi: 10.1056/NEJM199901073400103
51. Effoe VS, Rodriguez CJ, Wagenknecht LE, Evans GW, Chang PP, Mirabelli MC, Bertoni AG. Carotid intima-media thickness is associated with incident heart failure among middle-aged Whites and Blacks: the Atherosclerosis Risk in Communities study. *J Am Heart Assoc*. 2014;3:e000797. doi: 10.1161/JAHA.114.000797
52. Nambi V, Chambless L, Folsom AR, He M, Hu Y, Mosley T, Volcik K, Boerwinkle E, Ballantyne CM. Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease risk: the ARIC (Atherosclerosis Risk In Communities) study. *J Am Coll Cardiol*. 2010;55:1600–1607. doi: 10.1016/j.jacc.2009.11.075
53. Willeit P, Tschiderer L, Allara E, Reuber K, Seekircher L, Gao L, Liao X, Lonn E, Gerstein HC, Yusuf S, et al; PROG-IMT and the Proof-ATHERO Study Groups. Carotid intima-media thickness progression as surrogate marker for cardiovascular risk: meta-analysis of 119 clinical trials involving 100 667 patients. *Circulation*. 2020;142:621–642. doi: 10.1161/CIRCULATIONAHA.120.046361
54. Den Ruijter HM, Peters SA, Anderson TJ, Britton AR, Dekker JM, Eijkemans MJ, Engstrom G, Evans GW, de Graaf J, Grobbee DE, et al. Common carotid intima-media thickness measurements in cardiovascular risk prediction: a meta-analysis. *JAMA*. 2012;308:796–803. doi: 10.1001/jama.2012.9630
55. Polak JF, Szklo M, O'Leary DH. Carotid intima-media thickness score, positive coronary artery calcium score, and incident coronary heart disease: the Multi-Ethnic Study of Atherosclerosis. *J Am Heart Assoc*. 2017;6:e004612. doi: 10.1161/JAHA.116.004612
56. Georgiopoulos G, Mavraganis G, Delialis D, Georgiou S, Aivalioti E, Patras R, Petropoulos I, Dimopoulou MA, Angelidakis L, Sianis A, et al. Carotid ultrasonography improves residual risk stratification in guidelines-defined high cardiovascular risk patients. *Eur J Prev Cardiol*. 2022;29:1773–1784. doi: 10.1093/eurjpc/zwac095
57. Baber U, Mehran R, Sartori S, Schoos MM, Sillesen H, Muntendam P, Garcia MJ, Gregson J, Pocock S, Falk E, et al. Prevalence, impact, and predictive value of detecting subclinical coronary and carotid atherosclerosis in asymptomatic adults: the BioImage study. *J Am Coll Cardiol*. 2015;65:1065–1074. doi: 10.1016/j.jacc.2015.01.017
58. Bos D, Arshi B, van den Bouwhuijsen QJA, Ikram MK, Selwaness M, Vernooij MW, Kavousi M, van der Lugt A. Atherosclerotic carotid plaque composition and incident stroke and coronary events. *J Am Coll Cardiol*. 2021;77:1426–1435. doi: 10.1016/j.jacc.2021.01.038
59. Gepner AD, Young R, Delaney JA, Tattersall MC, Blaha MJ, Post WS, Gottesman RF, Kronmal R, Budoff MJ, Burke GL, et al. Comparison of coronary artery calcium presence, carotid plaque presence, and carotid intima-media thickness for cardiovascular disease prediction in the Multi-Ethnic Study of Atherosclerosis. *Circ Cardiovasc Imaging*. 2015;8:e002262. doi: 10.1161/CIRCIMAGING.114.002262
60. Kokubo Y, Watanabe M, Higashiyama A, Nakao YM, Nakamura F, Miyamoto Y. Impact of intima-media thickness progression in the common carotid arteries on the risk of incident cardiovascular disease in the Suita study. *J Am Heart Assoc*. 2018;7:e007720. doi: 10.1161/JAHA.117.007720
61. Cho I, Al'Aref SJ, Berger A, Hartaigh B, Gransar H, Valenti V, Lin FY, Achenbach S, Berman DS, Budoff MJ, et al. Prognostic value of coronary computed tomographic angiography findings in asymptomatic individuals: a 6-year follow-up from the prospective multicentre

international CONFIRM study. *Eur Heart J*. 2018;39:934–941. doi: 10.1093/eurheartj/ehx774
62. Sánchez-Cabo F, Rossello X, Fuster V, Benito F, Manzano JP, Silla JC, Fernández-Alvira JM, Oliva B, Fernández-Friera L, López-Melgar B, et al. Machine learning improves cardiovascular risk definition for young, asymptomatic individuals. *J Am Coll Cardiol*. 2020;76:1674–1685. doi: 10.1016/j.jacc.2020.08.017
63. Zhao J, Cheema FA, Bremner JD, Goldberg J, Su S, Snieder H, Maisano C, Jones L, Javed F, Murrah N, et al. Heritability of carotid intima-media thickness: a twin study. *Atherosclerosis*. 2008;197:814–820. doi: 10.1016/j.atherosclerosis.2007.07.030
64. Peyser PA, Bielak LF, Chu JS, Turner ST, Ellsworth DL, Boerwinkle E, Sheedy PF 2nd. Heritability of coronary artery calcium quantity measured by electron beam computed tomography in asymptomatic adults. *Circulation*. 2002;106:304–308. doi: 10.1161/01.cir.0000022664.21832.5d
65. Cassidy-Bushrow AE, Bielak LF, Sheedy PF 2nd, Turner ST, Kullo IJ, Lin X, Peyser PA. Coronary artery calcification progression is heritable. *Circulation*. 2007;116:25–31. doi: 10.1161/CIRCULATIONAHA.106.658583
66. Natarajan P, Bis J, Bielak L, Cox A, Dorr M, Feitosa M, Franceschini N, Guo X, Hwang SJ, Isaacs A, et al; CHARGE Consortium. Multiethnic exome-wide association study of subclinical atherosclerosis. *Circ Cardiovasc Genet*. 2016;9:511–520. doi: 10.1161/CIRCGENETICS.116.001572
67. Divers J, Palmer ND, Langefeld CD, Brown WM, Lu L, Hicks PJ, Smith SC, Xu J, Terry JG, Register TC, et al. Genome-wide association study of coronary artery calcified atherosclerotic plaque in African Americans with type 2 diabetes. *BMC Genet*. 2017;18:105. doi: 10.1186/s12863-017-0572-9
68. Wojczynski MK, Li M, Bielak LF, Kerr KF, Reiner AP, Wong ND, Yanek LR, Qu L, White CC, Lange LA, et al. Genetics of coronary artery calcification among African Americans, a meta-analysis. *BMC Med Genet*. 2013;14:75. doi: 10.1186/1471-2350-14-75
69. Vargas JD, Manichaikul A, Wang XQ, Rich SS, Rotter JI, Post WS, Polak JF, Budoff MJ, Bluemke DA. Common genetic variants and subclinical atherosclerosis: the Multi-Ethnic Study of Atherosclerosis (MESA). *Atherosclerosis*. 2016;245:230–236. doi: 10.1016/j.atherosclerosis.2015.11.034
70. Wai Yeung M, Wang S, van de Vegte YJ, Borisov O, van Setten J, Snieder H, Verweij N, Said MA, van der Harst P. Twenty-five novel loci for carotid intima-media thickness: a genome-wide association study in >45 000 individuals and meta-analysis of >100 000 individuals. *Arterioscler Thromb Vasc Biol*. 2022;42:484–501. doi: 10.1161/ATVBAHA.121.317007
71. Boua PR, Brandenburg JT, Choudhury A, Sorgho H, Nonterah EA, Agongo G, Asiki G, Micklesfield L, Choma S, Gomez-Olive FX, et al; AWI-Gen Study. Genetic associations with carotid intima-media thickness link to atherosclerosis with sex-specific effects in sub-Saharan Africans. *Nat Commun*. 2022;13:855. doi: 10.1038/s41467-022-28276-x
72. Gan W, Bragg F, Walters RG, Millwood IY, Lin K, Chen Y, Guo Y, Vaucher J, Bian Z, Bennett D, et al; China Kadoorie Biobank Collaborative Group. Genetic predisposition to type 2 diabetes and risk of subclinical atherosclerosis and cardiovascular diseases among 160,000 Chinese adults. *Diabetes*. 2019;68:2155–2164. doi: 10.2337/db19-0224
73. Mosley JD, Benson MD, Smith JG, Melander O, Ngo D, Shaffer CM, Ferguson JF, Herzig MS, McCarty CA, Chute CG, et al. Probing the virtual proteome to identify novel disease biomarkers. *Circulation*. 2018;138:2469–2481. doi: 10.1161/CIRCULATIONAHA.118.036063
74. Takashi H, Katsuyuki M, Takayoshi O, Hisatomi A, Akira F, Atsushi S, Aya K, Maryam Z, Naoyuki T, Seiko O, et al. Home blood pressure variability and subclinical atherosclerosis in multiple vascular beds: a population-based study. *J Hypertens*. 2018;36:2193–2203. doi: 10.1097/HJH.0000000000001810
75. Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, Foster E, Hlatky MA, Hodgson JM, Kushner FG, et al; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2010;122:e584–e636. doi: 10.1161/CIR.0b013e3182051b4c
76. Rodilla E, Lopez-Carmona MD, Cortes X, Cobos-Palacios L, Canales S, Saez MC, Campos Escudero S, Rubio-Rivas M, Diez Manglano J, Freire Castro SJ, et al; SEMI-COVID-19 Network. Impact of arterial stiffness on all-cause mortality in patients hospitalized with COVID-19 in Spain. *Hypertension*. 2021;77:856–867. doi: 10.1161/HYPERTENSIONAHA.120.16563
77. Willum Hansen T, Staessen JA, Torp-Pedersen C, Rasmussen S, Thijs L, Ibsen H, Jeppesen J. Prognostic value of aortic pulse wave velocity as index of arterial stiffness in the general population. *Circulation*. 2006;113:664–670. doi: 10.1161/circulationaha.105.579342
78. Mitchell GF, Hwang SJ, Vasan RS, Larson MG, Pencina MJ, Hamburg NM, Vita JA, Levy D, Benjamin EJ. Arterial stiffness and cardiovascular events: the Framingham Heart Study. *Circulation*. 2010;121:505–511. doi: 10.1161/CIRCULATIONAHA.109.886655
79. Tripathi A, Benjamin EJ, Musani SK, Hamburg NM, Tsao CW, Saraswat A, Vasan RS, Mitchell GF, Fox ER. The association of endothelial function and tone by digital arterial tonometry with MRI left ventricular mass in African Americans: the Jackson Heart Study. *J Am Soc Hypertens*. 2017;11:258–264. doi: 10.1016/j.jash.2017.03.005
80. Lamballais S, Sajjad A, Leening MJG, Gaillard R, Franco OH, Mattace-Raso FUS, Jaddoe VWV, Roza SJ, Tiemeier H, Ikram MA. Association of blood pressure and arterial stiffness with cognition in 2 population-based child and adult cohorts. *J Am Heart Assoc*. 2018;7:e009847. doi: 10.1161/JAHA.118.009847
81. Hughes TM, Wagenknecht LE, Craft S, Mintz A, Heiss G, Palta P, Wong D, Zhou Y, Knopman D, Mosley TH, et al. Arterial stiffness and dementia pathology: Atherosclerosis Risk in Communities (ARIC)-PET Study. *Neurology*. 2018;90:e1248–e1256. doi: 10.1212/WNL.0000000000005259
82. Cooper LL, Himali JJ, Torjesen A, Tsao CW, Beiser A, Hamburg NM, DeCarli C, Vasan RS, Seshadri S, Pase MP, et al. Inter-relations of orthostatic blood pressure change, aortic stiffness, and brain structure and function in young adults. *J Am Heart Assoc*. 2017;6:e006206. doi: 10.1161/JAHA.117.006206
83. Maillard P, Mitchell GF, Himali JJ, Beiser A, Fletcher E, Tsao CW, Pase MP, Satizabal CL, Vasan RS, Seshadri S, et al. Aortic stiffness, increased white matter free water, and altered microstructural integrity: a continuum of injury. *Stroke*. 2017;48:1567–1573. doi: 10.1161/STROKEAHA.116.016321
84. Maillard P, Mitchell GF, Himali JJ, Beiser A, Tsao CW, Pase MP, Satizabal CL, Vasan RS, Seshadri S, DeCarli C. Effects of arterial stiffness on brain integrity in young adults from the Framingham Heart Study. *Stroke*. 2016;47:1030–1036. doi: 10.1161/STROKEAHA.116.012949
85. Tsao CW, Himali JJ, Beiser AS, Larson MG, DeCarli C, Vasan RS, Mitchell GF, Seshadri S. Association of arterial stiffness with progression of subclinical brain and cognitive disease. *Neurology*. 2016;86:619–626. doi: 10.1212/WNL.0000000000002368
86. Xu Y, Arora RC, Hiebert BM, Lerner B, Szwajcer A, McDonald K, Rigatto C, Komenda P, Sood MM, Tangri N. Non-invasive endothelial function testing and the risk of adverse outcomes: a systematic review and meta-analysis. *Eur Heart J Cardiovasc Imaging*. 2014;15:736–746. doi: 10.1093/ehjci/jet256
87. Yeboah J, McClelland RL, Polonsky TS, Burke GL, Sibley CT, O'Leary D, Carr JJ, Goff DC, Greenland P, Herrington DM. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. *JAMA*. 2012;308:788–795. doi: 10.1001/jama.2012.9624
88. Kavousi M, Elias-Smale S, Rutten JH, Leening MJ, Vliegenthart R, Verwoert GC, Krestin GP, Oudkerk M, de Maat MP, Leebeek FW, et al. Evaluation of newer risk markers for coronary heart disease risk classification: a cohort study. *Ann Intern Med*. 2012;156:438–444. doi: 10.7326/0003-4819-156-6-201203200-00006
89. Blaha MJ, Cainzos-Achirica M, Greenland P, McEvoy JW, Blankstein R, Budoff MJ, Dardari Z, Sibley CT, Burke GL, Kronmal RA, et al. Role of coronary artery calcium score of zero and other negative risk markers for cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation*. 2016;133:849–858. doi: 10.1161/CIRCULATIONAHA.115.018524
90. Martin SS, Blaha MJ, Blankstein R, Agatston A, Rivera JJ, Virani SS, Ouyang P, Jones SR, Blumenthal RS, Budoff MJ, et al. Dyslipidemia, coronary artery calcium, and incident atherosclerotic cardiovascular disease: implications for statin therapy from the Multi-Ethnic Study of Atherosclerosis. *Circulation*. 2014;129:77–86. doi: 10.1161/CIRCULATIONAHA.113.003625
91. Silverman MG, Blaha MJ, Krumholz HM, Budoff MJ, Blankstein R, Sibley CT, Agatston A, Blumenthal RS, Nasir K. Impact of coronary artery calcium on coronary heart disease events in individuals at the extremes of traditional risk factor burden: the Multi-Ethnic Study of Atherosclerosis. *Eur Heart J*. 2014;35:2232–2241. doi: 10.1093/eurheartj/eht508
92. Cainzos-Achirica M, Miedema MD, McEvoy JW, Al Rifai M, Greenland P, Dardari Z, Budoff M, Blumenthal RS, Yeboah J, Duprez DA, et al. Coronary artery calcium for personalized allocation of aspirin in primary prevention of cardiovascular disease in 2019: the MESA study (Multi-Ethnic Study of Atherosclerosis). *Circulation*. 2020;141:1541–1553. doi: 10.1161/CIRCULATIONAHA.119.045010
93. Ajufo E, Ayers CR, Vigen R, Joshi PH, Rohatgi A, de Lemos JA, Khera A. Value of coronary artery calcium scanning in association with the net benefit of aspirin in primary prevention of atherosclerotic cardiovascular disease. *JAMA Cardiol*. 2021;6:179–187. doi: 10.1001/jamacardio.2020.4939

94. Venkataraman P, Kawakami H, Huynh Q, Mitchell G, Nicholls SJ, Stanton T, Tonkin A, Watts GF, Marwick TH; CAUGHT-CAD Investigators. Cost-effectiveness of coronary artery calcium scoring in people with a family history of coronary disease. *JACC Cardiovasc Imaging*. 2021;14:1206–1217. doi: 10.1016/j.jcmg.2020.11.008
95. Aghayan M, Asghari G, Yuzbashian E, Dehghan P, Khadem Haghighian H, Mirmiran P, Javadi M. Association of nuts and unhealthy snacks with subclinical atherosclerosis among children and adolescents with overweight and obesity. *Nutr Metab*. 2019;16:23. doi: 10.1186/s12986-019-0350-y
96. Blekkenhorst LC, Bondonno CP, Lewis JR, Woodman RJ, Devine A, Bondonno NP, Lim WH, Zhu K, Beilin LJ, Thompson PL, et al. Cruciferous and total vegetable intakes are inversely associated with subclinical atherosclerosis in older adult women. *J Am Heart Assoc*. 2018;7:e008391. doi: 10.1161/JAHA.117.008391
97. Wang D, Jackson EA, Karvonen-Gutierrez CA, Elliott MR, Harlow SD, Hood MM, Derby CA, Sternfeld B, Janssen I, Crawford SL, et al. Healthy lifestyle during the midlife is prospectively associated with less subclinical carotid atherosclerosis: the Study of Women's Health Across the Nation. *J Am Heart Assoc*. 2018;7:e010405. doi: 10.1161/JAHA.118.010405
98. Uzhova I, Mateo-Gallego R, Moreno-Franco B, Molina-Montes E, Leon-Latre M, Casasnovas Lenguas JA, Civeira F, Peñalvo JL. The additive effect of adherence to multiple healthy lifestyles on subclinical atherosclerosis: insights from the AWHS. *J Clin Lipidol*. 2018;12:615–625. doi: 10.1016/j.jacl.2018.03.081
99. Lee J, Song RJ, Musa Yola I, Shrout TA, Mitchell GF, Vasan RS, Xanthakis V. Association of estimated cardiorespiratory fitness in midlife with cardiometabolic outcomes and mortality. *JAMA Netw Open*. 2021;4:e2131284. doi: 10.1001/jamanetworkopen.2021.31284
100. Nasir K, Cainzos-Achirica M, Valero-Elizondo J, Ali SS, Havistin R, Lakshman S, Blaha MJ, Blankstein R, Shapiro MD, Arias L, et al. Coronary atherosclerosis in an asymptomatic U.S. population: Miami Heart Study at Baptist Health South Florida. *JACC Cardiovasc Imaging*. 2022;15:1604–1618. doi: 10.1016/j.jcmg.2022.03.010

# 21. CORONARY HEART DISEASE, ACUTE CORONARY SYNDROME, AND ANGINA PECTORIS

***See Tables 21-1 through 21-3 and Charts 21-1 through 21-8***

Click here to return to the Table of Contents

Click here to return to the Abbreviations

## Coronary Heart Disease

### *ICD-9* 410 to 414, 429.2; *ICD-10* I20 to I25 (includes MI *ICD-10* I21 to I22).

#### *Prevalence*

***(See Tables 21-1 and 21-2 and Charts 21-1 through 21-4)***

- On the basis of data from NHANES 2017 to 2020,[1] an estimated 20.5 million Americans ≥20 years of age have CHD (Table 21-1). The prevalence of CHD was higher for males than females in all age groups (Chart 21-1).
- According to NHANES 2017 to 2020, total CHD prevalence is 7.1% in US adults ≥20 years of age. CHD prevalence is 8.7% for males and 5.8% for females. CHD prevalence by sex and ethnicity is shown in Table 21-1.
- Based on data from the NHIS 2018, the CHD prevalence estimates are 5.7% among White people, 5.4% among Black people, 8.6% among American Indian/Alaska Native people, and 4.4% among Asian people ≥18 years of age.[2]
- According to data from NHANES 2017 to 2020 (unpublished NHLBI tabulation),[1] the overall prevalence of MI is 3.2% in US adults ≥20 years of age. Males have a higher prevalence of MI than females for all age groups (Chart 21-2). Overall MI prevalence is 4.5% for males and 2.1% for females. MI prevalence by sex and ethnicity is shown in Table 21-1.
- According to data from NHANES 2017 to 2020,[1] the overall prevalence of angina is 3.9% in US adults ≥20 years of age (Table 21-2).
- Data from the BRFSS 2021 survey indicate that 4.0% of respondents had been told that they had had an MI. The highest age-adjusted prevalence was in West Virginia (5.6%), and the lowest was in Colorado (2.4%; Chart 21-3).[3]
- In the same survey in 2021, 3.8% of respondents had been told that they had angina or CHD. The highest age-adjusted prevalence was in West Virginia (5.7%), and the lowest was in Hawaii (2.0%; Chart 21-4).[3]

#### *Incidence*

- Approximately every 40 seconds, an American will have an MI (AHA computation based on incidence data from the ARIC study of the NHLBI[4]).
- On the basis of data tabulated by the NHLBI from the 2005 to 2014 ARIC study[4]:
  - Approximately 720 000 Americans will have a new coronary event (defined as first hospitalized MI or CHD death), and ≈335 000 will have a recurrent event.
  - The estimated annual incidence of MI is 605 000 new attacks and 200 000 recurrent attacks. Of these 805 000 first and recurrent events, it is estimated that 170 000 are silent (without significant symptoms).
  - Average age at first MI is 65.6 years for males and 72.0 years for females.
- After adjustment for social determinants of health and cardiovascular risk factors, Black males and females have similar risk for fatal CHD (ARIC, 0.67 [95% CI, 0.36–1.24]; REGARDS, 1.00 [95% CI, 0.54–1.85]) but lower risk for nonfatal CHD (ARIC, 0.70 [95% CI, 0.51–0.97]; REGARDS, 0.70 [95% CI, 0.46–1.06]) compared with White males and females.[5]

#### *Secular Trends*

- Among Medicare beneficiaries between 2002 and 2011, the rates of MI hospitalization declined from 1485 to 1122 per 100 000 person-years.[6]
  - The rates of MI as the primary reason for hospitalization decreased over time (from 1063 to 677 per 100 000 person-years between 2002 and 2011). The percentage of MIs that were attributable to a primary reason for hospitalization decreased from 72% to 60% between 2002 and 2011.
  - However, the rates of MI as a secondary reason for hospitalization increased (from 190 to 245 per 100 000 person-years). The percentage of MIs that were attributable to a secondary diagnosis increased from 28% to 40%.
- In Olmsted County, Minnesota, between 2003 and 2012, the annual incidence declined for both type 1 MI (from 202 to 84 per 100 000; $P<0.001$) and type 2 MI (from 130 to 78 per 100 000; $P=0.02$).[7]

The 2024 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2024. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

- According to data from inpatient and ambulatory databases from 4 states (Michigan, Maryland, New York, and Florida), population trends in PCI use were examined between January 2010 and December 2017. Among a cohort of 333 819 patients (32% female; mean age, 65.7 years [SD, 12.2 years]), 1 044 698 PCIs were performed: 57.1% were elective, and 42.9% were urgent. PCI rates declined from 260.2 to 232.8 per 100 000 (−10.5%; $P_{trend}$<0.001) between 2010 and 2017. In the same period, outpatient PCI rates increased from 33.8 to 66.7 per 100 000 (+97.1%; $P_{trend}$<0.001), whereas inpatient PCI rates declined from 226.4 to 166.2 per 100 000 (−26.6%; $P_{trend}$<0.001).[8]

### Admissions and Mortality Trends

- In England, AMI hospitalizations during the COVID-19 period (February 1–May 14, 2020; n=9325) declined >50% compared with the pre–COVID-19 period (February 1–May 14, 2019; n=20 310), with a corresponding increase in the incidence of OHCA (see Chapter 19 [Sudden Cardiac Arrest, Ventricular Arrhythmias, and Inherited Channelopathies]).[9] A similar multisite study in France observed a reduction in STEMI (IRR, 0.72 [95% CI, 0.62–0.85]) and NSTEMI (IRR, 0.64 [95% CI, 0.55–0.76]) when the 4 weeks before and after lockdown were compared.[10]
- In a cohort of 1533 patients admitted with AMI (STEMI and NSTEMI) in a large health system in Washington, DC, and Maryland between March 1, 2020, and June 30, 2020, 86 had confirmed COVID-19. Furthermore, 20.0% of patients (n=17) with COVID-19 underwent coronary angiography. Those with concomitant COVID-19 and AMI had higher in-hospital mortality (27.9%) than patients without COVID-19 in the same period (3.7%; $P$<0.001).[11]
- Among 21 738 patients with type 2 MI in the National Readmission Database, in-hospital mortality and 30-day readmission for patients with type 2 MI were 9.0% and 19.1%, respectively. AF, PAD, male sex, coagulopathy, and fluid/electrolyte imbalances were associated with higher in-hospital mortality. In addition, AF/flutter, carotid artery stenosis, diabetes, anemia, COPD, CKD, and history of MI were associated with higher odds of 30-day readmission.[12]
- An observational analysis of ED and inpatient data among patients with HF (n=21 262) or AMI (n=6165) from 12 hospital health systems across the St. Louis metropolitan area found that patient volume decreased for AMI during COVID-19 (6.1–6.6 events/d before COVID-19, 4.9–5.5 events/d during COVID-19; $P$<0.001).[13] However, the proportion of patients with STEMI increased during COVID-19 (32.5%–37.6%) compared with before COVID-19 (29.0%–29.3%; $P$=0.005). Furthermore, in-hospital mortality increased for AMI (OR, 1.46 [95% CI, 1.21–1.76]) and STEMI (OR, 2.57 [95% CI, 2.24–2.96]) during the pandemic.
- A meta-analysis comparing AMI admissions during the COVID-19 pandemic with pre–COVID-19 levels found 35% fewer AMI hospitalizations during COVID-19 compared with the pre–COVID-19 period (OR, 0.65 [95% CI, 0.56–0.74]; $I^2$=99%; $P$<0.001; 28 studies).[14] Hospitalizations also declined for STEMI (OR, 0.71 [95% CI, 0.65–0.78]; $I^2$=93%; $P$<0.001; 22 studies) and NSTEMI (OR, 0.66 [95% CI, 0.58–0.73]; $I^2$=95%; $P$<0.001; 14 studies) during COVID-19 compared with before COVID-19.[14] Another meta-analysis of 79 articles across 57 countries found that during the height of the COVID-19 pandemic, the IRR of STEMI hospitalizations decreased (0.80 [95% CI, 0.76–0.84]; $P$<0.05) over the reference period. However, there was significant heterogeneity across studies ($I^2$=89%; $P$<0.0001).[15] There was an inverse association between IRRs for STEMI admissions and hospital bed availability in each country ($P$<0.05).

### Social Determinants of Health/Health Equity

- An NIS analysis of sex differences spanning 2004 to 2015 identified 7 026 432 hospitalizations for AMI. Compared with males, females were less likely to undergo coronary angiography (aOR, 0.92 [95% CI, 0.91–0.93]) and PCI (aOR, 0.82 [95% CI, 0.81–0.83]). Females had a higher risk of mortality (aOR, 1.03 [95% CI, 1.02–1.04]) compared with males.[16]
- An observational cohort analysis of Medicare beneficiaries hospitalized with MI (N=155 397) in a national MI registry between April 2018 and September 2019 showed that Black adults (compared with non-Black adults) had lower 30-day mortality rates in low-performing hospitals (OR: before the Hospital Readmission Reduction Program, 0.79 [95% CI, 0.63–0.97]; $P$=0.03; after the Hospital Readmission Reduction Program, 0.80 [95% CI, 0.68–0.95]; $P$=0.01) but not in high-performing hospitals.[17]
- In 3635 patients who underwent left-sided heart catheterization for CAD at Emory University between 2004 and 2014, low neighborhood SES (a composite measure using 6 census measures capturing income, housing, education, and occupation) was associated with increased risk of cardiovascular death or MI in patients without a prior MI (HR, 2.72 [95% CI, 1.73–4.28] for the lowest versus highest quartile of neighborhood SES), but no association was observed for those with a prior MI (HR, 1.02 [95% CI, 0.58–1.81]; $P_{interaction}$=0.02).[18]

- According to the CMS Hospital Inpatient Quality Reporting Program data on 2363 hospitals in 2018, the average 30-day mortality after AMI was 13.6% (IQR, 12.8%–14.3%), with higher mortality observed in rural hospitals (from 13.4%–13.8% for the most urban to most rural hospitals).[19]
- Among 3006 older adults in the SILVER-AMI study who were recruited across 94 hospitals in the United States, low emotional support, measured with the Medical Outcomes Study Social Support Survey, was associated with higher odds of mortality (OR, 1.43 [95% CI, 1.04–1.97]), whereas low informational support was associated with higher odds of readmission (OR, 1.22 [95% CI, 1.01–1.47]).[20]
- In a retrospective cohort study of Medicare fee-for-service patients (N=453 783) diagnosed with CAD, there was no significant difference in adherence to guideline-recommended care in practices that served the highest proportion of patients who were socioeconomically disadvantaged compared with practices serving the lowest proportion.[21] Yet, at the most socioeconomically disadvantaged–serving practices, patients had higher odds of being admitted for unstable angina (aOR, 1.46 [95% CI, 1.04–2.05]) and higher 30-day mortality rates after AMI (aOR, 1.31 [95% CI, 1.02–1.68]). After additional adjustment for patient-level area deprivation index, these associations were attenuated (unstable angina: aOR, 1.20 [95% CI, 1.02–1.68]; 30-day mortality after MI: aOR, 1.31 [95% CI, 1.02–1.68]).
- An NHANES analysis spanning 2007 to 2016 cycles examined differences in self-reported history of CAD by limited English proficiency status in individuals reporting angina. Participants with limited English proficiency were 2.8 times more likely not to report a history of CVD compared with those without limited English proficiency (aOR, 2.77 [95% CI, 1.38–5.55]).[22]
- Disparities in cardiac rehabilitation are well recognized: Individuals who are female, of Black race, of Hispanic ethnicity, of lower educational attainment, and eligible for dual Medicare/Medicaid coverage have significantly reduced attendance compared with referents.[23–25] Among Medicare beneficiaries, participation in cardiac rehabilitation is lower among females (18.9%) compared with males (28.6%; adjusted PR, 0.91 [95% CI, 0.90–0.93]) and among Hispanic adults (13.2%) and NH Black adults (13.6%) compared with NH White adults (25.8%; adjusted PR, 0.63 [95% CI, 0.61–0.66] and 0.70 [95% CI, 0.67–0.72], respectively).[23] Likewise, in the BRFSS 2011 to 2015, participants in cardiac rehabilitation were less likely to be female (OR, 0.76 [95% CI, 0.65–0.90]), Black (OR, 0.70 [95% CI, 0.53–0.93]), uninsured (OR, 0.53 [95% CI, 0.37–0.75]), and less educated (OR, 0.47 [95% CI, 0.37–0.61]) compared with the referents.[24] In Optum's Clinformatics database (N=107 199), cardiac rehabilitation attendance was 31% lower among Asian adults (95% CI, 27%–36%), 43% lower for Hispanic adults (95% CI, 40%–45%), and 19% lower for Black adults (95% CI, 16%–22%) after adjustment.[25]
- An administrative claims analysis of Medicaid, commercial insurance, and Medicare claims from 2015 to 2018 identified that patients with Medicaid were less likely to receive guideline-concordant testing for MI (aOR, 0.84 [95% CI, 0.73–0.98]) and HF (aOR, 0.59 [95% CI, 0.51–0.70]) than those with commercial insurance.[26]
- A study of 2 182 903 Medicare beneficiaries hospitalized with MI, HF, or stroke from 2016 to 2018 compared outcomes in rural hospitals with outcomes in urban hospitals. Patients at rural hospitals were less likely to undergo cardiac catheterization (49.7% versus 63.6%; $P<0.001$), PCI (42.1% versus 45.7%; $P<0.001$), or CABG (9.0% versus 10.2%; $P<0.001$). Mortality at 30 days was higher for patients at rural hospitals presenting with MI (aHR, 1.10 [95% CI, 1.08–1.12]), HF (aHR, 1.15 [95% CI, 1.13–1.16]), and ischemic stroke (aHR, 1.20 [95% CI, 1.18–1.22]) compared with their counterparts presenting at metropolitan hospitals.[27]
- In a subset of SILVER-AMI, a community-based longitudinal study of older adults (N=1345, ≥75 years of age), there was no association between neighborhood walkability scores and hospital-free survival time or physical or mental health.[28]
- REGARDS investigators tabulated the number of social determinants of health to determine a progressive increase in fatal CHD (0 social determinants of health, 1.30; 1 social determinant of health, 1.44; 2 social determinants of health, 2.05; ≥3 social determinants of health, 2.86) and nonfatal MI (0 social determinants of health, 3.91; 1 social determinant of health, 4.33; ≥2 social determinants of health, 5.44). Compared with those with no social determinants of health, those with ≥3 social determinants of health had an aHR of 1.67 (95% CI, 1.18–2.37) for risk of fatal CHD.[29]
- Among 22 152 participants free of CHD at baseline in the REGARDS cohort study, there were 463 fatal incident CHD events and 932 nonfatal MIs over a median of 10.7 years (IQR, 6.6–12.7). Compared with those without social determinants of health, those with ≥3 social determinants of health had a higher risk (aHR, 1.67 [95% CI, 1.18–2.37]) of fatal incident CHD, and those with ≥2 social determinants of health had a nonsignificant higher risk (aHR, 1.14 [95% CI, 0.93–1.41]) of nonfatal MI.[29]
- In an analysis of NIS data from, January 1, 2012, through December 31, 2017, Black adults and

individuals from other racial and ethnic groups with AMI compared with White individuals were less likely to undergo coronary angiography (61.9% versus 70.2% versus 73.1%) and PCI (44.6% versus 53.0% versus 58.1%; $P<0.001$).[30]
- A systematic review of 181 studies, conducted primarily in high-income countries, found that lower socioeconomic position (education, income, insurance, occupation, or composite) was associated with higher incidence of ACS (IRR, 1.1–4.7), higher prevalence of ACS (OR, 1.8–3.9), higher odds of receiving suboptimal medical care (OR, 1.1–10.0), and higher mortality after ACS (HR,1.1–4.13).[31]

### *Risk Prediction*

- In 9066 participants 45 to 79 years of age from the REGARDS study, the observed and predicted ASCVD risks using the Pooled Cohort Risk Equations were similar in people with high social deprivation, although ASCVD risk was overestimated in those with low social deprivation (observed incident rate, 6.23 [95% CI, 5.31–7.31] versus predicted incident rate, 8.02; Hosmer-Lemeshow $\chi^2=12.43$; $P=0.01$).[32]
- In the WHI, although the risk of ASCVD was overestimated with the Pooled Cohort Risk Equations, adding ASCVD events identified through linkage with CMS claims that were not self-reported resulted in alignment of the observed and predicted risks (observed [predicted] risks for baseline 10-year risk categories of <5%, 5%–7.5%, 7.5%–10%, and ≥10% were 3.8 [4.3], 7.1 [6.4], 8.3 [8.7], and 18.9 [18.7], respectively).[33]
- In 14 169 patients with ASCVD risk <5% and self-reported family history of CHD from the multicenter CAC Consortium followed up for ≈12 years, those with CAC scores >100 had a >10-fold higher risk of CHD mortality than patients with CAC=0 (HR, 10.4 [95% CI, 3.2–33.7]).[34] Furthermore, addition of CAC to a model with traditional risk factors (age, sex, race, hypertension, hyperlipidemia, diabetes, and smoking status) improved the prediction for CHD mortality (AUC, 0.72 for the model with traditional risk factors and 0.82 for the model adding CAC; $P=0.03$).
- In a large competing-risk analysis among 66 363 adults from the CAC Consortium, participants with CAC >10 had higher risk of CHD death (aHR, 2.83 [95% CI, 2.07–3.86]) than those with CAC=0.[35] This risk was not significantly higher among adults <40 years of age but was significantly higher among adults >40 to 50 years of age (aHR, 2.97 [95% CI, 1.32–6.69]), 50 to 60 years of age (aHR, 5.08 [95% CI, 2.68–9.63]), 60 to 70 years of age (aHR, 1.89 [95% CI, 1.08–3.31]), and ≥70 years of age (aHR, 2.43 [95% CI, 1.33–4.46]) compared with their age counterparts with CAC=0.
- Among 66 636 asymptomatic adults in the CAC Consortium, those with extremely high CAC scores (≥1000) had higher adjusted risk of CVD (HR, 5.04 [95% CI, 3.92–6.48]), CHD (HR, 6.79 [95% CI, 4.74 – 9.73]), all-cause mortality (HR, 2.89 [95% CI, 2.53–3.31]), and cancer (HR, 1.55 [95% CI, 1.23–1.95]) than those with CAC=0.[36] Moreover, those with CAC ≥1000 had higher adjusted risk of CVD (HR, 1.71 [95% CI, 1.41–2.08]), CHD (HR, 1.84 [95% CI, 1.43–2.36]), all-cause mortality (HR, 1.51 [95% CI, 1.33 –1.70]), and cancer (HR, 1.36 [95% CI, 1.07–1.73]) than those with CAC scores of 400 to 999.
- Among 16 289 adults (6526 males, 9763 females) in the HCHS/SOL, WC cut points of >102 cm in males (current joint interim statement criteria) and >97 cm (9 points above the joint interim statement criteria) in females provide optimal discrimination for CHD (evidence of prior MI from ECG or self-report of MI, angina, or coronary procedures).[37]
- A precatheterization model and bedside risk score were developed and validated with data from 706 263 PCIs at 1608 sites between July 2018 and June 2019 to predict in-hospital mortality. Variables that predicted in-hospital mortality included cardiovascular instability, level of consciousness after cardiac arrest, and procedural urgency. The C indexes of the precatheterization model and bedside risk score were 0.940 and 0.923, respectively. The simplified bedside score includes age, CKD, cardiovascular instability, and the presence or absence of cardiac arrest before PCI. The total score ranges from 2 to 31 points, with an overall score ≤5 corresponding to a predicted mortality rate of <0.1% and a score of ≥27 associated with mortality rate of >85%.[38]
- A coronary age calculator was derived with traditional risk factors and CAC score in a MESA cohort of 6727 adults and compared with chronological age, the MESA CHD Risk Score, and CAC alone. The derived coronary age with CAC was identical to the MESA CHD Risk Score in predicting 10-year risk of CHD and had the highest discrimination (AUC, 0.76) compared with chronological age (AUC, 0.63) and coronary age without CAC (AUC, 0.70).[39]
- In a cohort of 272 307 White adults in the UK Biobank study, the integrated PRS, PCE, and PRS-enhanced PCE were compared to predict incident CAD cases.[40] The C statistics for the integrated PRS, PCE, and PRS-enhanced PCE were 0.640 (95% CI, 0.634–0.646), 0.718 (95% CI, 0.713–0.723), and 0.753 (95% CI, 0.748–0.758), respectively. The addition of the integrated PRS to the PCE at a 7.5% risk threshold yielded a net reclassification improvement of 0.117 (95% CI, 0.102–0.129) for cases and − 0.023 (95% CI, − 0.025 to − 0.022)

for controls (overall, 0.093 [95% CI, 0.08–0.104]). Among the incident CAD cases, 14.2% were correctly reclassified to the higher-risk category and 2.6% were incorrectly reclassified to the lower-risk category.

- The T2-risk score, a risk stratification tool for predicting the primary outcome of death or future MI among patients with type 2 MI, was derived from the High-STEACS trial (2013–2016), the APACE study (2006–2018), and single-center consecutive patients at a hospital in Stockholm (2011–2014).[41] The T2-risk score, which includes age, IHD, diabetes, HF, myocardial ischemia on ECG, anemia, heart rate, eGFR, and maximal cardiac troponin concentration, had good discrimination (AUC, 0.76 [95% CI, 0.73–0.79]) for the primary outcome and was well calibrated. The T2-risk score improved discrimination over the Global Registry of Acute Coronary Events 2.0 risk score in all cohorts.

## Genetics and Family History

### Family History as a Risk Factor

- Among adults ≥20 years of age, 13.8% (SE, 0.6%) reported having a parent or sibling with a heart attack or angina before 50 years of age. The racial and ethnic breakdown from NHANES 2017 to 2020 is as follows (unpublished NHLBI tabulation)[1]:
  - For NH White people, 14.0% (SE, 1.5%) for males and 15.7% (SE, 0.9%) for females.
  - For NH Black people, 9.7% (SE, 1.5%) for males and 14.4% (SE, 1.2%) for females.
  - For Hispanic people, 8.1% (SE, 1.1%) for males and 12.9% (SE, 1.4%) for females.
  - For NH Asian people, 6.3% (SE, 1.3%) for males and 8.4% (SE, 1.5%) for females.
- Because the incidence of HD increases with age, the prevalence of family history will vary depending on the age at which family history is assessed. The distribution of reported family history of heart attack by age of survey respondent in the US population as measured by NHANES 2017 to 2020 is as follows (unpublished NHLBI tabulation)[1]:
  - 20 to 39 years of age, 7.8% (SE, 1.3%) for males and 10.1% (SE, 0.8%) for females.
  - 40 to 59 years of age, 16.1% (SE, 1.7%) for males and 16.9% (SE, 1.4%) for females.
  - 60 to 79 years of age, 15.8% (SE, 2.1%) for males and 21.2% (SE, 2.6%) for females.
  - ≥80 years of age, 11.1% (SE, 2.9%) for males and 13.3% (SE, 2.1%) for females.
- Data from a longitudinal observational study (N=49 255) demonstrated an association between family history of premature angina, MI, angioplasty, or bypass surgery and increased lifetime risk by ≈50% for both HD (from 8.9% to 13.7%) and CVD mortality (from 14.1% to 21%).[42]

### Genetic Predictors of CHD

- CHD is heritable. From 36 years of follow-up data in 20 966 Swedish twins, the heritability of CHD mortality was 57% for males and 38% for females.[43] Of note, estimated heritability was operative throughout the life span but more prominently at younger ages of death, particularly for males.
- The application of GWASs to large cohorts of subjects with CHD has identified consistent genetic variants associated with CHD. Although several CHD loci indicate roles for atherosclerosis and traditional CVD risk factors, other loci highlight the importance of biological processes (ie, cellular adhesion, leukocyte migration and atherosclerosis, coagulation and inflammation, and vascular smooth muscle cell differentiation) in the arterial wall.[44]
- The first GWAS identified a locus on chromosome 9p21.3, which is the most consistently replicated genetic marker for CHD and MI in populations of European ancestry.[45] The primary SNP at 9p21.3 is common; 50% of the population of European ancestry is estimated to harbor 1 risk allele, and 23% harbor 2 risk alleles.[46]
  - A meta-analysis of 22 studies (N=35 872 cases; N=95 837 controls) identified the 10-year HD risk for a male 65 years of age with two 9p21.3 risk alleles and no other traditional risk factors as ≈13.2%, whereas a similar male with 0 alleles would have a 10-year risk of ≈9.2%. The 10-year HD risk for a female 40 years of age with 2 alleles and no other traditional risk factors is ≈2.4%, whereas a similar female with 0 alleles would have a 10-year risk of ≈1.7%.[46]
- GWASs have identified multiple loci associated with CAD implicating pathways in blood vessel morphogenesis, lipid metabolism, nitric oxide signaling, and inflammation, as well as basic cellular processes governing the cell cycle, division/replication, and growth. One large, ancestrally diverse GWAS included n=243 392 CAD case and n=849 686 control Million Veterans Project participants.[47] After meta-analysis with predominantly European ancestry GWASs from CARDIOoGRAMplusC4D and the UK Biobank, this GWAS identified 33 novel loci. Further meta-analysis with Biobank Japan and inclusion of MVP Black and Hispanic participants identified an additional 66 novel loci. These loci did not demonstrate heterogeneity across ancestral populations. A majority of these novel loci (58%) were associated with CAD risk factors (eg, blood lipids, BP, diabetes, obesity, or smoking). Large-scale collaborative genetic studies of CAD (n=72 868 cases and n=120 770 controls) focused on the coding regions of the genome (exons) have identified additional loci, including loss-of-function variants in *ANGPTL4* (angiopoietin-like 4), which is an inhibitor

of lipoprotein lipase.[48] These variants are associated with low plasma triglycerides and high HDL-C.

- A study of X chromosome genetic variation in >500 000 multiancestry individuals from the TOPMed Consortium found common alleles on chromosome Xq23 to be strongly associated with lower TC, LDL-C, and triglycerides in both females and males and associated with a reduced odds for CHD and type 2 diabetes.[49] Every additional rs5942634-T allele, the lead cholesterol-lowering variant in chromosome Xq23, was associated estimated ORs of 0.98 (95% CI, 0.96–0.99) for CHD and 0.97 (95% CI, 0.96–0.99) for type 2 diabetes.
- In a network mendelian randomization analysis, a 1-unit-longer genetically determined telomere length was associated with a lower risk of CHD in the CARDIoGRAM Consortium (OR, 0.79 [95% CI, 0.65–0.97]; *P*=0.016) and the CARDIoGRAMplusC4D Consortium (OR, 0.89 [95% CI, 0.79–1.00]; *P*=0.052). Fasting insulin can partially mediate the association of telomere length with CHD, accounting for 18.4% of the effect of telomere length on CHD.[50]
- Hematopoietic somatic variants (clonal hematopoiesis of indeterminate potential) that accumulate with age also have been shown to be independent predictors of CHD events. Carriers of clonal hematopoiesis of indeterminate potential had a risk of CHD 1.9 times greater than that of noncarriers (95% CI, 1.4–2.7) and a risk of MI 4.0 times greater than that of noncarriers (95% CI, 2.4–6.7).[51] Clonal hematopoiesis of indeterminate potential itself has germline genetic determinants.[52]

### *Clinical Utility of Genetic Markers*

- Studies have shown that patients with early-onset MI have a higher proportion of high PRS than of FH variants; for example, ≈2% carry a rare FH genetic variant, whereas ≈17% have a high PRS.[53]
- Even in individuals with high genetic risk, prevention strategies may have benefit. For example, in 4 studies across 55 685 individuals, genetic and lifestyle factors were independently associated with CHD, but even in individuals at high genetic risk, a favorable lifestyle was associated with a nearly 50% lower RR of CHD than an unfavorable lifestyle (HR, 0.54 [95% CI, 0.47–0.63]).[54]
- A summary of the 5 most highly cited studies of PRS concluded that the change in C statistic with the addition of PRS to the standard risk model improves the C statistic by −0.001 to 0.021 and that the contribution of PRS has a limited contribution to primary prevention of CAD.[55]
- In the FOURIER study (N=14 298), patients without multiple clinical risk factors or high genetic risk as defined by a 27-CHD-variant PRS did not derive benefit from evolocumab, whereas patients with high genetic risk, regardless of clinical risk, had reduced risk of major coronary events (HR, 0.69 [95% CI, 0.55–0.86]; *P*=0.0012).[56]
- Studies suggest that addition of a PRS contributes modestly to clinical risk prediction. In the UK Biobank with >350 000 participants, the change in C statistic for incident CAD prediction between a PCE and GRS model was 0.02 (95% CI, 0.01–0.03) with an overall net reclassification improvement of 4.0% (95% CI, 3.1%–4.9%).[57] In the ARIC and MESA studies, adding a GRS to the PCE did not significantly increase the C statistic in either cohort for prediction of incident CHD events (change in C statistic: ARIC, −0.001 [95% CI, −0.009 to 0.006]; MESA, 0.021 [95% CI, −0.0004 to 0.043]).[58] In an East Asian cohort (N=41 271), addition of a PRS including 540 genetic variants to clinical risk factors had a net reclassification improvement for CAD of 3.2% (95% CI, 0.9%–5.8%).[59]
- GRSs derived in 1 ancestry may have limited generalizability to individuals of other ancestries, necessitating development of GRSs that are ancestry specific.[60] An example is a GRS for CAD derived and validated in South Asian individuals (OR per 1 SD, 1.58 [95% CI, 1.42–1.76]) that outperformed previous scores based on European ancestral populations.[61]

## *Awareness, Treatment, and Control*

### *Awareness of Warning Signs and Risk for HD*

- Data from the NHIS indicate that awareness of 5 common heart attack symptoms (jaw, neck, or back discomfort; weakness or lightheadedness; chest discomfort; arm or shoulder discomfort; and shortness of breath) increased from 39.6% in 2008 to 50.2% in 2017. In 2017, knowledge of the 5 symptoms was higher in females than in males (54.4% versus 45.6%) and differed by race and ethnicity (White participants, 54.8%; Black participants, 43.1%; Asian participants, 33.5%; Hispanic participants, 38.9%).[62]
- Data from the NHIS 2017 indicate that being unaware of all 5 MI symptoms was more common in males (OR, 1.23 [95% CI, 1.05–1.44]), Hispanic individuals (OR, 1.89 [95% CI, 1.47–2.43]), those not born in the United States (OR, 1.85 [95% CI, 1.47–2.33]), and those with a high school or lower education (OR, 1.31 [95% CI, 1.09–1.58]).[63] Compared with adults born in the United States, adults born in Europe, Russia, Africa, the Middle East, the Indian subcontinent, Asia, and Southeast Asia were likely to be aware of all 5 MI symptoms in the NHIS 2017 cycle.[64]

- Data from an online survey of US females (≥25 years of age) showed that awareness related to CHD as a leading cause of death among females declined from 65% in 2009 to 44% in 2019. The decline in awareness was observed in all racial and ethnic groups and ages except females ≥65 years of age. Moreover, NH Black (OR, 0.31 [95% CI, 0.19–0.49]) and Hispanic (OR, 0.14 [95% CI, 0.07–0.28]) females and 25- to 34-year-old females (OR, 0.19 [95% CI, 0.10–0.34]) experienced the greatest 10-year decline in awareness from 2019 to 2009.[65]

### *Time of Symptom Onset and Arrival at Hospital*

- The weekend effect, that is, presentation with ACS on a weekend rather than weekday, has been examined with regard to timing and use of invasive management strategies. An analysis of NIS data spanning 2000 to 2016 identified statistically different rates of coronary angiography (59.9% versus 58.8%; $P<0.001$) and PCI (38.4% versus 37.6%; $P<0.001$) between weekend and weekday ACS presentations, more pronounced when early coronary angiography was examined (26% versus 21%; $P<0.001$).[66] Weekend presentation was not associated with increased risk of mortality compared with weekday presentation with ACS (OR, 1.01 [95% CI, 1.00–1.01]). A meta-analysis of 56 studies (N=384 452) concluded that individuals with STEMI presenting during off-hours had similar short-term (RR, 1.07 [95% CI, 1.00–1.14]), midterm (RR, 1.00 [95% CI, 0.95–1.05]), and long-term (RR, 0.95 [95% CI, 0.86–1.04]) mortality compared with those presenting during regular working hours.[67]
- A European registry of 6609 patients treated at 77 high-volume PCI centers determined that the COVID-19 pandemic was associated with a significant increase in door-to-balloon and total ischemia times.[68] Door-to-balloon time >30 minutes was 57.0% in the period of March to April 2020 compared with 52.9% in March to April 2019 ($P=0.003$), and total ischemia time >12 hours was 11.7% in the 2020 period compared with 9.1% in 2019 ($P=0.001$).
- In a meta-analysis including 57 136 patients from 10 studies, door-to-balloon time of >90 minutes versus ≤90 minutes was associated with higher in-hospital or 30-day mortality (OR, 1.52 [95% CI, 1.40–1.65]). An increased risk of 6-month to 12-month mortality was also observed for >90-minute door-to-balloon delay in 14 261 patients from 8 studies (OR, 1.53 [95% CI, 1.13–2.06]).[69]
- Rural EMS response has been longer than activation from suburban or metropolitan locations. National data from 2015 indicated that the mean response time for EMS was 14.5 minutes (9.5 minutes) in rural zip codes, 7.0 minutes (4.4 minutes) in urban zip codes, and 7.7 minutes (5.4 minutes) in suburban zip codes.[70]
- Analysis of a multinational registry of PCI for STEMI that included 109 high-volume centers determined that in 2020 the incidence of PCI was significantly less than in 2019 (IRR, 0.84 [95% CI, 0.83–0.86]), accompanied by increased likelihood of door-to-balloon time >30 minutes (OR, 1.1 [95% CI, 1.03-1.17]).[71]

### *Operations and Procedures*

- In 2020, an estimated 434 230 PCIs, 169v705 CABGs, 104 000 CEA and stenting procedures, and 90 375 pacemaker and defibrillator procedures were performed for inpatients in the United States (unpublished NHLBI tabulation using HCUP[72]).

### *Comparison of Outcomes: Surgery Versus Percutaneous Intervention*

- An analysis of 30 studies determined that compared with males, females undergoing CABG and combined CABG and valve surgery had higher short-term (ie, in hospital or within 30 days) mortality (OR, 1.40 [95% CI, 1.32–1.49]; $I^2=79\%$) and postoperative stroke (OR, 1.2 [95% CI, 1.07–1.34]; $I^2=90\%$) risks.[73]
- In an analysis of the BEST, PRECOMBAT, and SYNTAX trials comparing individuals with a previous MI and left main or multivessel CAD, CABG (versus PCI) was associated with a lower risk of MI (HR, 0.29 [95% CI, 0.16–0.55]) over a median follow-up of 59.8 months (IQR, 50.7–60.3 months).[74]
- At 10 years of follow-up in the SYNTAX trial, among 1800 trial participants, no difference in all-cause death was observed between PCI and CABG overall and among the subgroup of patients with left main CAD; however, for patients with 3-vessel disease, a greater risk of death was observed for those treated with PCI (HR, 1.42 [95% CI, 1.11–1.81]).[75]
- The ISCHEMIA trial randomized 5179 individuals with stable CAD and moderate or severe ischemia on stress testing to invasive or initial conservative treatment. Over the 4-year follow-up, there was no difference in primary end-point events (defined as cardiovascular death, MI, hospitalization for unstable angina, HF, or cardiac arrest) between those randomized to the invasive (18.2 per 100 patients [95% CI, 15.8–20.9]) and conservative (19.7 per 100 patients [95% CI, 17.5–22.2]) management arms.[76]
- In patients (N=1905) with left main CAD with low or intermediate complexity (SYNTAX scores ≤32), no difference in the composite outcome of MI, stroke, or death was observed between PCI (n=948) and CABG (n=957) at 5 years of follow-up, although

ischemia-driven revascularization (OR, 1.84 [95% CI, 1.39–2.44]) and all-cause death (OR, 1.39 [95% CI, 1.03–1.85]) were more common after PCI.[77]

- In the NCDR CathPCI registry, 1% of PCI procedures were for unprotected left main coronary lesions. A composite end point of in-hospital MI, stroke, emergency CABG, or death was more frequent in unprotected left main PCI (OR, 1.46 [95% CI, 1.39–1.53]) compared with all other PCIs.[78]
- In 4041 patients with STEMI with multivessel CAD randomized to complete revascularization versus culprit lesion–only PCI, those with complete revascularization experienced lower rates of a composite end point of cardiovascular death or MI (HR, 0.74 [95% CI, 0.60–0.91]; *P*=0.004) and a composite end point of cardiovascular death, MI, or ischemia-driven revascularization (HR, 0.51 [95% CI, 0.43–0.61]; *P*<0.001) at a median follow-up of 3 years.[79]
- In 27 840 patients with STEMI transported by EMS to 744 hospitals in the ACTION registry, preactivation of the catheterization laboratory >10 minutes before hospital arrival compared with no preactivation was associated with shorter times to the catheterization laboratory (median, 17 minutes [IQR, 7–25 minutes] versus 28 minutes [IQR, 18–39 minutes]), shorter door-to-device time (median, 40 minutes [IQR, 30–51 minutes] versus 52 minutes [IQR, 41–65 minutes]), and lower in-hospital mortality (2.8% versus 3.4%; *P*=0.01).[80]
- In the ISCHEMIA randomized trial including 5179 patients with stable coronary disease and moderate or severe ischemia, an initial invasive strategy did not reduce ischemic cardiovascular events or death compared with an initial conservative strategy (risk difference, −1.8% [95% CI, −4.7% to 1%] at 5 years).[81]

### *Secular Trends in Procedures*

- In an analysis of the NIS, among patients ≥70 years of age with non–ST-segment–elevation ACS or STEMI, the proportion of patients undergoing PCI increased from 7.3% in 1998 to 24.9% in 2013 in those with non–ST-segment–elevation ACS and from 11% in 1998 to 35.7% in 2013 in those with STEMI.[82]
- In a meta-analysis of 13 observational studies and 3 RCTs (N=777 841), a transradial approach for PCI was associated with a reduction in vascular complications (OR, 0.36 [95% CI, 0.30–0.43]) and stroke (OR, 0.81 [95% CI, 0.66–1.00]) compared with a transfemoral approach.[83] A transradial approach also was associated with a reduced risk of death (OR, 0.56 [95% CI, 0.45–0.69]), although this was driven by the observational studies because no association between transradial approach and death was observed in the randomized trials.
- An analysis of HCUP Inpatient and State Ambulatory and Surgery and Services Databases quantified the number of patients who underwent PCI from 2010 to 2017 in Florida, Maryland, Michigan, and New York.[8] In these 4 states, PCI rates declined from 260.2 per 100 000 individuals in 2010 to 232.8 per 100 000 individuals in 2017 (−10.5%; $P_{trend}$<0.001). This decline was attributed to a decrease in elective PCI across these years of −34.4%. Rates of urgent PCI increased from 95.0 per 100 000 individuals in 2010 to 109.2 in 2017 (+15.0%; $P_{trend}$<0.001).
- Among 216 657 adults with type 1 MI, 37 675 adults with type 2 MI, and 1521 with both type 1 and type 2 MI in the Nationwide Readmissions Database, use of coronary angiography (10.9% versus 57.3%; *P*<0.001), PCI (1.7% versus 38.5%; *P*<0.001), and CABG (0.4% versus 7.8%; *P*<0.001) was lower among patients with type 2 MI than those with type 1 MI. Furthermore, the risks of in-hospital mortality (aOR, 0.57 [95% CI, 0.54–0.60]) and 30-day MI readmission (aOR, 0.46 [95% CI, 0.35– 0.59]) were lower among those with type 2 MI than those with type 1 MI.[84]
- In a Swedish population–based registry (N=4085), PCI for unprotected left main CAD increased from 121 procedures in 2005 to 589 in 2017.[85] The risk of major adverse cardiovascular and cerebrovascular events was 44% less in 2017 compared with 2005 (HR, 0.56 [95% CI, 0.41–0.78]).

### *Cardiac Rehabilitation*

- In the BRFSS from 2005 to 2015, <40% of patients self-reported participation in cardiac rehabilitation after AMI. Between 2011 and 2015, patients who declared participation in cardiac rehabilitation were less likely to be female (OR, 0.76 [95% CI, 0.65–0.90]; *P*=0.002) or Black (OR, 0.70 [95% CI, 0.53–0.93]; *P*=0.014), were less well educated (high school versus college graduate: OR, 0.69 [95% CI, 0.59–0.81]; *P*<0.001; less than high school versus college graduate: OR, 0.47 [95% CI, 0.37–0.61]; *P*<0.001), and were more likely to be retired or self-employed (OR, 1.39 [95% CI, 1.24–1.73]; *P*=0.003) than patients who did not participate in cardiac rehabilitation.[24]
- Among 366 103 Medicare fee-for-service beneficiaries eligible for cardiac rehabilitation in 2016, only 24.4% participated in cardiac rehabilitation; among those who participated, the mean time to initiation was 47.0 days (SD, 38.6 days), and 26.9% completed cardiac rehabilitation with ≥36 sessions. Participation decreased with increasing age and was lower in females, Hispanic people, Asian people, those eligible for dual Medicare/Medicaid coverage, and those with ≥5 comorbidities.[23]

- A systematic review of 9 studies concluded that home-based cardiac rehabilitation is cost-effective, albeit recognizing heterogeneity across studies, limited duration of follow-up, and absence of consideration of diversity of cardiac rehabilitation participants.[86]
- In an administrative analysis of individuals eligible for cardiac rehabilitation (N=107 199), 28 433 (26.5%) attended cardiac rehabilitation.[25] After adjustment, compared with White individuals, the probability of attending cardiac rehabilitation was 31% lower for Asian individuals (95% CI, 27%–36%), 19% lower for Black individuals (95% CI, 16%–22%), and 43% lower for Hispanic individuals (95% CI, 40%–45%).
- In a randomized trial in patients undergoing cardiac rehabilitation after ACS with PCI, patients receiving digital health lifestyle interventions had more weight loss at 90 days than the control group (−5.1±6.5 kg versus −0.8±3.8 kg [mean±SD]; *P*=0.02) and a nonsignificant decrease in cardiovascular-related rehospitalizations and ED visits at 180 days (8.1% versus 26.6%; RR, 0.30 [95% CI, 0.08–1.10]; *P*=0.054).[87]
- In an observational study (N=1120) of individuals with IHD, the 1-year mortality risk did not differ between those who accepted home-based cardiac rehabilitation (n=490) compared with those who did not (HR, 0.67 [95% CI, 0.31–1.45]).[88] In contrast, during a median follow-up of 4.2 years, those who participated in home-based cardiac rehabilitation had an HR of 0.64 (95% CI, 0.45–0.90) compared with those who declined.

### *Mortality*

### *(See Table 21-1)*

- On the basis of 2021 mortality data[89]:
  - CHD mortality was 375 476, and CHD any-mention mortality was 612 817 (Table 21-1).
  - MI mortality was 109 097. MI any-mention mortality was 162 350 (Table 21-1).
- From 2011 to 2021, the annual death rate attributable to CHD declined 15.0%, whereas the actual number of deaths decreased by 0.05% (unpublished NHLBI tabulation using CDC WONDER[90]).
- In 2021, CHD age-adjusted death rates per 100 000 were 132.6 for NH White males, 149.8 for NH Black males, and 94.5 for Hispanic males. For NH White females, the rate was 66.2; for NH Black females, it was 81.7; and for Hispanic females, it was 51.0 (unpublished NHLBI tabulation using CDC WONDER[90]).
- In 2021, 79% of CHD deaths occurred out of hospital. According to US mortality data, 296 794 CHD deaths occurred out of hospital or in hospital EDs in 2021 (unpublished NHLBI tabulation using CDC WONDER[90]).
- The estimated average number of YLL because of an MI death was 13.7 in 2021 (unpublished NHLBI tabulation using CDC WONDER[90]).
- Approximately 35% of the people who experience a coronary event in a given year will die as a result of it, and ≈14% who experience an MI will die of it (unpublished NHLBI tabulation using ARIC Community Surveillance [2005–2014]).[4]
- An analysis of the multicenter NCDR Chest Pain–MI Registry (N=155 397 patients and 763 hospitals) reported that 30-day mortality among hospitalized patients with MI decreased from 6.6% to 5.0% in Black individuals and from 5.2% to 4.0% in non-Black individuals in the period of 2008 to 2016. Furthermore, racial differences in readmission were not significant after covariate adjustment.[17]
- According to data on >4 million Medicare fee-for-service beneficiaries with AMI, 30-day mortality declined from 1995 through 2014 (20.0% to 12.4%). Mortality was higher in females, but over time, the difference in 30-day mortality between males and females reduced.[91]
- Other data indicate that the rapid increase in the population ≥65 years of age has contributed to the reduction of HD mortality. From CDC WONDER data from 2011 through 2017, a deceleration in the decline in HD mortality was observed with a <1% annualized decrease. Taking into account the increase in the growth of the population ≥65 years of age combined with the slowing of the decrease in HD mortality resulted in an increase in the absolute number of HD deaths since 2011 (50 880 deaths; 8.5% total increase). However, the age-adjusted mortality for CHD continued to decline (2.7% annualized decrease) and the absolute number of CHD deaths declined (2.5% total decrease over the time period) between 2011 and 2017.[92]
- An analysis of those enrolled in Medicare Advantage or traditional Medicare from 2009 to 2018 presenting with STEMI (n=557 309) and NSTEMI (n=1 670 193) identified significant 30-day mortality rate differences in 2009 that were no longer present in 2018.[93] In 2018, the 30-day mortality for STEMI was 17.7% in those with Medicare Advantage and 17.8% in those with traditional Medicare (difference, 0.0 percentage points [95% CI, −0.7 to 0.6]); for NSTEMI, the 30-day mortality rate was 10.9% in those with Medicare Advantage and 11.1% in those with traditional Medicare (difference, −0.2 percentage points [95% CI, −0.4 to 0.1]).

- An analysis of the ISCHEMIA trial (N=5179) compared 4-year mortality in trial participants classified as having mild/no ischemia, moderate ischemia, or severe ischemia. Compared with those with mild/no ischemia, 4-year mortality rates were similar in those with moderate (HR, 0.89 [95% CI, 0.61–1.30]) and severe (HR, 0.83 [95% CI, 0.57–1.21]) ischemia.[94]
- In extended follow-up (median, 5.7 years), ISCHEMIA participants randomized to an initial invasive strategy did not have increased mortality (HR, 1.00 [95% CI, 0.85–1.18]) compared with those randomized to an initial invasive strategy.[95]
- A meta-analysis of 56 studies determined that females with STEMI have higher mortality risk (OR, 1.91 [95% CI, 1.84–1.99]) than males.[96]
- An NIS analysis spanning 2004 to 2018 determined that females had a higher incidence of mortality after PCI than males (1.12% mortality compared with 0.78%).[97]
- A prospective analysis of data on 5064 Black adults in the JHS between 2019 and 2021 found that participants with CHD (HR, 1.59 [95% CI, 1.22–2.08]), diabetes (HR, 1.50 [95% CI, 1.22–1.85]), or stroke (HR, 1.74 [95% CI, 1.24–2.42]) had higher risk for all-cause mortality compared with those with no cardiometabolic morbidities.[98] Those with ≥2 cardiometabolic morbidities had higher risk of all-cause mortality with the highest risk among those with diabetes, stroke, and CHD (HR, 3.68 [95% CI, 1.96–6.93].

### *Social Determinants and Health Equity of Mortality*

- In-hospital mortality is higher in females than in males with STEMI (7.4% versus 4.6%) and NSTEMI (4.8% versus 3.9%). An analysis of NCDR data from 2010 to 2015 reported that females admitted with STEMI had decreased survival to discharge compared with males (OR, 0.63 [95% CI, 0.52–0.76]).[99,100] Females experience longer door-to-balloon times and lower rates of guideline-directed medical therapy than males; however, a 4-step systems-based approach to minimize STEMI care variability at the Cleveland Clinic decreased the difference in 30-day mortality between males and females.[101]
- Among patients hospitalized for STEMI between 2003 and 2014 in the NIS database, lack of health insurance (OR, 1.77 [95% CI, 1.72–1.82]; $P<0.001$) and below-median income (OR, 1.08 [95% CI, 1.07–1.09]; $P<0.001$) were associated with in-hospital mortality.[102]
- An analysis conducted in NHIS determined that compared with ineligible individuals, participants in the Supplemental Nutrition Assistance Program have twice the risk of CVD mortality (HR, 2.00 [95% CI, 1.90–2.10]).[103]
- An analysis of the STS database including 1 042 056 patients who underwent isolated CABG between 2011 and 2018 found that Black individuals had higher overall mortality than White individuals (OR, 1.11 [95% CI, 1.05–1.18]).[104] Likewise, odds of death were higher in females compared with males (OR, 1.26 [95% CI, 1.21–1.30]).
- A pooled analysis of 21 randomized PCI trials including 32 877 patients (27.8% females) found that in multivariable-adjusted analyses, female sex was associated with 5-year risks of MACEs (HR, 1.14 [95% CI, 1.01–1.30]) and ischemia-driven target lesion vascularization (HR, 1.23 [95% CI, 1.05–1.44]) but not all-cause or cardiovascular mortality (HR, 0.91 [95% CI, 0.75–1.09] and 0.97 [95% CI, 0.73–1.29], respectively).[105]
- On the basis of pooled data from the FHS, ARIC, CHS, MESA, CARDIA, and JHS studies of the NHLBI (1995–2012), within 1 year after a first MI (unpublished NHLBI tabulation):
  - At ≥45 years of age, 18% of males and 23% of females will die.
  - At 45 to 64 years of age, 3% of White males, 5% of White females, 9% of Black males, and 10% of Black females will die.
  - At 65 to 74 years of age, 14% of White males, 18% of White females, 22% of Black males, and 21% of Black females will die.
  - At ≥75 years of age, 27% of White males, 29% of White females, 19% of Black males, and 31% of Black females will die.
  - In part because females have MIs at older ages than males, they are more likely to die of MI within a few weeks.
- On the basis of pooled data from the FHS, ARIC, CHS, MESA, CARDIA, and JHS studies of the NHLBI (1995–2012), within 5 years after a first MI (unpublished NHLBI tabulation):
  - At ≥45 years of age, 36% of males and 47% of females will die.
  - At 45 to 64 years of age, 11% of White males, 17% of White females, 16% of Black males, and 28% of Black females will die.
  - At 65 to 74 years of age, 25% of White males, 30% of White females, 33% of Black males, and 44% of Black females will die.
  - At ≥75 years of age, 55% of White males, 60% of White females, 61% of Black males, and 64% of Black females will die.
- An analysis conducted in the CARDIA study (N=5112) with a median follow-up >33 years identified that premature CVD risk in Black participants was attenuated after adjustment for

lifestyle, neighborhood, and socioeconomic factors.[106] For example, the 2.4-fold increased CVD risk in Black females (95% CI, 1.71–3.49) relative to White females was no longer significant after adjustment for clinical, lifestyle, socioeconomic, and neighborhood factors. The largest decreases in the race-specific estimate for CVD risk occurred with adjustment for clinical (87%), neighborhood (32%), and socioeconomic (23%) factors.[106]

- In MESA, an analysis (N=6814) similarly reported that compared with White participants, Black participants had increased risk of mortality (HR, 1.34 [95% CI, 1.19–1.51]), which decreased after adjustment for socioeconomic factors (HR, 1.16 [95% CI, 1.01–1.34]).[107]
- A large regional health care system in Northern California conducted an analysis of 1-year mean residential-level estimates of PM2.5 in individuals with ASCVD. A 10–μg/m$^3$ increase in PM2.5 exposure was associated with an HR of 1.20 (95%, 1.11–1.30) increased risk of cardiovascular mortality but not stroke or MI.[108]
- A meta-analysis of 30 cardiac surgery studies identified that females have an increased risk of short-term mortality after CABG (aOR, 1.40 [95% CI, 1.32–1.49]; $I^2$=79%) compared with males.[73]
- Sex differences in outcomes after MI are well established. In Olmsted County, Minnesota, mortality risk after premature MI (defined as 18–55 years of age in males and 18–65 years of age in females) declined by 66% in females (HR, 0.34 [95% CI, 0.17–0.68]) from 1987 through 2012. In contrast, no significant decline in mortality was observed in males.[109] A multicenter study in London, UK (N=26 799), determined that multivariable-adjusted sex differences in survival after STEMI over a median of 4.1 years (IQR, 2.2–5.8 years) of follow-up were significant in those >55 years of age (HR, 1.20 [95% CI, 1.09–1.41] for females compared with males).[110]

### Complications

- STEMI confers greater in-hospital risks than NSTEMI, including death (6.4% for STEMI, 3.4% for NSTEMI), cardiogenic shock (4.4% versus 1.6%, respectively), and bleeding (8.5% versus 5.5%, respectively).[111] In the NCDR ACTION Registry–GWTG, a measure of neighborhood SES based on census data was associated with in-hospital deaths and major bleeding in patients with AMI. Compared with those in the highest quintile of neighborhood SES, those residing in the lowest SES quintile experienced higher rates of in-hospital death (OR, 1.10 [95% CI, 1.02–1.18]) and major bleeding (OR, 1.10 [95% CI, 1.05–1.15]).[112]
- In an analysis of the NIS, females with AMI presenting with spontaneous coronary artery dissection had higher odds of in-hospital mortality (6.8%) than females without spontaneous coronary artery dissection (3.8%; OR, 1.87 [95% CI, 1.65–2.11]; $P$<0.001) in a propensity-matched analysis.[113]
- In the NCDR ACTION Registry–GWTG, patients with STEMI or NSTEMI with nonobstructive coronary arteries (<50% stenosis) had lower in-hospital mortality than patients with obstructive CAD (1.1% versus 2.9%; $P$<0.001). Nonobstructive coronary arteries were more common in females than males (10.5% versus 3.4%; $P$<0.001), but no difference in in-hospital mortality was observed between females and males with nonobstructive coronary arteries ($P$=0.84).[114]
- In a propensity score–matched analysis from the NIS HCUP that included discharges with MI as the principal diagnosis from 2012 to 2014, patients with concomitant delirium had higher rates of in-hospital mortality than those without delirium (10.5% versus 7.6%; RR, 1.39 [95% CI, 1.2–1.6]; $P$<0.001).[115]
- In a trial of patients presenting with STEMI (N=402), those with HF symptoms (New York Heart Association functional class ≥2; n=76) within 30 days after PCI for STEMI experienced increased risk of death or hospitalization for HF within 1 year compared with those without HF symptoms (HR, 3.78 [95% CI, 1.16–12.22]; $P$=0.03).[116]
- The burden of rehospitalizations for AMI is substantial. Among Medicare fee-for-service patients ≥65 years of age who were discharged alive after AMI in 2009 to 2014, the rate of 1-year recurrent AMI was 5.3% (95% CI, 5.27%–5.41%) with a median of 115 days (IQR, 34–230 days) of time from discharge to recurrent AMI.[117]
- Sudden death after MI is common. A secondary analysis of IMPROVE-IT (N=18 144) determined the cumulative IR of sudden death after MI as 2.47% (95% CI, 2.23%–2.73%) at the 7-year follow-up.[118]

### *Age, Sex, Race, and Complications*

- On the basis of pooled data from the FHS, ARIC, CHS, MESA, CARDIA, and JHS studies of the NHLBI (1995–2012; unpublished NHLBI tabulation), of those who have a first MI, the percentage with a recurrent MI or fatal CHD within 5 years is as follows:
  - At ≥45 years of age, 17% of males and 21% of females.
  - At 45 to 64 years of age, 11% of White males, 15% of White females, 22% of Black males, and 32% of Black females.
  - At 65 to 74 years of age, 12% of White males, 17% of White females, 30% of Black males, and 30% of Black females.

  - At ≥75 years of age, 21% of White males, 20% of White females, 45% of Black males, and 20% of Black females.
- The percentage of people with a first MI who will have HF in 5 years is as follows:
  - At ≥45 years of age, 16% of males and 22% of females.
  - At 45 to 64 years of age, 6% of White males, 10% of White females, 13% of Black males, and 25% of Black females.
  - At 65 to 74 years of age, 12% of White males, 16% of White females, 20% of Black males, and 32% of Black females.
  - At ≥75 years of age, 25% of White males, 27% of White females, 23% of Black males, and 19% of NH Black females.
- The percentage of people with a first MI who will have an incident stroke within 5 years is as follows:
  - At ≥45 years of age, 4% of males and 7% of females.
  - At ≥45 years of age, 5% of White males, 6% of White females, 4% of Black males, and 10% of Black females.
- The median survival time (in years) after a first MI is as follows:
  - At ≥45 years of age, 8.2 for males and 5.5 for females.
  - At ≥45 years of age, 8.4 for White males, 5.6 for White females, 7.0 for Black males, and 5.5 for Black females.
- A systematic review and pooled analysis of 4 CABG trials compared sex differences in outcomes between females (n=2714) and males (n=10 479). Over the 5-year follow-up, females had a significantly increased risk of major adverse cardiac and cerebrovascular events (aHR, 1.12 [95% CI, 1.04–1.21]), MI (aHR, 1.30 [95% CI, 1.11–1.52]), and repeat revascularization (aHR, 1.22 [95% CI, 1.04–1.43]) but not stroke (aHR, 1.17 [95% CI, 0.90–1.43]).[119]
- A meta-analysis of 56 studies of STEMI identified that compared with males, females hospitalized with STEMI are more likely to experience repeat MI (OR, 1.25 [95% CI, 1.00–1.56]), stroke (OR, 1.67 [95% CI, 1.27–2.20]), and major bleeding (OR, 1.82 [95% CI, 1.56–2.12]).[96]
- An analysis of the US Nationwide Readmissions Database determined that after hospitalization for AMI, females had 13% increased risk of 6-month HF hospitalization compared with males (6.4% in females versus 5.8% in males; HR, 1.13 [95% CI, 1.05–1.21]).[120]
- An Australian registry of individuals who had undergone PCI (N=13 996) from 2008 to 2020 determined that female sex was associated with increased 2-year readmission (HR, 1.29 [95% CI, 1.11–1.48]) compared with male sex.[121]

### *Hospital Discharges and Ambulatory Care (See Table 21-1 and Chart 21-5)*

- From 2010 to 2020, the number of inpatient discharges from short-stay hospitals with CHD as the first-listed diagnosis decreased from 1 224 434 to 854 760 (Table 21-1).
- From 1997 through 2020, the number of hospital discharges for CHD generally declined (Chart 21-5).
- In 2019, there were 14 167 000 physician office visits for CHD (unpublished NHLBI tabulation using NAMCS[122]). In 2020, there were 948 673 ED visits with a primary diagnosis of CHD (unpublished NHLBI tabulation using HCUP[72]).
- In the NIS, the mean length of hospital stay for patients with STEMI with primary PCI declined from 3.3 days in 2005 to 2.7 days in 2014; the proportion of hospitalizations with length of stay >3 days declined from 31.9% in 2005 to 16.9% in 2014.[123]
- In the CathPCI registry, a composite of use of evidence-based medical therapies, including aspirin, P2Y12 inhibitors, and statins, was high (89.1% in 2011 and 93.5% in 2014). However, in the ACTION-GWTG registry, metrics shown to need improvement were defect-free care (median hospital performance rate, 78.4% in 2014), P2Y12 inhibitor use in eligible medically treated patients with AMI (56.7%), and use of aldosterone antagonists in patients with LV systolic dysfunction and either diabetes or HF (12.8%).[111]
- Among 147 600 individuals with premature ASCVD (≤55 years of age) receiving care in the Veterans Affairs health care system from October 1, 2014, through September 30, 2015, there were 10 413 females and 137 187 males. In adjusted analyses, females were less likely to receive antiplatelet therapy (OR, 0.47 [95% CI, 0.45–0.50]), any statin (OR, 0.62 [95% CI, 0.59–0.66]), or high-intensity statin (OR, 0.63 [95% CI, 0.59–0.66]) than males.[124]
- Among individuals presenting with an MI or undergoing coronary revascularization in the Veterans Affairs health care system from July 24, 2015, through December 9, 2019 (N=81 372), the proportions receiving lipid-lowering intensification were 33.3% at 14 days, 41.9% at 3 months, and 47.3% at 12 months after hospitalization.[125] Lipid-lowering intensification was defined as increasing or initiating therapies to achieve LDL target goals of 70 or 100 mg/dL.
- An analysis of the ISCHEMIA trial (N=5179) compared days alive out of the hospital or extended care facilities among trial participants classified as having mild/no ischemia, moderate ischemia, or severe ischemia and randomized to invasive or initially conservative management strategies. At 4 years, there was no significant difference between the 2 groups (1415.0 days with conservative management and 1412.2 days with invasive management; *P*=0.65).[126]

### Cost

- The estimated direct cost of HD in 2019 to 2020 (average annual) was $120.2 billion (MEPS,[127] unpublished NHLBI tabulation).
- The estimated direct and indirect cost of HD in 2019 to 2020 (average annual) was $252.2 billion (MEPS,[127] unpublished NHLBI tabulation).
- MI ($14.3 billion) and CHD ($8.7 billion) were 2 of the 10 most expensive conditions treated in US hospitals in 2017.[128]
- In 642 105 Medicare beneficiaries hospitalized for AMI between 2011 and 2014, 30-day episode payments averaged $22 128 but varied 2-fold across hospitals. Median costs were $20 207 in the lowest quartile versus $24 174 in the highest quartile of hospitals.[129]
- In Medicare beneficiaries hospitalized with AMI, the 180-day expenditures increased from an average of $32 182 per person in 1999 to 2000 to $36 836 in 2008 and remained relatively stable thereafter, with expenditures of $36 668 in 2013 to 2014.[130]
- In 11 969 patients with AMI from 233 US hospitals who underwent PCI from 2010 to 2013, average hospital costs were higher for patients with STEMI ($19 327) compared with patients with NSTEMI ($18 465; $P$=0.002) and higher among elderly patients ($19 575 for those ≥65 years of age versus $18 652 for those <65 years of age; $P$=0.004). Forty-five percent of costs were related to the catheterization laboratory, 22% to room and board, 14% to supplies, and 9% to pharmacy costs. At 1 year after discharge, hospital and ED costs averaged $8037, with three-quarters attributable to hospitalizations ($6116 for hospitalizations, $1334 for outpatient hospital stays, and $587 for ED visits).[131]
- Among 26 255 patients with isolated CABG in a regional STS database between 2012 and 2019, the median hospital cost was higher among those with open CABG ($35 011) than those with minimally invasive CABG surgery ($27 906; $P$<0.001) after propensity score matching. There was no significant difference in mortality or morbidity, although patients with open CABG had longer hospital stays (7 days versus 6 days; $P$=0.005) than those with minimally invasive CABG surgery.[132]
- An observational analysis of data on young adults (18–45 years of age) who underwent PCI in the 2004 to 2018 NIS found that the inflation-adjusted care cost significantly increased from $21 567 in 2004 to $24 173 in 2018 ($P_{trend}$<0.01).[97]

### Global Burden

#### (See Table 21-3 and Charts 21-6 and 21-7)

- Based on 204 countries and territories in 2021[133]:
  - An estimated 9.21 (95% UI, 8.55–9.78) million deaths due to IHD occurred (Table 21-3). IHD mortality rates were highest in Central Asia, Eastern Europe, and North Africa and the Middle East. Mortality was lowest in high-income Asia Pacific (Chart 21-6).
  - Globally, it was estimated that 254.20 (95% UI, 211.36–290.50) million people lived with IHD, and it was more prevalent in males than in females (145.27 [95% UI, 121.79–164.23] and 108.93 [95% UI, 89.72–125.48] million people, respectively). North Africa and the Middle East had the highest prevalence rates of IHD, followed by Eastern Europe and South and Central Asia. (Chart 21-7).
- Among 31 443 respondents ≥50 years of age from 6 low- and middle-income countries participating in the WHO SAGE Wave 1, prevalence of angina ranged between 8% in China and 39% in Russia and was higher in females than males.[134]

## Acute Coronary Syndrome

### *ICD-9* 410, 411; *ICD-10* I20.0, I21, I22.

- In 2020, there were 577 275 ACS principal diagnosis discharges. This estimate was derived by adding the principal diagnoses for MI (570 440) to those for unstable angina (6835; unpublished NHLBI tabulation using HCUP[72]).
- When all listed discharge diagnoses in 2020 were included, the corresponding number of inpatient hospital discharges was 1 278 385 unique hospitalizations for ACS. Of the total, 1 262 265 were for MI alone, and 16 120 were for unstable angina alone (HCUP,[72] unpublished NHLBI tabulation).
- In a population-level study in Italy, the incidence rate of PCI for ACS decreased from 178 (before the COVID-19 outbreak) to 120 (after the COVID-19 outbreak) cases per 100 000 residents per year (IRR, 0.68 [95% CI, 0.65–0.70]).[135] Females (IRR, 0.60 [95% CI, 0.57–0.65]) had fewer PCIs for ACS than males (IRR, 0.70 [95% CI: 0.68–0.73]; $P_{interaction}$<0.011).
- Among 17 562 patients with ACS between 2005 and 2017 who lived beyond 30 days in a large PCI registry in Australia, 83.3% were on a β-blocker. Risk of overall mortality was lower among those who were on a β-blocker (aHR, 0.87 [95% CI, 0.78–0.97]; $P$=0.014) compared with those who were not. This mortality benefit was observed among patients with LVEF <35% (aHR, 0.63 [95% CI, 0.44–0.91]; $P$=0.013) and 35% to 50% (aHR, 0.80 [95% CI, 0.68–0.95]; $P$=0.01]) but not among those with LVEF >50%.[136]
- In a retrospective analysis of 43 446 patients who were referred for cardiac catheterization at a medical center in Massachusetts between January 2006

and June 2017, 26 545 patients had ACS. Younger patients with ACS (<35 years of age) were more likely to be White, obese, and a smoker and to report a family history of CAD, but they were less likely to have diabetes, hypertension, and hyperlipidemia than older patients. Younger patients with ACS also had a higher prevalence of elevated troponin, late-presentation STEMI, and cardiogenic shock than older patients. Compared with patients with ACS who were 36 to 54 years of age, those who were ≤35 years of age had higher odds of 30-day mortality (aOR, 5.65 [95% CI, 2.49–12.82]; *P*<0.001).[137]

- A retrospective analysis of 801 195 patients with ACS in the NIS identified disparities in outcomes of patients admitted based on insurance (Medicaid, Medicare, private, and no insurance). Patients who had no insurance (aOR,1.46 [95% CI, 1.26–1.69]; *P*≤0.01) or were on Medicaid (aOR, 1.16 [95% CI, 1.03–1.30]; *P*=0.01) had higher mortality than those who had private insurance.[138]
- A retrospective analysis of data on 10 019 patients from the Epi-Cardio Registry in Argentina was conducted to examine sex differences in the presentation of ACS.[139] Females were more likely than males to present with non–ST-segment–elevation ACS (60.3% versus 46.7%; *P*<0.001). This sex difference was driven mainly by a higher prevalence of ACS with nonobstructive coronary arteries (20.9% versus 6.6%) in young females because ACS without coronary lesions was mostly non–ST-segment–elevation ACS (77.7% versus 22.3%). There was no significant sex difference in the clinical presentation among patients with obstructive CHD.
- Among adults with ACS from the PLATO trial, the ABC-ACS ischemia model for predicting 1-year risk of CVD and MI that included growth differentiation factor 15 and NT-proBNP had greater prognostic value than all candidate variables (C indices, 0.71 and 0.72 in the development and validation cohorts, respectively).[140]
- A retrospective cohort study of 257 948 adults in the National Institute for Health Research Health Informatics Collaborative with suspected ACS in the United Kingdom between 2010 and 2017 found a positive and graded association between high-sensitivity CRP level and mortality at baseline.[141] This association persisted after 3 years for those with high-sensitivity CRP of 2.0 to 4.9 mg/L (aHR, 1.32 [95% CI, 1.18–1.48]), 5 to 9.9 mg/L (aHR, 1.40 [95% CI, 1.26–1.57]), and 10 to 15 mg/L (aHR, 2.00 [95% CI, 1.75–2.28]).

## Stable AP

### *ICD-9* 413; *ICD-10* I20.1 to I20.9.

#### *Prevalence*

#### *(See Table 21-2 and Chart 21-8)*

- According to data from NHANES 2017 to 2020, the prevalence of AP among adults (≥20 years of age) was 3.9% (10.8 million adults; Table 21-2).
- On the basis of NHANES 2017 to 2020, the prevalence of AP increased with age from <1% among males and females 20 to 39 years of age to >9% among males and females ≥80 years of age (Chart 21-8).
- On the basis of data from NHANES in 2009 to 2012, an average of 3.4 million people ≥40 years of age in the United States had angina each year compared with 4 million in 1988 to 1994. Declines in angina symptoms have occurred for NH White but not for NH Black people.[142]
- Among patients with a history of CAD (ACS, prior coronary revascularization procedure, or stable angina), 32.7% self-reported at least 1 episode of angina over the past month. Of those reporting angina, 23.3% reported daily or weekly symptoms of angina, and 56.3% of these patients with daily or weekly angina were taking at least 2 antianginal medications.[143]
- Among 1612 of 4139 eligible patients diagnosed with CAD in a network consisting of 15 primary care clinics in Massachusetts, the prevalence of angina was measured with the Seattle Angina Questionnaire-7; 21.2% reported angina symptoms at least once monthly, and among those, 12.5% reported daily or weekly angina symptoms, and 8.7% reported monthly angina symptoms.[144]

**Table 21-1. CHD in the United States**

| Population group | Prevalence, CHD, 2017–2020, ≥20 y of age | Prevalence, MI, 2017–2020, ≥20 y of age | New and recurrent MI and fatal CHD, 2005–2014, ≥35 y of age | New and recurrent MI, 2005–2014, ≥35 y of age | Mortality,* CHD, 2021, all ages | Mortality,* MI, 2021, all ages | Hospital discharges: CHD, 2020, all ages |
|---|---|---|---|---|---|---|---|
| Both sexes | 20 500 000 (7.1%) [95% CI, 6.1%–8.3%] | 9 300 000 (3.2%) [95% CI, 2.5%–4.0%] | 1 055 000 | 805 000 | 375 476 | 109 097 | 854 760 |
| Males | 11 700 000 (8.7%) | 6 100 000 (4.5%) | 610 000 | 470 000 | 226 452 (60.3%)† | 65 673 (60.2%)† | |
| Females | 8 800 000 (5.8%) | 3 200 000 (2.1%) | 445 000 | 335 000 | 149 024 (39.7%)† | 43 424 (39.8%)† | |
| NH White males | 9.4% | 4.8% | 520 000‡ | … | 174 148 | 50 529 | … |

(*Continued*)

**Table 21-1. Continued**

| Population group | Prevalence, CHD, 2017–2020, ≥20 y of age | Prevalence, MI, 2017–2020, ≥20 y of age | New and recurrent MI and fatal CHD, 2005–2014, ≥35 y of age | New and recurrent MI, 2005–2014, ≥35 y of age | Mortality,* CHD, 2021, all ages | Mortality,* MI, 2021, all ages | Hospital discharges: CHD, 2020, all ages |
|---|---|---|---|---|---|---|---|
| NH White females | 5.9% | 2.2% | 370 000‡ | … | 112 940 | 32 636 | … |
| NH Black males | 6.2% | 4.0% | 90 000‡ | … | 25 543 | 7295 | … |
| NH Black females | 6.3% | 2.3% | 75 000‡ | … | 18 925 | 5638 | … |
| Hispanic males | 6.8% | 3.1% | … | … | 17 095 | 5051 | … |
| Hispanic females | 6.1% | 1.9% | … | … | 10 999 | 3337 | … |
| NH Asian males | 5.2% | 2.8% | … | … | 6305§ | 1942§ | … |
| NH Asian females | 3.9% | 0.5% | … | … | 4242§ | 1296§ | … |
| NH American Indian or Alaska Native | … | … | … | … | 2012 | 601 | … |
| NH Native Hawaiian or Pacific Islander | | | | | 543 | 147 | |

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.[145] CHD includes people who responded "yes" to at least 1 of the questions in "Has a doctor or other health professional ever told you that you had CHD, angina or AP, heart attack, or MI?" Those who answered "no" but were diagnosed with Rose angina are also included (the Rose questionnaire is administered only to survey participants >40 years of age). CIs have been added for overall prevalence estimates in key chapters. CIs have not been included in this table for all subcategories of prevalence for ease of reading.

AP indicates angina pectoris; CHD, coronary heart disease; COVID-19, coronavirus disease 2019; ellipses (…), data not available; MI, myocardial infarction; NH, non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

*Mortality for Hispanic, NH American Indian or Alaska Native, and NH Asian, and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting Hispanic origin or race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native, Asian and Pacific Islander, and Hispanic decedents, as well as undercounts of these groups in censuses.

†These percentages represent the portion of total CHD and MI mortality that is for males vs females.

‡Estimates include Hispanic and NH people. Estimates for White people include other non-Black races.

§Includes Chinese, Filipino,, Japanese, and other Asian people.

Sources: Prevalence: unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using National Health and Nutrition Examination Survey.[1] Percentages for racial and ethnic groups are age adjusted for Americans ≥20 years of age. Age-specific percentages are extrapolated to the 2020 US population estimates. These data are based on self-reports. Incidence: Atherosclerosis Risk in Communities study (2005–2014),[4] unpublished tabulation by NHLBI, extrapolated to the 2014 US population. Mortality (for underlying cause of CHD): unpublished NHLBI tabulation using National Vital Statistics System.[89] Hospital discharges (with a principal diagnosis of CHD): unpublished NHLBI tabulation using Healthcare Cost and Utilization Project[72] (data include those inpatients discharged alive, dead, or status unknown).

**Table 21-2. AP* in the United States**

| Population group | Prevalence, 2017–2020, age ≥20 y | Hospital discharges, 2020, all ages |
|---|---|---|
| Both sexes | 10 800 000 (3.9%) [95% CI, 3.3%–4.5%] | 11 970 |
| Males | 5 600 000 (4.3%) | |
| Females | 5 200 000 (3.6%) | |
| NH White males | 4.7% | … |
| NH White females | 3.5% | … |
| NH Black males | 2.7% | … |
| NH Black females | 4.1% | … |
| Hispanic males | 3.6% | … |
| Hispanic females | 4.3% | … |
| NH Asian or Pacific Islander males | 2.7% | … |
| NH Asian or Pacific Islander females | 2.7% | … |

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.[145] AP includes people who either answered "yes" to the question of ever having angina or AP or being diagnosed with Rose angina (the Rose questionnaire is administered only to survey participants >40 years of age).

AP indicates angina pectoris; COVID-19, coronavirus disease 2019; ellipses (…), data not available; NH, non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

*AP is chest pain or discomfort that results from insufficient blood flow to the heart muscle. Stable AP is predictable chest pain on exertion or under mental or emotional stress. The incidence estimate is for AP without myocardial infarction.

Sources: Prevalence: unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using NHANES.[1] Percentages for racial and ethnic groups are age adjusted for US adults ≥20 years of age. Estimates from NHANES 2017 to 2020 were applied to 2020 population estimates (≥20 years of age). Hospital discharges (with a principal diagnosis of AP): unpublished NHLBI tabulation using Healthcare Cost and Utilization Project[72]; data include those inpatients discharged alive, dead, or status unknown.

**Table 21-3. Global Mortality and Prevalence of IHD by Sex, 2021**

| | Both sexes | | Male | | Female | |
|---|---|---|---|---|---|---|
| | Deaths (95% UI) | Prevalence (95% UI) | Deaths (95% UI) | Prevalence (95% UI) | Deaths (95% UI) | Prevalence (95% UI) |
| Total number (millions), 2021 | 9.21 (8.55 to 9.78) | 254.20 (211.36 to 290.50) | 5.12 (4.78 to 5.43) | 145.27 (121.79 to 164.23) | 4.09 (3.63 to 4.42) | 108.93 (89.72 to 125.48) |
| Percent change in total number, 1990–2021 | 71.55 (63.81 to 81.04) | 126.67 (117.76 to 135.26) | 83.14 (71.72 to 95.01) | 123.61 (114.44 to 131.13) | 58.95 (47.66 to 68.99) | 130.88 (121.66 to 141.80) |
| Percent change in total number, 2010–2021 | 24.20 (19.26 to 30.20) | 39.55 (31.76 to 47.68) | 26.22 (18.44 to 35.00) | 36.64 (29.27 to 43.96) | 21.75 (15.01 to 28.16) | 43.64 (35.31 to 53.00) |
| Rate per 100 000, age standardized, 2021 | 109.83 (101.85 to 116.75) | 2960.68 (2464.13 to 3378.39) | 136.95 (127.75 to 145.52) | 3627.27 (3039.76 to 4109.40) | 86.80 (77.31 to 93.77) | 2370.10 (1956.15 to 2726.70) |
| Percent change in rate, age standardized, 1990–2021 | −31.97 (−34.68 to −28.67) | 1.40 (−2.85 to 5.25) | −28.08 (−32.37 to −23.75) | −2.15 (−6.18 to 1.42) | −36.63 (−40.63 to −32.88) | 4.70 (0.15 to 9.68) |
| Percent change in rate, age standardized, 2010–2021 | −12.92 (−16.29 to −8.79) | 2.91 (−2.72 to 8.64) | −10.98 (−16.24 to −5.38) | 0.47 (−4.89 to 5.68) | −15.01 (−19.71 to −10.75) | 5.99 (0.03 to 12.80) |

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Disease; IHD, ischemic heart disease, and UI, uncertainty interval.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[133]

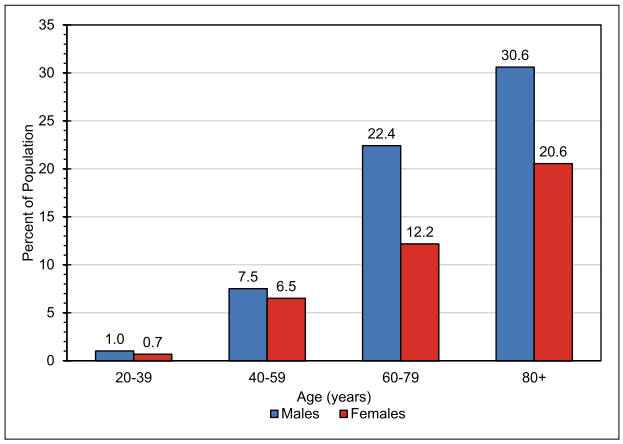



**Chart 21-1. Prevalence of CHD by age and sex, United States (NHANES, 2017–2020).**

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.[145]

CHD indicates coronary heart disease; COVID-19, coronavirus disease 2019; and NHANES, National Health and Nutrition Examination Survey.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.[1]

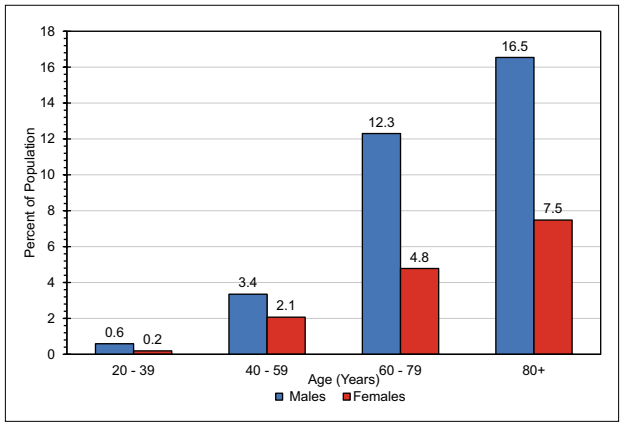



**Chart 21-2. Prevalence of MI by age and sex, United States (NHANES, 2017–2020).**

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.[145]

MI includes people who answered "yes" to the question of ever having had a heart attack or MI.

COVID-19 indicates coronavirus disease 2019; MI, myocardial infarction; and NHANES, National Health and Nutrition Examination Survey.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.[1]

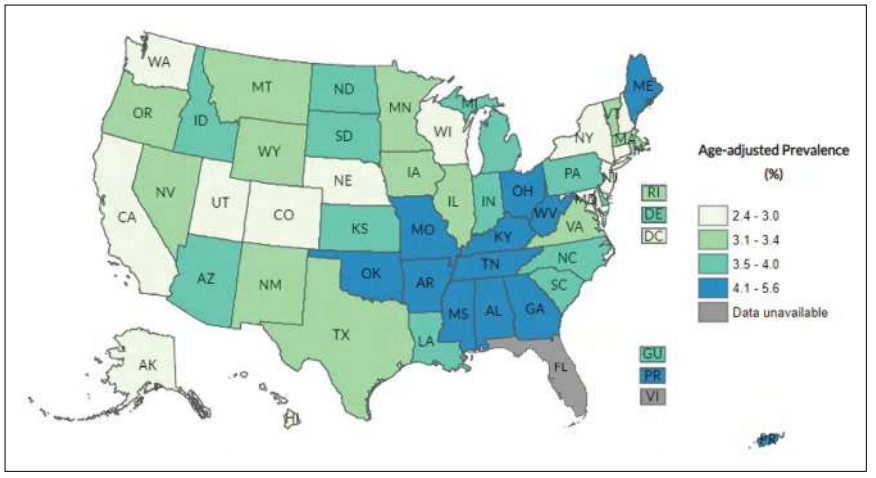



**Chart 21-3. "Ever told you had a heart attack (MI)?" Age-adjusted US prevalence by state (BRFSS prevalence and trends data, 2021).**
Original chart has been modified to remove white space between map and legend.
BRFSS indicates Behavioral Risk Factor Surveillance System; and MI, myocardial infarction.
Source: BRFSS prevalence and trends data.[3]

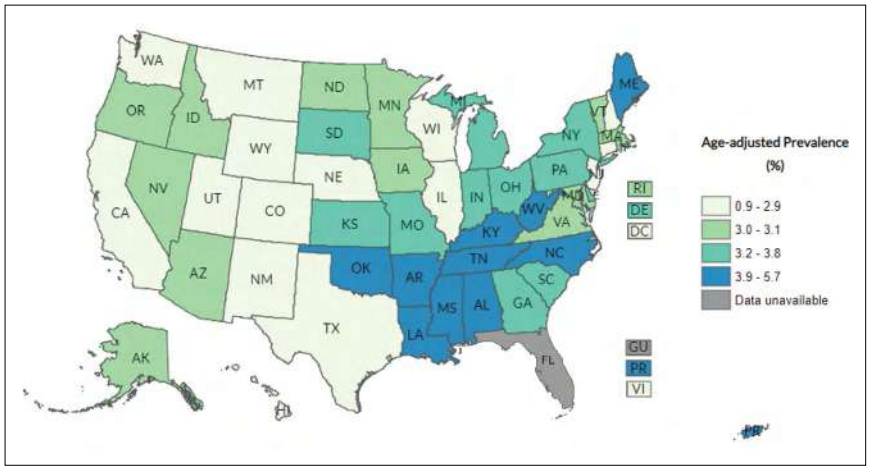



**Chart 21-4. "Ever told you had angina or CHD?" Age-adjusted US prevalence by state (BRFSS prevalence and trends data, 2021.**
Original chart has been modified to remove white space between map and legend.
BRFSS indicates Behavioral Risk Factor Surveillance System; and CHD, coronary heart disease.
Source: BRFSS prevalence and trends data.[3]

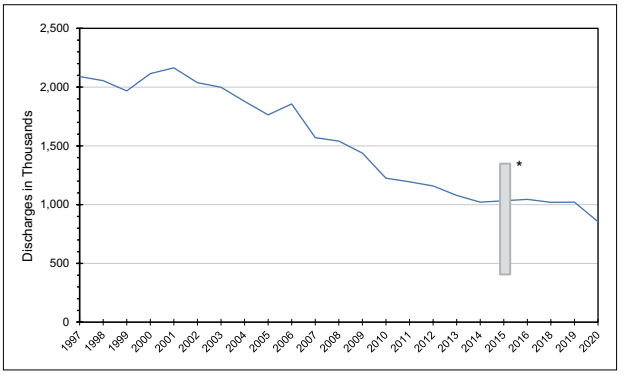



**Chart 21-5. Hospital discharges for CHD, United States (HCUP, 1997–2020).**
Hospital discharges include people discharged alive, dead, and status unknown.
CHD indicates coronary heart disease; and HCUP, Healthcare Cost and Utilization Project.
*Data not available for 2015. Readers comparing data across years should note that beginning October 1, 2015, a transition was made from the 9th revision to the 10th revision of the *International Classification of Diseases*. This should be kept in consideration because coding changes could affect some statistics, especially when comparisons are made across these years.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using HCUP.[72]



 *Circulation*. 2024;149:e347–e913. DOI: 10.1161/CIR.0000000000001209

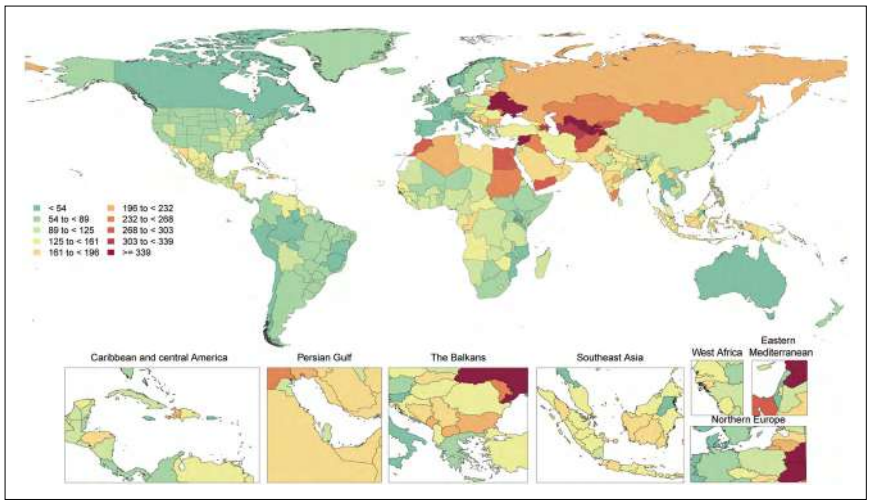



**Chart 21-6. Age-standardized global mortality rates of IHD per 100 000, both sexes, 2021.**
During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.
GBD indicates Global Burden of Disease; and IHD, ischemic heart disease.
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[133]

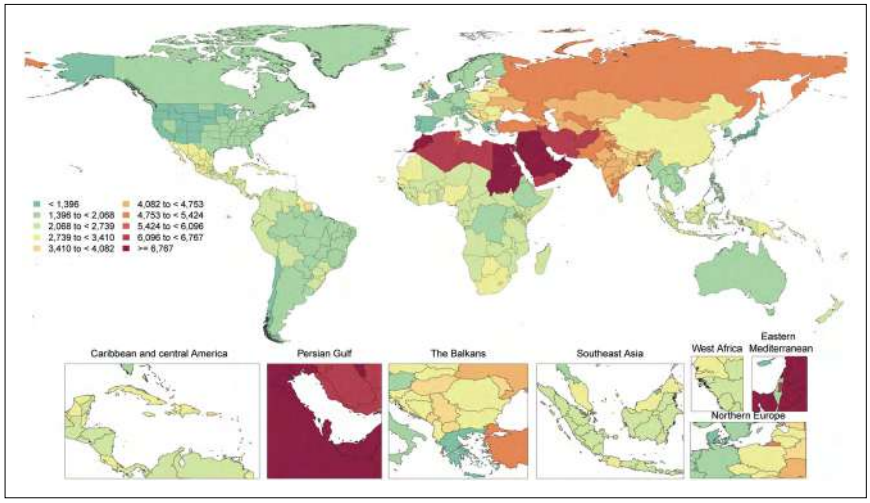



**Chart 21-7. Age-standardized global prevalence rates of IHD per 100 000, both sexes, 2021.**
During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.
GBD indicates Global Burden of Disease; and IHD, ischemic heart disease.
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[133]

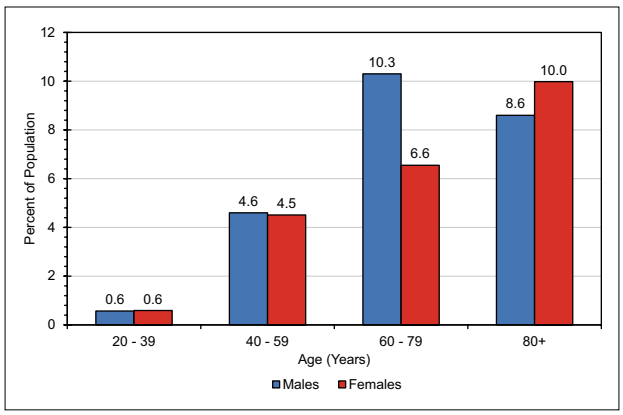



**Chart 21-8. Prevalence of AP by age and sex, United States (NHANES, 2017–2020).**
In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.[145] AP includes people who either answered "yes" to the question of ever having angina or AP or being diagnosed with Rose angina.
AP indicates anginal pectoris; COVID-19, coronavirus disease 2019; and NHANES, National Health and Nutrition Examination Survey.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.[1]

## REFERENCES


1. Centers for Disease Control and Prevention and National Center for Health Statistics. National Health and Nutrition Examination Survey (NHANES) public use data files. Accessed April 1, 2023. https://cdc.gov/nchs/nhanes/
2. Centers for Disease Control and Prevention and National Center for Health Statistics. Summary health statistics: National Health Interview Survey, 2018: table A-1. Accessed March 22, 2023. https://ftp.cdc.gov/pub/Health_Statistics/NCHS/NHIS/SHS/2018_SHS_Table_A-1.pdf
3. Centers for Disease Control and Prevention and National Center for Chronic Disease Prevention and Health Promotion. Behavioral Risk Factor Surveillance System (BRFSS): BRFSS prevalence & trends data. Accessed March 27, 2023. https://cdc.gov/brfss/brfssprevalence/
4. Atherosclerosis Risk in Communities (ARIC) Study. Community surveillance component, 2005–2014. Accessed April 1, 2023. https://sites.cscc.unc.edu/aric/
5. Colantonio LD, Gamboa CM, Richman JS, Levitan EB, Soliman EZ, Howard G, Safford MM. Black-White differences in incident fatal, nonfatal, and total coronary heart disease. *Circulation*. 2017;136:152–166. doi: 10.1161/CIRCULATIONAHA.116.025848
6. Sacks NC, Ash AS, Ghosh K, Rosen AK, Wong JB, Rosen AB. Trends in acute myocardial infarction hospitalizations: are we seeing the whole picture? *Am Heart J*. 2015;170:1211–1219. doi: 10.1016/j.ahj.2015.09.009
7. Raphael CE, Roger VL, Sandoval Y, Singh M, Bell M, Lerman A, Rihal CS, Gersh BJ, Lewis B, Lennon RJ, et al. Incidence, trends, and outcomes of type 2 myocardial infarction in a community cohort. *Circulation*. 2020;141:454–463. doi: 10.1161/CIRCULATIONAHA.119.043100
8. Almarzooq ZI, Wadhera RK, Xu J, Yeh RW. Population trends in rates of percutaneous coronary interventions, 2010 to 2017. *JAMA Cardiol*. 2021;6:1219–1220. doi: 10.1001/jamacardio.2021.2639
9. Rashid M, Gale CP, Curzen N, Ludman P, De Belder M, Timmis A, Mohamed MO, Lüscher TF, Hains J, et al. Impact of coronavirus disease 2019 pandemic on the incidence and management of out-of-hospital cardiac arrest in patients presenting with acute myocardial infarction in England. *J Am Heart Assoc*. 2020;9:e018379. doi: 10.1161/JAHA.120.018379
10. Mesnier J, Cottin Y, Coste P, Ferrari E, Schiele F, Lemesle G, Thuaire C, Angoulvant D, Cayla G, Bouleti C, et al. Hospital admissions for acute myocardial infarction before and after lockdown according to regional prevalence of COVID-19 and patient profile in France: a registry study. *Lancet Public Health*. 2020;5:e536–e542. doi: 10.1016/S2468-2667(20)30188-2
11. Case BC, Yerasi C, Forrestal BJ, Shea C, Rappaport H, Medranda GA, Zhang C, Satler LF, Ben-Dor I, Hashim H, et al. Comparison of characteristics and outcomes of patients with acute myocardial infarction with versus without coronarvirus-19. *Am J Cardiol*. 2021;144:8–12. doi: 10.1016/j.amjcard.2020.12.059
12. Tripathi B, Tan BE, Sharma P, Gaddam M, Singh A, Solanki D, Kumar V, Sharma A, Akhtar T, Michos ED, et al. Characteristics and outcomes of patients admitted with type 2 myocardial infarction. *Am J Cardiol*. 2021;157:33–41. doi: 10.1016/j.amjcard.2021.07.013
13. Fox DK, Waken RJ, Johnson DY, Hammond G, Yu J, Fanous E, Maddox TM, Joynt Maddox KE. Impact of the COVID-19 pandemic on patients without COVID-19 with acute myocardial infarction and heart failure. *J Am Heart Assoc*. 2022;11:e022625. doi: 10.1161/JAHA.121.022625
14. Pourasghari H, Tavolinejad H, Soleimanpour S, Abdi Z, Arabloo J, Bragazzi NL, Behzadifar M, Rashedi S, Omidi N, Ayoubian A, et al. Hospitalization, major complications and mortality in acute myocardial infarction patients during the COVID-19 era: a systematic review and meta-analysis. *Int J Cardiol Heart Vasc*. 2022;41:101058. doi: 10.1016/j.ijcha.2022.101058
15. Sofi F, Dinu M, Reboldi G, Stracci F, Pedretti RFE, Valente S, Gensini G, Gibson CM, Ambrosio G. Worldwide differences of hospitalization for ST-segment elevation myocardial infarction during COVID-19: a systematic review and meta-analysis. *Int J Cardiol*. 2022;347:89–96. doi: 10.1016/j.ijcard.2021.10.156
16. Matetic A, Shamkhani W, Rashid M, Volgman AS, Van Spall HGC, Coutinho T, Mehta LS, Sharma G, Parwani P, Mohamed MO, et al. Trends of sex differences in clinical outcomes after myocardial infarction in the United States. *CJC Open*. 2021;3:S19–S27. doi: 10.1016/j.cjco.2021.06.012
17. Pandey A, Keshvani N, Khera R, Lu D, Vaduganathan M, Joynt Maddox KE, Das SR, Kumbhani DJ, Goyal A, Girotra S, et al. Temporal trends in racial differences in 30-day readmission and mortality rates after acute myocardial infarction among Medicare beneficiaries. *JAMA Cardiol*. 2020;5:136–145. doi: 10.1001/jamacardio.2019.4845
18. Topel ML, Kim JH, Mujahid MS, Sullivan SM, Ko Y-A, Vaccarino V, Quyyumi AA, Lewis TT. Neighborhood socioeconomic status and adverse outcomes in patients with cardiovascular disease. *Am J Cardiol*. 2019;123:284–290. doi: 10.1016/j.amjcard.2018.10.011
19. Alghanem F, Clements JM. Narrowing performance gap between rural and urban hospitals for acute myocardial infarction care. *Am J Emerg Med*. 2020;38:89–94. doi: 10.1016/j.ajem.2019.04.030
20. Green YS, Hajduk AM, Song X, Krumholz HM, Sinha SK, Chaudhry SI. Usefulness of social support in older adults after hospitalization for acute myocardial infarction (from the SILVER-AMI study). *Am J Cardiol*. 2020;125:313–319. doi: 10.1016/j.amjcard.2019.10.038
21. Wadhera RK, Bhatt DL, Kind AJH, Song Y, Williams KA, Maddox TM, Yeh RW, Dong L, Doros G, Turchin A, et al. Association of outpatient practice-level socioeconomic disadvantage with quality of care and outcomes among older adults with coronary artery disease: implications for value-based payment. *Circ Cardiovasc Qual Outcomes*. 2020;13:e005977. doi: 10.1161/CIRCOUTCOMES.119.005977
22. Herbert BM, Johnson AE, Paasche-Orlow MK, Brooks MM, Magnani JW. Disparities in reporting a history of cardiovascular disease among adults with limited English proficiency and angina. *JAMA Netw Open*. 2021;4:e2138780. doi: 10.1001/jamanetworkopen.2021.38780
23. Ritchey MD, Maresh S, McNeely J, Shaffer T, Jackson SL, Keteyian SJ, Brawner CA, Whooley MA, Chang T, Stolp H, et al. Tracking cardiac rehabilitation participation and completion among Medicare beneficiaries to inform the efforts of a national initiative. *Circ Cardiovasc Qual Outcomes*. 2020;13:e005902. doi: 10.1161/CIRCOUTCOMES.119.005902
24. Peters AE, Keeley EC. Trends and predictors of participation in cardiac rehabilitation following acute myocardial infarction: data from the Behavioral Risk Factor Surveillance System. *J Am Heart Assoc*. 2018;7:e007664. doi: 10.1161/JAHA.117.007664
25. Garfein J, Guhl EN, Swabe G, Sekikawa A, Barinas-Mitchell E, Forman DE, Magnani JW. Racial and ethnic differences in cardiac rehabilitation participation: effect modification by household income. *J Am Heart Assoc*. 2022;11:e025591. doi: 10.1161/JAHA.122.025591
26. Kini V, Mosley B, Raghavan S, Khazanie P, Bradley SM, Magid DJ, Ho PM, Masoudi FA. Differences in high- and low-value cardiovascular testing by health insurance provider. *J Am Heart Assoc*. 2021;10:e018877. doi: 10.1161/JAHA.120.018877
27. Loccoh EC, Joynt Maddox KE, Wang Y, Kazi DS, Yeh RW, Wadhera RK. Rural-urban disparities in outcomes of myocardial infarction, heart failure, and stroke in the United States. *J Am Coll Cardiol*. 2022;79:267–279. doi: 10.1016/j.jacc.2021.10.045
28. Roy B, Hajduk AM, Tsang S, Geda M, Riley C, Krumholz HM, Chaudhry SI. The association of neighborhood walkability with health outcomes in older adults after acute myocardial infarction: the SILVER-AMI study. *Prev Med Rep*. 2021;23:101391. doi: 10.1016/j.pmedr.2021.101391
29. Safford MM, Reshetnyak E, Sterling MR, Richman JS, Muntner PM, Durant RW, Booth J, Pinheiro LC. Number of social determinants of health and fatal and nonfatal incident coronary heart disease in the REGARDS study. *Circulation*. 2021;143:244–253. doi: 10.1161/CIRCULATIONAHA.120.048026
30. Subramaniam AV, Patlolla SH, Cheungpasitporn W, Sundaragiri PR, Miller PE, Barsness GW, Bell MR, Holmes DR Jr, Vallabhajosyula S. Racial and ethnic disparities in management and outcomes of cardiac arrest complicating acute myocardial infarction. *J Am Heart Assoc*. 2021;10:e019907. doi: 10.1161/JAHA.120.019907
31. Simoni AH, Frydenlund J, Kragholm KH, Bøggild H, Jensen SE, Johnsen SP. Socioeconomic inequity in incidence, outcomes and care for acute coronary syndrome: a systematic review. *Int J Cardiol*. 2022;356:19–29. doi: 10.1016/j.ijcard.2022.03.053
32. Colantonio LD, Richman JS, Carson AP, Lloyd-Jones DM, Howard G, Deng L, Howard VJ, Safford MM, Muntner P, Goff DC Jr. Performance of the atherosclerotic cardiovascular disease Pooled Cohort Risk Equations by social deprivation status. *J Am Heart Assoc*. 2017;6:e005676. doi: 10.1161/JAHA.117.005676
33. Mora S, Wenger NK, Cook NR, Liu J, Howard BV, Limacher MC, Liu S, Margolis KL, Martin LW, Paynter NP, et al. Evaluation of the Pooled Cohort Risk Equations for cardiovascular risk prediction in a multiethnic cohort from the Women's Health Initiative. *JAMA Intern Med*. 2018;178:1231–1240. doi: 10.1001/jamainternmed.2018.2875
34. Dudum R, Dzaye O, Mirbolouk M, Dardari ZA, Orimoloye OA, Budoff MJ, Berman DS, Rozanski A, Miedema MD, Nasir K, et al. Coronary artery calcium scoring in low risk patients with family history of coronary heart disease: validation of the SCCT guideline approach in the Coronary Artery Calcium Consortium. *J Cardiovasc Comput Tomogr*. 2019;13:21–25. doi: 10.1016/j.jcct.2019.03.012

35. Blaha MJ, Cainzos-Achirica M, Dardari Z, Blankstein R, Shaw LJ, Rozanski A, Rumberger JA, Dzaye O, Michos ED, Berman DS, et al. All-cause and cause-specific mortality in individuals with zero and minimal coronary artery calcium: a long-term, competing risk analysis in the Coronary Artery Calcium Consortium. *Atherosclerosis*. 2020;294:72–79. doi: 10.1016/j.atherosclerosis.2019.11.008
36. Peng AW, Mirbolouk M, Orimoloye OA, Osei AD, Dardari Z, Dzaye O, Budoff MJ, Shaw L, Miedema MD, Rumberger J, et al. Long-term all-cause and cause-specific mortality in asymptomatic patients with CAC ≥ 1,000: results from the CAC Consortium. *JACC Cardiovasc Imaging*. 2020;13:83–93. doi: 10.1016/j.jcmg.2019.02.005
37. Chirinos DA, Llabre MM, Goldberg R, Gellman M, Mendez A, Cai J, Sotres-Alvarez D, Daviglus M, Gallo LC, Schneiderman N. Defining abdominal obesity as a risk factor for coronary heart disease in the US: results from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). *Diabetes Care*. 2020;43:1774–1780. doi: 10.2337/dc19-1855
38. Castro-Dominguez YS, Wang Y, Minges KE, McNamara RL, Spertus JA, Dehmer GJ, Messenger JC, Lavin K, Anderson C, Blankinship K, et al. Predicting in-hospital mortality in patients undergoing percutaneous coronary intervention. *J Am Coll Cardiol*. 2021;78:216–229. doi: 10.1016/j.jacc.2021.04.067
39. Blaha MJ, Naazie IN, Cainzos-Achirica M, Dardari ZA, DeFilippis AP, McClelland RL, Mirbolouk M, Orimoloye OA, Dzaye O, Nasir K, et al. Derivation of a coronary age calculator using traditional risk factors and coronary artery calcium: the Multi-Ethnic Study of Atherosclerosis. *J Am Heart Assoc*. 2021;10:e019351. doi: 10.1161/JAHA.120.019351
40. King A, Wu L, Deng HW, Shen H, Wu C. Polygenic risk score improves the accuracy of a clinical risk score for coronary artery disease. *BMC Med*. 2022;20:385. doi: 10.1186/s12916-022-02583-y
41. Taggart C, Monterrubio-Gómez K, Roos A, Boeddinghaus J, Kimenai DM, Kadesjo E, Bularga A, Wereski R, Ferry A, Lowry M, et al. Improving risk stratification for patients with type 2 myocardial infarction. *J Am Coll Cardiol*. 2023;81:156–168. doi: 10.1016/j.jacc.2022.10.025
42. Bachmann JM, Willis BL, Ayers CR, Khera A, Berry JD. Association between family history and coronary heart disease death across long-term follow-up in men: the Cooper Center Longitudinal Study. *Circulation*. 2012;125:3092–3098. doi: 10.1161/CIRCULATIONAHA.111.065490
43. Zdravkovic S, Wienke A, Pedersen NL, Marenberg ME, Yashin AI, De Faire U. Heritability of death from coronary heart disease: a 36-year follow-up of 20 966 Swedish twins. *J Intern Med*. 2002;252:247–254. doi: 10.1046/j.1365-2796.2002.01029.x
44. Howson JMM, Zhao W, Barnes DR, Ho WK, Young R, Paul DS, Waite LL, Freitag DF, Fauman EB, Salfati EL, et al. Fifteen new risk loci for coronary artery disease highlight arterial-wall-specific mechanisms. *Nat Genet*. 2017;49:1113–1119. doi: 10.1038/ng.3874
45. Helgadottir A, Thorleifsson G, Manolescu A, Gretarsdottir S, Blondal T, Jonasdottir A, Jonasdottir A, Sigurdsson A, Baker A, Palsson A, et al. A common variant on chromosome 9p21 affects the risk of myocardial infarction. *Science*. 2007;316:1491–1493. doi: 10.1126/science.1142842
46. Palomaki GE, Melillo S, Bradley LA. Association between 9p21 genomic markers and heart disease: a meta-analysis. *JAMA*. 2010;303:648–656. doi: 10.1001/jama.2010.118
47. Tcheandjieu C, Zhu X, Hilliard AT, Clarke SL, Napolioni V, Ma S, Lee KM, Fang H, Chen F, Lu Y, et al; Regeneron Genetics Center. Large-scale genome-wide association study of coronary artery disease in genetically diverse populations. *Nat Med*. 2022;28:1679–1692. doi: 10.1038/s41591-022-01891-3
48. Myocardial Infarction Genetics and CARDIoGRAM Exome Consortia Investigators; Stitziel NO, Stirrups KE, Masca NG, Erdmann J, Ferrario PG, König IR, Weeke PE, Webb TR, Auer PL, Schick UM. Coding variation in *ANGPTL4*, *LPL*, and *SVEP1* and the Risk of Coronary Disease. *N Engl J Med*. 2016;374:1134–1144. doi: 10.1056/NEJMoa1507652
49. Natarajan P, Pampana A, Graham SE, Ruotsalainen SE, Perry JA, de Vries PS, Broome JG, Pirruccello JP, Honigberg MC, Aragam K, et al; NHLBI Trans-Omics for Precision Medicine (TOPMed) Consortium. Chromosome Xq23 is associated with lower atherogenic lipid concentrations and favorable cardiometabolic indices. *Nat Commun*. 2021;12:2182. doi: 10.1038/s41467-021-22339-1
50. Zhan Y, Karlsson IK, Karlsson R, Tillander A, Reynolds CA, Pedersen NL, Hagg S. Exploring the causal pathway from telomere length to coronary heart disease: a network mendelian randomization study. *Circ Res*. 2017;121:214–219. doi: 10.1161/CIRCRESAHA.116.310517
51. Jaiswal S, Natarajan P, Silver AJ, Gibson CJ, Bick AG, Shvartz E, McConkey M, Gupta N, Gabriel S, Ardissino D, et al. Clonal hematopoiesis and risk of atherosclerotic cardiovascular disease. *N Engl J Med*. 2017;377:111–121. doi: 10.1056/NEJMoa1701719
52. Bick AG, Weinstock JS, Nandakumar SK, Fulco CP, Bao EL, Zekavat SM, Szeto MD, Liao X, Leventhal MJ, Nasser J, et al; NHLBI Trans-Omics for Precision Medicine Consortium. Inherited causes of clonal haematopoiesis in 97,691 whole genomes. *Nature*. 2020;586:763–768. doi: 10.1038/s41586-020-2819-2
53. Khera AV, Chaffin M, Zekavat SM, Collins RL, Roselli C, Natarajan P, Lichtman JH, D'Onofrio G, Mattera J, Dreyer R, et al. Whole-genome sequencing to characterize monogenic and polygenic contributions in patients hospitalized with early-onset myocardial infarction. *Circulation*. 2019;139:1593–1602. doi: 10.1161/CIRCULATIONAHA.118.035658
54. Khera AV, Emdin CA, Drake I, Natarajan P, Bick AG, Cook NR, Chasman DI, Baber U, Mehran R, Rader DJ, et al. Genetic risk, adherence to a healthy lifestyle, and coronary disease. *N Engl J Med*. 2016;375:2349–2358. doi: 10.1056/NEJMoa1605086
55. Groenendyk JW, Greenland P, Khan SS. Incremental value of polygenic risk scores in primary prevention of coronary heart disease: a review. *JAMA Intern Med*. 2022;182:1082–1088. doi: 10.1001/jamainternmed.2022.3171
56. Marston NA, Kamanu FK, Nordio F, Gurmu Y, Roselli C, Sever PS, Pedersen TR, Keech AC, Wang H, Lira Pineda A, et al. Predicting benefit from evolocumab therapy in patients with atherosclerotic disease using a genetic risk score: results from the FOURIER trial. *Circulation*. 2020;141:616–623. doi: 10.1161/CIRCULATIONAHA.119.043805
57. Elliott J, Bodinier B, Bond TA, Chadeau-Hyam M, Evangelou E, Moons KGM, Dehghan A, Muller DC, Elliott P, Tzoulaki I. Predictive accuracy of a polygenic risk score-enhanced prediction model vs a clinical risk score for coronary artery disease. *JAMA*. 2020;323:636–645. doi: 10.1001/jama.2019.22241
58. Mosley JD, Gupta DK, Tan J, Yao J, Wells QS, Shaffer CM, Kundu S, Robinson-Cohen C, Psaty BM, Rich SS, et al. Predictive accuracy of a polygenic risk score compared with a clinical risk score for incident coronary heart disease. *JAMA*. 2020;323:627–635. doi: 10.1001/jama.2019.21782
59. Lu X, Liu Z, Cui Q, Liu F, Li J, Niu X, Shen C, Hu D, Huang K, Chen J, et al. A polygenic risk score improves risk stratification of coronary artery disease: a large-scale prospective Chinese cohort study. *Eur Heart J*. 2022;43:1702–1711. doi: 10.1093/eurheartj/ehac093
60. Dikilitas O, Schaid DJ, Kosel ML, Carroll RJ, Chute CG, Denny JA, Fedotov A, Feng Q, Hakonarson H, Jarvik GP, et al. Predictive utility of polygenic risk scores for coronary heart disease in three major racial and ethnic groups. *Am J Hum Genet*. 2020;106:707–716. doi: 10.1016/j.ajhg.2020.04.002
61. Wang M, Menon R, Mishra S, Patel AP, Chaffin M, Tanneeru D, Deshmukh M, Mathew O, Apte S, Devanboo CS, et al. Validation of a genome-wide polygenic score for coronary artery disease in South Asians. *J Am Coll Cardiol*. 2020;76:703–714. doi: 10.1016/j.jacc.2020.06.024
62. Fang J, Luncheon C, Ayala C, Odom E, Loustalot F. Awareness of heart attack symptoms and response among adults: United States, 2008, 2014, and 2017. *MMWR Morb Mortal Wkly Rep*. 2019;68:101–106. doi: 10.15585/mmwr.mm6805a2
63. Mahajan S, Valero-Elizondo J, Khera R, Desai NR, Blankstein R, Blaha MJ, Virani SS, Kash BA, Zoghbi WA, Krumholz HM, et al. Variation and disparities in awareness of myocardial infarction symptoms among adults in the United States. *JAMA Netw Open*. 2019;2:e1917885. doi: 10.1001/jamanetworkopen.2019.17885
64. Mannoh I, Turkson-Ocran RA, Mensah J, Mensah D, Yi SS, Michos ED, Commodore-Mensah Y. Disparities in awareness of myocardial infarction and stroke symptoms and response among United States- and foreign-born adults in the National Health Interview Survey. *J Am Heart Assoc*. 2021;10:e020396. doi: 10.1161/JAHA.121.020396
65. Cushman M, Shay CM, Howard VJ, Jiménez MC, Lewey J, McSweeney JC, Newby LK, Poudel R, Reynolds HR, Rexrode KM, et al; on behalf of the American Heart Association. Ten-year differences in women's awareness related to coronary heart disease: results of the 2019 American Heart Association national survey: a special report from the American Heart Association. *Circulation*. 2021;143:e239–e248. doi: 10.1161/CIR.0000000000000907
66. Vallabhajosyula S, Patlolla SH, Miller PE, Cheungpasitporn W, Jaffe AS, Gersh BJ, Holmes DR Jr, Bell MR, Barsness GW. Weekend effect in the management and outcomes of acute myocardial infarction in the United States, 2000-2016. *Mayo Clin Proc Innov Qual Outcomes*. 2020;4:362–372. doi: 10.1016/j.mayocpiqo.2020.02.004
67. Dharma S, Kamarullah W, Sabrina AP. Association of admission time and mortality in STEMI patients: a systematic review and meta-analysis. *Int J Angiol*. 2022;31:273–283. doi: 10.1055/s-0042-1742610

68. De Luca G, Verdoia M, Cercek M, Jensen LO, Vavlukis M, Calmac L, Johnson T, Ferrer GR, Ganyukov V, Wojakowski W, et al. Impact of COVID-19 pandemic on mechanical reperfusion for patients with STEMI. *J Am Coll Cardiol*. 2020;76:2321–2330. doi: 10.1016/j.jacc.2020.09.546
69. Foo CY, Bonsu KO, Nallamothu BK, Reid CM, Dhippayom T, Reidpath DD, Chaiyakunapruk N. Coronary intervention door-to-balloon time and outcomes in ST-elevation myocardial infarction: a meta-analysis. *Heart*. 2018;104:1362–1369. doi: 10.1136/heartjnl-2017-312517
70. Cui ER, Fernandez AR, Zegre-Hemsey JK, Grover JM, Honvoh G, Brice JH, Rossi JS, Patel MD. Disparities in emergency medical services time intervals for patients with suspected acute coronary syndrome: findings from the North Carolina Prehospital Medical Information System. *J Am Heart Assoc*. 2021;10:e019305. doi: 10.1161/JAHA.120.019305
71. De Luca G, Algowhary M, Uguz B, Oliveira DC, Ganyukov V, Zimbakov Z, Cercek M, Jensen LO, Loh PH, Calmac L, et al; ISACS-STEMI COVID-19. COVID-19 pandemic, mechanical reperfusion and 30-day mortality in ST elevation myocardial infarction. *Heart*. 2022;108:458–466. doi: 10.1136/heartjnl-2021-319750
72. Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project (HCUP). Accessed April 1, 2023. http://hcupnet.ahrq.gov/
73. Dixon LK, Di Tommaso E, Dimagli A, Sinha S, Sandhu M, Benedetto U, Angelini GD. Impact of sex on outcomes after cardiac surgery: a systematic review and meta-analysis. *Int J Cardiol*. 2021;343:27–34. doi: 10.1016/j.ijcard.2021.09.011
74. Chang M, Lee CW, Ahn JM, Cavalcante R, Sotomi Y, Onuma Y, Zeng Y, Park DW, Kang SJ, Lee SW, et al. Coronary artery bypass grafting versus drug-eluting stents implantation for previous myocardial infarction. *Am J Cardiol*. 2016;118:17–22. doi: 10.1016/j.amjcard.2016.04.009
75. Thuijs DJFM, Kappetein AP, Serruys PW, Mohr F-W, Morice M-C, Mack MJ, Holmes DR Jr, Curzen N, Davierwala P, Noack T, et al; SYNTAX Extended Survival Investigators. Percutaneous coronary intervention versus coronary artery bypass grafting in patients with three-vessel or left main coronary artery disease: 10-year follow-up of the multicentre randomised controlled SYNTAX trial. *Lancet*. 2019;394:1325–1334. doi: 10.1016/S0140-6736(19)31997-X
76. Lopez-Sendon JL, Cyr DD, Mark DB, Bangalore S, Huang Z, White HD, Alexander KP, Li J, Nair RG, Demkow M, et al. Effects of initial invasive vs initial conservative treatment strategies on recurrent and total cardiovascular events in the ISCHEMIA trial. *Eur Heart J*. 2021;43:148–149. doi: 10.1093/eurheartj/ehab509
77. Stone GW, Kappetein AP, Sabik JF, Pocock SJ, Morice M-C, Puskas J, Kandzari DE, Karmpaliotis D, Brown WM 3rd, Lembo NJ, et al; EXCEL Trial Investigators. Five-year outcomes after PCI or CABG for left main coronary disease. *N Engl J Med*. 2019;381:1820–1830. doi: 10.1056/NEJMoa1909406
78. Valle JA, Tamez H, Abbott JD, Moussa ID, Messenger JC, Waldo SW, Kennedy KF, Masoudi FA, Yeh RW. Contemporary use and trends in unprotected left main coronary artery percutaneous coronary intervention in the United States: an analysis of the National Cardiovascular Data Registry Research to Practice Initiative. *JAMA Cardiol*. 2019;4:100–109. doi: 10.1001/jamacardio.2018.4376
79. Mehta SR, Wood DA, Storey RF, Mehran R, Bainey KR, Nguyen H, Meeks B, Di Pasquale G, López-Sendón J, Faxon DP, et al; COMPLETE Trial Steering Committee and Investigators. Complete revascularization with multivessel PCI for myocardial infarction. *N Engl J Med*. 2019;381:1411–1421. doi: 10.1056/NEJMoa1907775
80. Shavadia JS, Roe MT, Chen AY, Lucas J, Fanaroff AC, Kochar A, Fordyce CB, Jollis JG, Tamis-Holland J, Henry TD, et al. Association between cardiac catheterization laboratory pre-activation and reperfusion timing metrics and outcomes in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention: a report from the ACTION registry. *JACC Cardiovasc Interv*. 2018;11:1837–1847. doi: 10.1016/j.jcin.2018.07.020
81. Maron DJ, Hochman JS, Reynolds HR, Bangalore S, O'Brien SM, Boden WE, Chaitman BR, Senior R, Lopez-Sendon J, Alexander KP, et al; ISCHEMIA Research Group. Initial invasive or conservative strategy for stable coronary disease. *N Engl J Med*. 2020;382:1395–1407. doi: 10.1056/NEJMoa1915922
82. Elbadawi A, Elgendy IY, Ha LD, Mahmoud K, Lenka J, Olorunfemi O, Reyes A, Ogunbayo GO, Saad M, Abbott JD. National trends and outcomes of percutaneous coronary intervention in patients ≥70 years of age with acute coronary syndrome (from the National Inpatient Sample Database). *Am J Cardiol*. 2019;123:25–32. doi: 10.1016/j.amjcard.2018.09.030
83. Alnasser SM, Bagai A, Jolly SS, Cantor WJ, Dehghani P, Rao SV, Cheema AN. Transradial approach for coronary angiography and intervention in the elderly: a meta-analysis of 777,841 patients. *Int J Cardiol*. 2017;228:45–51. doi: 10.1016/j.ijcard.2016.11.207
84. McCarthy CP, Kolte D, Kennedy KF, Vaduganathan M, Wasfy JH, Januzzi JL Jr. Patient characteristics and clinical outcomes of type 1 versus type 2 myocardial infarction. *J Am Coll Cardiol*. 2021;77:848–857. doi: 10.1016/j.jacc.2020.12.034
85. Mohammad MA, Persson J, Buccheri S, Odenstedt J, Sarno G, Angerås O, Völz S, Tödt T, Götberg M, Isma N, et al. Trends in clinical practice and outcomes after percutaneous coronary intervention of unprotected left main coronary artery. *J Am Heart Assoc*. 2022;11:e024040. doi: 10.1161/JAHA.121.024040
86. Shields GE, Rowlandson A, Dalal G, Nickerson S, Cranmer H, Capobianco L, Doherty P. Cost-effectiveness of home-based cardiac rehabilitation: a systematic review. *Heart*. 2023;109:913–920. doi: 10.1136/heartjnl-2021-320459
87. Widmer RJ, Allison TG, Lennon R, Lopez-Jimenez F, Lerman LO, Lerman A. Digital health intervention during cardiac rehabilitation: a randomized controlled trial. *Am Heart J*. 2017;188:65–72. doi: 10.1016/j.ahj.2017.02.016
88. Krishnamurthi N, Schopfer DW, Shen H, Rohrbach G, Elnaggar A, Whooley MA. Association of home-based cardiac rehabilitation with lower mortality in patients with cardiovascular disease: results from the Veterans Health Administration Healthy Heart Program. *J Am Heart Assoc*. 2023;12:e025856. doi: 10.1161/JAHA.122.025856
89. Centers for Disease Control and Prevention and National Center for Health Statistics. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death micro-data files. Accessed April 8, 2023. https://cdc.gov/nchs/nvss/mortality_public_use_data.htm
90. Centers for Disease Control and Prevention and National Center for Health Statistics. Multiple cause of death, CDC WONDER online database. Accessed April 1, 2023. https://wonder.cdc.gov/mcd-icd10.html
91. Krumholz HM, Normand ST, Wang Y. Twenty-year trends in outcomes for older adults with acute myocardial infarction in the United States. *JAMA Netw Open*. 2019;2:e191938. doi: 10.1001/jamanetworkopen.2019.1938
92. Sidney S, Go AS, Jaffe MG, Solomon MD, Ambrosy AP, Rana JS. Association between aging of the US population and heart disease mortality from 2011 to 2017. *JAMA Cardiol*. 2019;4:1280–1286. doi: 10.1001/jamacardio.2019.4187
93. Landon BE, Anderson TS, Curto VE, Cram P, Fu C, Weinreb G, Zaslavsky AM, Ayanian JZ. Association of Medicare Advantage vs traditional Medicare with 30-day mortality among patients with acute myocardial infarction. *JAMA*. 2022;328:2126–2135. doi: 10.1001/jama.2022.20982
94. Reynolds HR, Shaw LJ, Min JK, Page CB, Berman DS, Chaitman BR, Picard MH, Kwong RY, O'Brien SM, Huang Z, et al. Outcomes in the ISCHEMIA trial based on coronary artery disease and ischemia severity. *Circulation*. 2021;144:1024–1038. doi: 10.1161/CIRCULATIONAHA.120.049755
95. Hochman JS, Anthopolos R, Reynolds HR, Bangalore S, Xu Y, O'Brien SM, Mavromichalis S, Chang M, Contreras A, Rosenberg Y, et al; ISCHEMIA-EXTEND Research Group. Survival after invasive or conservative management of stable coronary disease. *Circulation*. 2023;147:8–19. doi: 10.1161/CIRCULATIONAHA.122.062714
96. Shah T, Haimi I, Yang Y, Gaston S, Taoutel R, Mehta S, Lee HJ, Zambahari R, Baumbach A, Henry TD, et al. Meta-analysis of gender disparities in in-hospital care and outcomes in patients with ST-segment elevation myocardial infarction. *Am J Cardiol*. 2021;147:23–32. doi: 10.1016/j.amjcard.2021.02.015
97. Minhas AMK, Awan MU, Raza M, Virani SS, Sharma G, Blankstein R, Blaha MJ, Al-Kindi SG, Kaluksi E, Nasir K, et al. Clinical and economic burden of percutaneous coronary intervention in hospitalized young adults in the United States, 2004-2018. *Curr Probl Cardiol*. 2022;47:101070. doi: 10.1016/j.cpcardiol.2021.101070
98. Joseph JJ, Rajwani A, Roper D, Zhao S, Kline D, Odei J, Brock G, Echouffo-Tcheugui JB, Kalyani RR, Bertoni AG, et al. Associations of cardiometabolic multimorbidity with all-cause and coronary heart disease mortality among Black adults in the Jackson Heart Study. *JAMA Netw Open*. 2022;5:e2238361. doi: 10.1001/jamanetworkopen.2022.38361
99. Langabeer JR 2nd, Henry TD, Fowler R, Champagne-Langabeer T, Kim J, Jacobs AK. Sex-based differences in discharge disposition and outcomes for ST-segment elevation myocardial infarction patients within a regional network. *J Womens Health (Larchmt)*. 2018;27:1001–1006. doi: 10.1089/jwh.2017.6553
100. Langabeer JR 2nd, Champagne-Langabeer T, Fowler R, Henry T. Gender-based outcome differences for emergency department presentation of

non-STEMI acute coronary syndrome. *Am J Emerg Med*. 2019;37:179–182. doi: 10.1016/j.ajem.2018.05.005
101. Huded CP, Johnson M, Kravitz K, Menon V, Abdallah M, Gullett TC, Hantz S, Ellis SG, Podolsky SR, Meldon SW, et al. 4-Step protocol for disparities in STEMI care and outcomes in women. *J Am Coll Cardiol*. 2018;71:2122–2132. doi: 10.1016/j.jacc.2018.02.039
102. Pancholy S, Patel G, Pancholy M, Nanavaty S, Coppola J, Kwan T, Patel T. Association between health insurance status and in-hospital outcomes after ST-segment elevation myocardial infarction. *Am J Cardiol*. 2017;120:1049–1054. doi: 10.1016/j.amjcard.2017.06.041
103. Conrad Z, Rehm CD, Wilde P, Mozaffarian D. Cardiometabolic mortality by Supplemental Nutrition Assistance Program participation and eligibility in the United States. *Am J Public Health*. 2017;107:466–474. doi: 10.2105/AJPH.2016.303608
104. Enumah ZO, Canner JK, Alejo D, Warren DS, Zhou X, Yenokyan G, Matthew T, Lawton JS, Higgins RSD. Persistent racial and sex disparities in outcomes after coronary artery bypass surgery: a retrospective clinical registry review in the drug-eluting stent era. *Ann Surg*. 2020;272:660–667. doi: 10.1097/SLA.0000000000004335
105. Kosmidou I, Leon MB, Zhang Y, Serruys PW, von Birgelen C, Smits PC, Ben-Yehuda O, Redfors B, Madhavan MV, Maehara A, et al. Long-term outcomes in women and men following percutaneous coronary intervention. *J Am Coll Cardiol*. 2020;75:1631–1640. doi: 10.1016/j.jacc.2020.01.056
106. Shah NS, Ning H, Petito LC, Kershaw KN, Bancks MP, Reis JP, Rana JS, Sidney S, Jacobs DR, Kiefe CI, et al. Associations of clinical and social risk factors with racial differences in premature cardiovascular disease. *Circulation*. 2022;146:201–210. doi: 10.1161/CIRCULATIONAHA.121.058311
107. Post WS, Watson KE, Hansen S, Folsom AR, Szklo M, Shea S, Barr RG, Burke G, Bertoni AG, Allen N, et al. Racial and ethnic differences in all-cause and cardiovascular disease mortality: the MESA study. *Circulation*. 2022;146:229–239. doi: 10.1161/CIRCULATIONAHA.122.059174
108. Liao NS, Sidney S, Deosaransingh K, Van Den Eeden SK, Schwartz J, Alexeeff SE. Particulate air pollution and risk of cardiovascular events among adults with a history of stroke or acute myocardial infarction. *J Am Heart Assoc*. 2021;10:e019758. doi: 10.1161/JAHA.120.019758
109. Dugani SB, Fabbri M, Chamberlain AM, Bielinski SJ, Weston SA, Manemann SM, Jiang R, Roger VL. Premature myocardial infarction: a community study. *Mayo Clin Proc Innov Qual Outcomes*. 2021;5:413–422. doi: 10.1016/j.mayocpiqo.2021.01.011
110. Rathod KS, Jones DA, Jain AK, Lim P, Maccarthy PA, Rakhit R, Lockie T, Kalra S, Dalby MC, Malik IS, et al. The influence of biological age and sex on long-term outcome after percutaneous coronary intervention for ST-elevation myocardial infarction. *Am J Cardiovasc Dis*. 2021;11:659–678.
111. Masoudi FA, Ponirakis A, de Lemos JA, Jollis JG, Kremers M, Messenger JC, Moore JW, Moussa I, Oetgen WJ, Varosy PD, et al. Trends in US cardiovascular care: 2016 report from 4 ACC National Cardiovascular Data Registries. *J Am Coll Cardiol*. 2017;69:1427–1450. doi: 10.1016/j.jacc.2016.12.005
112. Udell JA, Desai NR, Li S, Thomas L, de Lemos JA, Wright-Slaughter P, Zhang W, Roe MT, Bhatt DL. Neighborhood socioeconomic disadvantage and care after myocardial infarction in the National Cardiovascular Data Registry. *Circ Cardiovasc Qual Outcomes*. 2018;11:e004054. doi: 10.1161/CIRCOUTCOMES.117.004054
113. Mahmoud AN, Taduru SS, Mentias A, Mahtta D, Barakat AF, Saad M, Elgendy AY, Mojadidi MK, Omer M, Abuzaid A, et al. Trends of incidence, clinical presentation, and in-hospital mortality among women with acute myocardial infarction with or without spontaneous coronary artery dissection: a population-based analysis. *JACC Cardiovasc Interv*. 2018;11:80–90. doi: 10.1016/j.jcin.2017.08.016
114. Smilowitz NR, Mahajan AM, Roe MT, Hellkamp AS, Chiswell K, Gulati M, Reynolds HR. Mortality of myocardial infarction by sex, age, and obstructive coronary artery disease status in the ACTION Registry-GWTG (Acute Coronary Treatment and Intervention Outcomes Network Registry–Get With The Guidelines). *Circ Cardiovasc Qual Outcomes*. 2017;10:e003443. doi: 10.1161/CIRCOUTCOMES.116.003443
115. Abdullah A, Eigbire G, Salama A, Wahab A, Awadalla M, Hoefen R, Alweis R. Impact of delirium on patients hospitalized for myocardial infarction: a propensity score analysis of the National Inpatient Sample. *Clin Cardiol*. 2018;41:910–915. doi: 10.1002/clc.22972
116. Giustino G, Redfors B, Brener SJ, Kirtane AJ, Genereux P, Maehara A, Dudek D, Neunteufl T, Metzger DC, Crowley A, et al. Correlates and prognostic impact of new-onset heart failure after ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention: insights from the INFUSE-AMI trial. *Eur Heart J Acute Cardiovasc Care*. 2018;7:339–347. doi: 10.1177/2048872617719649
117. Wang Y, Leifheit E, Normand ST, Krumholz HM. Association between subsequent hospitalizations and recurrent acute myocardial infarction within 1 year after acute myocardial infarction. *J Am Heart Assoc*. 2020;9:e014907. doi: 10.1161/JAHA.119.014907
118. Fordyce CB, Giugliano RP, Cannon CP, Roe MT, Sharma A, Page C, White JA, Lokhnygina Y, Braunwald E, Blazing MA. Cardiovascular events and long-term risk of sudden death among stabilized patients after acute coronary syndrome: insights from IMPROVE-IT. *J Am Heart Assoc*. 2022;11:e022733. doi: 10.1161/JAHA.121.022733
119. Gaudino M, Di Franco A, Alexander JH, Bakaeen F, Egorova N, Kurlansky P, Boening A, Chikwe J, Demetres M, Devereaux PJ, et al. Sex differences in outcomes after coronary artery bypass grafting: a pooled analysis of individual patient data. *Eur Heart J*. 2021;43:18–28. doi: 10.1093/eurheartj/ehab504
120. Yandrapalli S, Malik A, Pemmasani G, Aronow W, Shah F, Lanier G, Cooper H, Jain D, Naidu S, Frishman W, et al. Sex differences in heart failure hospitalisation risk following acute myocardial infarction. *Heart*. 2021;107:1657–1663. doi: 10.1136/heartjnl-2020-318306
121. Conradie A, Atherton J, Chowdhury E, Duong M, Schwarz N, Worthley S, Eccleston D. The association of sex with unplanned cardiac readmissions following percutaneous coronary intervention in australia: results from a multicentre outcomes registry (GenesisCare Cardiovascular Outcomes Registry). *J Clin Med*. 2022;11:6866. doi: 10.3390/jcm11226866
122. Centers for Disease Control and Prevention and National Center for Health Statistics. National Ambulatory Medical Care Survey (NAMCS) public use data files. Accessed April 1, 2023. https://cdc.gov/nchs/ahcd/datasets_documentation_related.htm#data
123. Velagapudi P, Kolte D, Ather K, Khera S, Gupta T, Gordon PC, Aronow HD, Kirtane AJ, Abbott JD. Temporal trends and factors associated with prolonged length of stay in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Am J Cardiol*. 2018;122:185–191. doi: 10.1016/j.amjcard.2018.03.365
124. Lee MT, Mahtta D, Ramsey DJ, Liu J, Misra A, Nasir K, Samad Z, Itchhaporia D, Khan SU, Schofield RS, et al. Sex-related disparities in cardiovascular health care among patients with premature atherosclerotic cardiovascular disease. *JAMA Cardiol*. 2021;6:782–790. doi: 10.1001/jamacardio.2021.0683
125. Zheutlin AR, Derington CG, Herrick JS, Rosenson RS, Poudel B, Safford MM, Brown TM, Jackson EA, Woodward M, Reading S, et al. Lipid-lowering therapy use and intensification among United States veterans following myocardial infarction or coronary revascularization between 2015 and 2019. *Circ Cardiovasc Qual Outcomes*. 2022;15:e008861. doi: 10.1161/CIRCOUTCOMES.121.008861
126. White HD, O'Brien SM, Alexander KP, Boden WE, Bangalore S, Li J, Manjunath CN, Lopez-Sendon JL, Peteiro J, Gosselin G, et al. Comparison of days alive out of hospital with initial invasive vs conservative management: a prespecified analysis of the ISCHEMIA trial. *JAMA Cardiol*. 2021;6:1023–1031. doi: 10.1001/jamacardio.2021.1651
127. Agency for Healthcare Research and Quality. Medical Expenditure Panel Survey (MEPS): household component summary tables: medical conditions, United States. Accessed April 2, 2023. https://meps.ahrq.gov/mepsweb/
128. Moore BJ, Liang L. Medicare Advantage versus the traditional Medicare program: costs of inpatient stays, 2009-2017. Healthcare Cost and Utilization Project (HCUP) Statistical Brief. August 2020. HCUP Statistical Brief #262. Accessed November 27, 2020. https://hcup-us.ahrq.gov/reports/statbriefs/sb262-Medicare-Advantage-Costs-2009-2017.pdf#:~:text=Between%202009%20and%202017%2C%20the%20number%20and%20inflation-adjusted,a%20primary%20expected%20payer%20of%20traditional%20Medicare%20decreased
129. Wadhera RK, Joynt Maddox KE, Wang Y, Shen C, Bhatt DL, Yeh RW. Association between 30-day episode payments and acute myocardial infarction outcomes among Medicare beneficiaries. *Circ Cardiovasc Qual Outcomes*. 2018;11:e004397. doi: 10.1161/CIRCOUTCOMES.117.004397
130. Likosky DS, Van Parys J, Zhou W, Borden WB, Weinstein MC, Skinner JS. Association between Medicare expenditure growth and mortality rates in patients with acute myocardial infarction: a comparison from 1999 through 2014. *JAMA Cardiol*. 2018;3:114–122. doi: 10.1001/jamacardio.2017.4771
131. Cowper PA, Knight JD, Davidson-Ray L, Peterson ED, Wang TY, Mark DB; TRANSLATE-ACS Investigators. Acute and 1-year hospitalization costs for acute myocardial infarction treated with percutaneous coronary intervention: results from the TRANSLATE-ACS Registry. *J Am Heart Assoc*. 2019;8:e011322. doi: 10.1161/JAHA.118.011322

132. Teman NR, Hawkins RB, Charles EJ, Mehaffey JH, Speir AM, Quader MA, Ailawadi G; Investigators for the Virginia Cardiac Services Quality Initiative. Minimally invasive vs open coronary surgery: a multi-institutional analysis of cost and outcomes. *Ann Thorac Surg*. 2021;111:1478–1484. doi: 10.1016/j.athoracsur.2020.06.136
133. Global Burden of Disease Study and Institute for Health Metrics and Evaluation. University of Washington. Accessed August 2, 2023. http://ghdx.healthdata.org/
134. Quashie NT, D'Este C, Agrawal S, Naidoo N, Kowal P. Prevalence of angina and co-morbid conditions among older adults in six low- and middle-income countries: evidence from SAGE Wave 1. *Int J Cardiol*. 2019;285:140–146. doi: 10.1016/j.ijcard.2019.02.068
135. Piccolo R, Bruzzese D, Mauro C, Aloia A, Baldi C, Boccalatte M, Bottiglieri G, Briguori C, Caiazzo G, Calabro P, et al; Collaborators. Population trends in rates of percutaneous coronary revascularization for acute coronary syndromes associated with the COVID-19 outbreak. *Circulation*. 2020;141:2035–2037. doi: 10.1161/CIRCULATIONAHA.120.047457
136. Peck KY, Andrianopoulos N, Dinh D, Roberts L, Duffy SJ, Sebastian M, Clark D, Brennan A, Oqueli E, Ajani AE, et al. Role of beta blockers following percutaneous coronary intervention for acute coronary syndrome. *Heart*. 2021;107:728–733. doi: 10.1136/heartjnl-2020-316605
137. Qureshi WT, Kakouros N, Fahed J, Rade JJ. Comparison of prevalence, presentation, and prognosis of acute coronary syndromes in ≤35 years, 36 - 54 years, and ≥ 55 years patients. *Am J Cardiol*. 2021;140:1–6. doi: 10.1016/j.amjcard.2020.10.054
138. Chakraborty S, Bandyopadhyay D, Amgai B, Sidhu JS, Paudel R, Koirala S, Hajra A, Ghosh RK, Lavie CJ. Does insurance effect the outcome in patients with acute coronary syndrome? An insight from the most recent National Inpatient Sample. *Curr Probl Cardiol*. 2021;46:100411. doi: 10.1016/j.cpcardiol.2019.02.003
139. de Abreu M, Zylberman M, Vensentini N, Villarreal R, Zaidel E, Antonietti L, Mariani J, Gagliardi J, Doval H, Tajer C. Sex differences in the clinical presentation of acute coronary syndromes. *Curr Probl Cardiol*. 2022;47:101300. doi: 10.1016/j.cpcardiol.2022.101300
140. Batra G, Lindbäck J, Becker RC, Harrington RA, Held C, James SK, Kempf T, Lopes RD, Mahaffey KW, Steg PG, et al. Biomarker-based prediction of recurrent ischemic events in patients with acute coronary syndromes. *J Am Coll Cardiol*. 2022;80:1735–1747. doi: 10.1016/j.jacc.2022.08.767
141. Kaura A, Hartley A, Panoulas V, Glampson B, Shah ASV, Davies J, Mulla A, Woods K, Omigie J, Shah AD, et al. Mortality risk prediction of high-sensitivity C-reactive protein in suspected acute coronary syndrome: a cohort study. *PLoS Med*. 2022;19:e1003911. doi: 10.1371/journal.pmed.1003911
142. Will JC, Yuan K, Ford E. National trends in the prevalence and medical history of angina: 1988 to 2012. *Circ Cardiovasc Qual Outcomes*. 2014;7:407–413. doi: 10.1161/CIRCOUTCOMES.113.000779
143. Kureshi F, Shafiq A, Arnold SV, Gosch K, Breeding T, Kumar AS, Jones PG, Spertus JA. The prevalence and management of angina among patients with chronic coronary artery disease across US outpatient cardiology practices: insights from the Angina Prevalence and Provider Evaluation of Angina Relief (APPEAR) study. *Clin Cardiol*. 2017;40:6–10. doi: 10.1002/clc.22628
144. Blumenthal DM, Howard SE, Searl Como J, O'Keefe SM, Atlas SJ, Horn DM, Wagle NW, Wasfy JH, Yeh RW, Metlay JP. Prevalence of angina among primary care patients with coronary artery disease. *JAMA Netw Open*. 2021;4:e2112800. doi: 10.1001/jamanetworkopen.2021.12800
145. Stierman B, Afful J, Carroll M, Chen T, Davy O, Fink S, Fryar C, Gu Q, Hales C, Hughes J, et al. National Health and Nutrition Examination Survey 2017-March 2020 prepandemic data files: development of files and prevalence estimates for selected health outcomes. *Natl Health Stat Rep*. 2021;158:1–9.

# 22. CARDIOMYOPATHY AND HEART FAILURE

***See Tables 22-1 and 22-2 and Charts 22-1 through 22-3***

Click here to return to the Table of Contents

Click here to return to the Abbreviations

## Cardiomyopathy

### *ICD-9* 425; *ICD-10* I42.

2021, United States: Underlying cause mortality—19 975. Any-mention mortality—46 065.

Cardiomyopathy diagnoses account for a substantial number of inpatient and outpatient encounters annually. According to HCUP 2020 data[1] for inpatient hospitalizations, cardiomyopathy was the principal diagnosis for 14 270, and it was included among all-listed diagnoses for 1 083 430.

### *Hypertrophic Cardiomyopathy*

- HCM is a monogenic disorder with primarily autosomal dominant inheritance that is caused by 1 of hundreds of variants in >30 genes that encode primarily components of the sarcomere, with variants in *MYH7* and *MYBPC3* (cardiac myosin-binding protein C) being the most common.[2–4] A variant is identifiable in 30% to 60% of cases of familial HCM.
- A meta-analysis of prior GWASs found a strong correlation between common genetic variants associated with several LV traits, including increased LV mass, mean LV wall thickness, and radial strain, and HCM.[5] Two-sample mendelian randomization suggests a causal link between increased LV contractility and risk of developing HCM.
- The Sarcomeric Human Cardiomyopathy Registry studied 4591 patients with HCM, contributing >24 000 person-years of follow-up, and observed a higher mortality rate in patients with HCM compared with unaffected individuals of a similar age in the US general population: 20 to 29 years of age, 0.39% versus 0.09% ($P$<0.05); 40 to 49 years of age, 0.66% versus 0.28% ($P$=0.09); and 60 to 69 years of age, 3.99% versus 1.33% ($P$<0.01). Risk for adverse events (ie, any ventricular arrhythmia, HF, AF, stroke, or death) was highest in patients diagnosed before 40 years of age versus after 60 years of age (cumulative incidence, 77% [95% CI, 72%–80%] by 60 years of age versus 32% [95% CI, 29%–36%] by 70 years of age). Adverse events were also higher in patients with versus without pathogenic sarcomere variants (HR, 1.98 [95% CI, 1.72–2.28]). AF (HR, 2.41 [95% CI, 1.98–2.94]) and HF (HR, 2.03 [95% CI, 1.68–2.45]) accounted for a substantial proportion of the adverse events despite typically not manifesting until years to decades after the initial diagnosis. Compared with males, females with HCM were at lower risk for ventricular arrhythmia (HR, 0.69 [95% CI, 0.51–0.94]; $P$<0.05) and AF (HR, 0.72 [95% CI, 0.60–0.87]; $P$<0.001) but higher risk for HF (HR, 1.28 [95% CI, 1.07–1.52]; $P$<0.01). There was no statistically significant difference in risk of each outcome for patients from underrepresented racial groups (all $P$>0.05).[6]
- A meta-analysis of 98 studies encompassing 70 510 patients with HCM from 1985 to 2020 demonstrated an overall incidence rate of sudden cardiac death of 0.43%/y (95% CI, 0.37–0.50).[7] This rate decreased over time from 0.73%/y (95% CI, 0.53–1.02) in 1985 to 2000 to 0.32%/y (95% CI, 0.20–0.52) in 2015 to 2020.
- Sex disparities exist in the treatment of HCM. Among 9306 patients with obstructive HCM in the MarketScan database, females were less likely to be prescribed β-blockers (42.7% versus 45.2%; $P$=0.600) or to receive an ICD (1.7% versus 2.6%; $P$=0.005).[8]

### *Genetic Testing*

- The NIH-funded Clinical Genome Resource framework identified that of the 33 speculated HCM genes, 8 genes (*MYBPC3*, *MYH7*, *TNNT2*, *TNNI3*, *TPM1*, *ACTC1*, *MYL2*, and *MYL3*) have definitive evidence, 3 genes (*CSRP3*, *TNNC1*, and *JPH2*) have moderate evidence, and the remaining genes have limited to no evidence supporting an association with HCM.[9]
- Given the heterogeneous nature of the underlying genetics, manifestation of the disease is highly variable, even in cases for which the causal variant has been identified.[10] Among clinically unaffected individuals with pathogenic sarcomere variants discovered as part of cascade testing, 46% developed HCM over 15 years of follow-up.[11]

### *Dilated Cardiomyopathy*

- Familial DCM is a common mendelian cardiomyopathy with a causal genetic variant identified in 10% to 14% of cases.[2]

The 2024 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2024. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

- Familial DCM has a prevalence of 1 in 2500, but it is likely underestimated.[12] Familial DCM often displays an age-dependent penetrance.[13]
- In a cross-sectional survey of 1220 probands with confirmed DCM and 1693 first-degree relatives who underwent clinical screening, including transthoracic echocardiography, the prevalence of familial DCM was 11.6%.[14]
  - If all living first-degree relatives had been screened, the estimated prevalence of familial DCM was 29.7% (95% CI, 23.5%–36.0%).
  - The estimated prevalence of familial DCM was higher in Black compared with White probands (difference, 11.3% [95% CI, 1.9%–20.8%]).
- With the use of an expanded definition of familial DCM, which included the presence of DCM, LV enlargement, or LV systolic dysfunction without a known cause in at least 1 first-degree relative, the estimated prevalence was 56.9% (95% CI, 50.8%–63.0%). Missense and truncating variants in the titin gene have been linked to autosomal dominant cardiomyopathy[15] and to DCM with incomplete penetrance in the general population.[15] Analysis of sequence data in 7855 cases with cardiomyopathy and >60 000 controls revealed the range in penetrance of putative disease variants, which further highlights the challenges in clinical interpretation of variation in mendelian disease genes.[16]
- Other causes of DCM of variable chronicity and reversibility include cardiomyopathies developing after an identifiable exposure such as tachyarrhythmia, stress, neurohormonal disorder, alcoholism, chemotherapy, infection, autoimmunity, or pregnancy (see the Peripartum Cardiomyopathy section).[17,18] The annual incidence of chronic idiopathic DCM has been reported to be between 5 and 8 cases per 100 000, although these estimates might be low because of underrecognition, especially in light of prevalent asymptomatic LV dysfunction observed in community-based studies.[19,20]

### *Genetic Testing*

- Among patients with DCM, a recent multisite nationwide cross-sectional study indicates an estimated familial prevalence of ≈30% in first-degree relatives and an estimated 19% risk of developing DCM by 80 years of age.[14] This study also indicates that first-degree relatives of NH Black probands (index patients with DCM) or probands diagnosed at a young age have a higher risk of DCM. These findings suggest a potential yield of phenotypic screening of first-degree relatives of index DCM cases, especially those identified at a young age. The clinical outcomes in familial DCM have been described recently.[21]
- In 186 families who underwent genetic screening because of having a relative with DCM, 37% (95% CI, 30%–45%) were discovered to have a likely pathogenic or pathogenic genetic variant for DCM.[22]
- In an appraisal of the 51 genes hypothesized to be associated with DCM, the recent Clinical Genome Resource framework panel noted that only 12 genes from 8 gene ontologies have definitive (*BAG3*, *DES*, *FLNC*, *LMNA*, *MYH7*, *PLN*, *RBM20*, *SCN5A*, *TNNC1*, *TNNT2*, and *TTN*) or strong (*DSP*) evidence and only 7 genes from the additional 2 ontologies (*ACTC1*, *ACTN2*, *JPH2*, *NEXN*, *TNNI3*, *TPM1*, and *VCL*) have moderate evidence supporting a robust association with DCM.[23] Because DCM is often the final disease manifestation of several cardiomyopathies, it shares genetic architecture with other inherited cardiomyopathies. Among the previously mentioned 19 genes linked to DCM, the Clinical Genome Resource panel noted that 6 had a similar classification for HCM and 3 had a similar classification for ARVC.[23]
- Missense and truncating variants in the titin gene have been linked to autosomal dominant cardiomyopathy, as well as to DCM, with incomplete penetrance in the general population.[15] Analysis of sequence data in 7855 cases with cardiomyopathy and >60 000 controls revealed the variance in penetrance of putative disease variants, which further highlights the challenges in clinical interpretation of variation in mendelian disease genes.[16]
- A recent GWAS has identified common genetic variants associated with HCM (16 loci identified) and DCM (13 loci identified), indicating a potential oligogenic pattern (instead of a conventionally understood monogenic pattern) for the genetic risk of HCM and DCM.[5,24] It is notable that 2 HCM loci (chromosome 1 near *HSPB7* and chromosome 10 near *BAG3*) have opposite directions of effect for DCM and require further evaluation in subsequent investigations.

## *Peripartum Cardiomyopathy*

- PPCM is a global problem with the highest incidence (1 in 102 births) seen in Nigeria and lowest incidence (1 in 15 533 births) seen in Japan.[25] Accordingly, worldwide and in the United States, females with Black ancestry appear to have highest risk, especially females with Nigerian (1 per 100 live births) and Haitian (1 per 300 live births) background.[26–28]
- In the United States, according to NIS data, the incidence of PPCM increased between 2004 and 2011 from 8.5 to 11.8 per 10 000 live births ($P_{trend}$<0.001), likely related to rising average maternal age and prevalence of PPCM risk factors such as

obesity, hypertension, pregnancy-related hypertension, and diabetes.[29] Stratified by race and ethnicity, incidence of PPCM was lowest in Hispanic females (3.6 per 10 000 live births) and highest in Black females (22.8 per 10 000 live births). Stratified by region, incidence was lowest in the West (6.5 [95% CI, 6.3–6.7] per 10 000 live births) and highest in the South (13.1 [95% CI, 12.9–13.1] per 10 000 live births).[29]

- Genetic analyses suggest that ≈15% of individuals with PPCM have rare truncating variants in genes also linked to idiopathic DCM. The majority of these are truncating variants in *TTN*, which encodes the sarcomeric protein titin, and truncating variants in *TTN* in females with PPCM are associated with lower EF after 1 year of follow-up.[30]
- Global mortality from PPCM is 9% and is lower in developed (4%) than developing (14%) countries; in addition, a high prevalence of females of African descent was positively correlated with mortality (weight correlation coefficient, 0.29 [95% CI, 0.13–0.52]).[31]
- In a cohort of 55 804 hospitalized patients with PPCM, Black (OR, 1.17 [95% CI, 1.15–1.57]; $P<0.001$) and Hispanic (OR, 1.37 [95% CI, 1.17–1.59]; $P<0.001$) individuals were more likely to develop cardiogenic shock than White individuals.[32] Similarly, Black (OR, 1.67 [95% CI, 1.21–2.23]; $P=0.002$) and Hispanic (OR, 2.20 [95% CI, 1.45–3.33]; $P<0.001$) individuals were more likely to have in-hospital mortality than White individuals.
- In most cases of PPCM (50%–80%), LVEF recovers to at least near-normal (≥50%) function and often within 6 months.[33–36] However, an initial LVEF <30%, LV end-diastolic dimension ≥6.0 cm, Black race, and initial presentation >6 weeks after delivery are associated with lower LVEF at 1 year.[30]

### Youth

- Since 1996, the Pediatric Cardiomyopathy Registry has collected data on children with cardiomyopathy in New England and central southwestern states.[37]
  - Overall incidence of cardiomyopathy is 1.13 cases per 100 000 in children <18 years of age.
  - Incidence is 8.34 (95% CI, 7.21–9.61) per 100 000 for children <1 year of age.
  - Annual incidence (cases per 100 000) is higher in Black (1.47) than in White (1.06) children ($P=0.02$), in male (1.32) than in female (0.92) children ($P<0.001$), and in New England (1.44) than in the central Southwest (0.98; $P<0.001$).
- The annual incidence of HCM in children is ≈4.7 per 1 million (95% CI, 4.1–5.3) with higher incidence in New England (5.9 per 1 million [95% CI, 4.8–7.2]) than in the central Southwest region (4.2 per 1 million [95% CI, 3.5–4.9]) and in males (5.9 per 1 million [95% CI, 5.0–6.9]) than in females (3.4 per 1 million [95% CI, 2.8–4.2]).[38] Approximately 9% progress to HF and 12% to SCD over a median follow-up of 6.5 years.[39] Chapter 18 (Disorders of Heart Rhythm) provides statistics on SCD. Data from the NIS indicate that hospitalization is more likely with increasing age (OR, 5.59 [95% CI, 2.03–15.37] for ≥10 years of age versus 1–9 years of age) and in Black individuals compared with White individuals (OR, 2.78 [95% CI, 1.19–6.47]).[40]
- The annual incidence of DCM in children is ≈0.57 per 100 000 (95% CI, 0.52–0.63) with a higher incidence in males than females (0.66 versus 0.47; $P<0.001$) and in Black children than White children (0.98 versus 0.46; $P<0.001$). Commonly recognized causes include myocarditis (46%) and neuromuscular disease (26%).[41] The 5-year incidence rate of SCD is 3% at the time of DCM diagnosis.[42]
- For all cardiomyopathies seen in children, 5-year transplantation-free survival rate of DCM, HCM, restrictive cardiomyopathy, and LV noncompaction is 50%, 90%, 30%, and 60%, respectively.[43]
- Data from the Childhood Cancer Survivor Study cohort of 14 358 survivors of childhood or adolescent cancers showed a 5.9-fold (95% CI, 3.4–9.6) increased risk for HF compared with siblings,[44] usually preceded by asymptomatic cardiomyopathy persisting up to 30 years after the cancer diagnosis, especially in patients treated with chest radiation or anthracycline chemotherapy.

### Global Burden of Cardiomyopathy

### (See Table 22-1 and Charts 22-1 and 22-2)

- Based on 204 countries and territories in 2021[45]:
  - There were 0.41 (95% UI, 0.38–0.44) million deaths estimated for cardiomyopathy and myocarditis and an age-standardized mortality rate of 4.95 (95% UI, 4.59–5.29) per 100 000 (Table 22-1).
  - The highest age-standardized death rates estimated for cardiomyopathy and myocarditis were in Eastern Europe, followed by Central Asia and central sub-Saharan Africa (Chart 22-1).
  - Globally, there were 5.70 (95% UI, 4.94–6.65) million prevalent cases of cardiomyopathy and myocarditis and an age-standardized prevalence rate of 71.45 (95% UI, 62.08–83.09) per 100 000 (Table 22-1).
  - Age-standardized prevalence of cardiomyopathy and myocarditis was highest in eastern sub-Saharan Africa and high-income North America. The lowest prevalence rates were in Oceania and east Asia. (Chart 22-2).
- Rates of SCD in patients with HCM vary by geographic region. In a meta-analysis of data from

2015 to 2020, the reported incidence rate per 100 person-years was highest in Asia (0.67% [95% CI, 0.54%–0.84%]) followed by Europe (0.37% [95% CI, 0.31%–0.46%]) and North America (0.28% [95% CI, 0.18%–0.43%]).[7]

## Heart Failure

### *ICD-9* 428; *ICD-10* I50. For hospital discharges, *ICD-10* I50, I11.0, I13.0, I13.2, I09.81.

2021, United States: Underlying cause mortality—85 037. Any-mention mortality—421 938.

2020, United States: Hospital discharges—1 111 500

#### *Prevalence*

*(See Table 22-2 and Chart 22-3)*

- On the basis of data from NHANES 2017 to 2020, 6.7 million Americans ≥20 years of age had HF (Table 22-2). This is increased from ≈6.0 million according to NHANES 2015 to 2018 (NHLBI unpublished tabulation using NHANES). The breakdown of HF prevalence by age and sex is shown in Chart 22-3.
- Prevalence of HF is projected to increase by 46% from 2012 to 2030, affecting >8 million people ≥18 years of age. The total percentage of the population with HF is projected to rise from 2.4% in 2012 to 3.0% in 2030.

#### *Incidence*

*(See Table 22-2)*

- Of 1 799 027 unique Medicare beneficiaries at risk for HF (median age, 73 years [IQR, 68–79 years]; 56% female), 249 832 had a new diagnosis of HF.[46] HF incidence was 26.5 cases per 1000 beneficiaries in 2016, consistent across subgroups based on sex and race and ethnicity.

#### *Risk Factors*

- Hypertension, diabetes, obesity, and smoking account for 52% of incident HF with PARs as follows[47]: CHD, 20% (23% in males versus 16% in females); cigarette smoking, 14%; hypertension, 20% (28% in females versus 13% in males); obesity, 12%; and diabetes, 12%.
- Data from NHANES show that one-third of US adults have at least 1 HF risk factor.[48]
- Risk factors differ by HF subtype: among 4 community-based studies (CHS, FHS, PREVEND, MESA)[49]:
  - Older age was more strongly associated with incident HFpEF versus HFrEF (subdistribution HR, 1.91 [95% CI, 1.78–2.06] versus 1.69 [95% CI, 1.59–1.81] per 10-year age increase in HFpEF versus HFrEF, respectively; *P* for equality=0.02).
  - In contrast, the following risk factors were more strongly associated with incident HFrEF than HFpEF: male sex (subdistribution HR, 1.87 [95% CI, 1.63–2.16] in HFrEF versus 0.91 [95% CI, 0.79–1.05] in HFpEF; *P* for equality<0.0001), previous MI (subdistribution HR, 2.70 [95% CI, 2.25–3.24] in HFrEF versus 1.30 [95% CI, 1.02–1.67] in HFpEF; *P* for equality<0.0001), LVH (subdistribution HR, 2.08 [95% CI, 1.60–2.69] in HFrEF versus 1.16 [95% CI, 0.84–1.60] in HFpEF; *P* for equality=0.009), and left bundle-branch block (subdistribution HR, 3.65 [95% CI, 2.62–5.09] in HFrEF versus 1.30 [95% CI, 0.81–2.09] in HFpEF; *P* for equality=0.0008).
- Age dependency of risk factors: Although the absolute risk of HF is lower among younger individuals, the PAR of modifiable risk factors is greater among young (<55 years of age) compared with older (≥75 years of age) individuals: obesity, 21% versus 13%; hypertension, 35% versus 23%; diabetes, 14% versus 7%; and smoking, 32% versus 1%.[50]
- Lifestyle factors also affect HF risk. Among WHI, MESA, and CHS participants, individuals with more than twice the minimum guideline-recommended leisure-time PA had lower risk of HFpEF compared with those with no leisure-time PA (HR, 0.81 [95% CI, 0.68–0.97]), whereas no such association was observed for risk of HFrEF.[51]
- In the ARIC study, greater alignment with the AHA's Life's Simple 7 guidelines (better profiles in smoking, BMI, PA, diet, cholesterol, BP, and glucose) was associated with lower lifetime risk of HF.[52] Specifically, the lifetime risk of HF among those with 5 to 7 ideal components in middle age was 12% (95% CI, 9%–15%), whereas those with 0 ideal components had a lifetime risk of 45% (95% CI, 35%–52%).

#### *Race and Sex Differences*

- In 6 US longitudinal population-based cohorts, hypertension had the highest PAR among Black males and females (28% [95% CI, 19%–37%] and 26% [95% CI, 16%–34%], respectively), whereas obesity had the highest PAR among White males and females (21% [95% CI, 15%–27%] and 18% [95% CI, 13%–23%]).[53]
- Sex-specific risk factors for incident HF include disorders of pregnancy (eclampsia/preeclampsia, gestational diabetes), PPCM, polycystic ovarian syndrome, and premature menopause, although the exact contribution of these conditions to the incidence of HF among women is unknown.[54] The penetrance of genetic cardiomyopathies may be influenced by sex, with males often more severely affected.

### Family History and Genetics

- In the multigenerational FHS, HF in at least 1 parent was associated with a higher prevalence of asymptomatic LV systolic dysfunction (5.7% versus 3.1%, *P* adjusted for age, sex, and height=0.046) and greater risk of incident HF (age- and sex-adjusted 10-year incidence rate, 2.72% [95% CI, 1.80%–4.11%] versus 1.62% [95% CI, 1.10%–2.39%]; age- and sex-adjusted HR, 1.72 [95% CI, 1.13–2.61]; *P*=0.01).[55]
- Several GWASs have been conducted to identify common variations associated with cardiomyopathy and HF in the general population, albeit with modest results, highlighting a small number of putative loci, including *HSPB7*[56–58] and *CACNB4*.[59] In a GWAS of >47 000 cases and >930 000 controls, 11 HF loci were identified, all of which have known relationships with other CVD traits.[60]
- Multiple GWASs of cardiac structure and function have highlighted the association of genetic architecture of LV phenotypes with the risk of future HF.[61,62] A transancestry meta-analysis of GWASs including >1 500 000 individuals identified 47 risk loci for all-cause HF. Integrating cardiac MRI intermediary phenotypes into this GWAS led to the identification of 61 loci.[63]
- A single-cell profiling study showed that HCM and DCM share a common final transcriptional pathway at the cellular level. Furthermore, cardiomyopathy was associated with a shift in the macrophage population and presence of a unique population of activated fibroblasts.[64]
- The genetic basis of specific cardiomyopathies is summarized in the previous cardiomyopathy section.

### Treatment

- Mortality declines have been attributed primarily to evidence-based approaches to treat HFrEF, including pharmacotherapies, ICDs, and cardiac resynchronization therapies.[65]
- Initiation of contemporary guideline-directed medical therapy for HFrEF (quadruple therapy with ARNIs or ACE inhibitors or ARBs; β-blockers; mineralocorticoid receptor antagonists; and SGLT-2 inhibitors) is estimated to reduce the hazard of cardiovascular death or HF hospitalization in HFrEF by up to 62% (HR, 0.38 [95% CI, 0.30–0.47]) compared with limited conventional therapy, resulting in an estimated 1.4 to 6.3 additional years alive based on modeling from clinical trials.[66] Treatment efficacy with these classes for the outcome of death is attenuated as LVEF increases, and there is no clear evidence to support β-blockers in HFpEF.[67,68]
- Across jurisdictions, there are significant gaps in the use and dose of guideline-directed medical and device therapy for HFrEF. Data from the CHAMP-HF registry suggest that among eligible patients with HFrEF, 27% were not prescribed ACE inhibitors/ARBs/ARNIs, 33% were not prescribed β-blockers, and 67% were not prescribed mineralocorticoid antagonists.[69]

### Mortality

#### Secular Trends

- Among adults ≥75 years of age with HF in the CDC WONDER data set[70]:
  - –AAMR per 100 000 declined from 141.0 in 1999 to 108.3 in 2012 (APC, –2.1 [95% CI, –2.4 to –1.9]), after which it increased to 121.3 in 2019 (APC, 1.7 [95% CI, 1.2–2.2]).
- Across jurisdictions, the COVID-19 pandemic was associated with increased mortality among those with decompensated HF and with a shift in deaths from hospital to community.[71,72] There was an increase in both in-hospital and postdischarge mortality among patients hospitalized with HF despite similar care quality. In the GWTG–Heart Failure registry, in-hospital mortality increased from 2.5% in 2019 to 2020 to 3.0% during 2020 to 2021, with in-hospital mortality as high as 8.2% among those with concurrent COVID-19 infection.[72]

#### Mortality by HF Subtype

- Among 4 community-based cohorts, including CHS, FHS, PREVEND, and MESA, all-cause mortality rates after HF diagnosis were 459 per 10 000 person-years among those with HFrEF and 394 per 10 000 person-years in individuals with HFpEF.[73]
- Phenotypes based on clinical comorbidities may stratify all-cause death or readmissions with greater discrimination than LVEF categories.[74] In an unsupervised machine-learning cluster analysis of 1693 patients hospitalized for HF, 6 discrete phenogroups characterized by a predominant comorbidity were identified: CHD, valvular HD, AF, sleep apnea, chronic obstructive pulmonary disease, or minimal comorbidities. Phenogroups were LVEF independent, with each phenogroup encompassing a wide range of LVEFs. For the primary composite outcome of all-cause death or rehospitalization at 6 months, the HRs for phenogroups ranged from 1.25 (95% CI, 1.00–1.58) for AF to 2.04 (95% CI, 1.62–2.57) for chronic obstructive pulmonary disease (log-rank *P*<0.001). LVEF-based classifications did not separate patients into different risk categories for the primary outcomes at 6 months (*P*=0.69).

### CVD Death

#### (See Table 22-2)

- Among optimally treated clinical trial patients with HF across the LVEF continuum, 53.5% of deaths

were ascribed to CVD causes (of which 33.1% were from HF and 50.6% from SCD), 29.9% to non-CVD causes, and 16.5% to undetermined causes.[75] The proportion of non-CVD deaths was higher in those with higher EF. In the same analysis, the rate of death per 100 000 patient-years resulting from sudden death, HF, and cardiovascular causes decreased as LVEF increased.

- Data from the CDC WONDER database show that age-adjusted rates of HF-related CVD death declined from 1999 (78.7 per 100 000 [95% CI, 78.2–79.2]) to 2012 (53.7 per 100 000 [95% CI, 53.3–54.1]) and subsequently increased through 2017 (59.3 per 100 000 [95% CI, 58.9–59.6]).[76] There is geographic variation in HF-related CVD mortality, with the highest increases in annual AAMR after 2011 occurring in the Midwest (1.14 per 100 000 per year [95% CI, 0.75–1.53]) and South (0.96 per 100 000 per year [95% CI, 0.66–1.26]) compared with the Northeast (0.35 per 100 000 per year [95% CI, 0.03–0.68]).[77]
- Given improvements in HF survival overall, the number of individuals carrying a diagnosis of HF at death has increased. Mortality associated with HF is substantial, such that ≈1 in 8 deaths in 2021 has HF mentioned on the death certificate (unpublished NHLBI tabulation).[78]
- In 2021, HF was the underlying cause in 85 037 deaths (40 344 males and 44 693 females; Table 22-2).
- The number of deaths attributable to HF was 45.8% higher in 2021 than in 2011 (58 309; unpublished NHLBI tabulation using NVSS[78]).

### *Age, Sex, and Race and Ethnicity Differences in Mortality*

- Among older adults in the CDC WONDER data set between 1999 and 2019[70]:
  - –Males had consistently a higher AAMR than females throughout the period, with an AAMR of 141.1 in males and 107.8 in females in 2019.
  - –NH White adults had the highest overall AAMR (127.2) followed by NH Black (108.7), NH American Indian/Alaska Native (102.0), Hispanic or Latino (78.0), and NH Asian or Pacific Islander (57.1) adults.
- In the Southern Community Cohort Study, all-cause mortality after a diagnosis code for HF varied by sex, with HRs of 1.63 (95% CI, 1.27–2.08), 1.38 (95% CI, 1.11–1.72), and 0.90 (95% CI, 0.73–1.12) for White males, Black males, and Black females, respectively, compared with White females.[79] In the ARIC study, the 30-day, 1-year, and 5-year case fatality rates after hospitalization for HF were 10.4%, 22%, and 42.3%, respectively, with Black individuals having a greater 5-year case fatality rate than White individuals ($P<0.05$).[80]
- In 2021, the overall any-mention age-adjusted death rate for HF was 106.3 per 100 000 with variation across racial and ethnic groups. In males, the rates were 133.6 for NH White males, 146.5 for NH Black males, 53.7 for NH Asian males, 152.5 for NH Native Hawaiian or Pacific Islander males, 121.7 for NH American Indian or Alaska Native males, and 83.5 for Hispanic males. In females, the rates were 95.2 for NH White females, 105.6 for NH Black females, 37.4 for NH Asian females, 99.4 for NH Native Hawaiian or Pacific Islander females, 89.4 for NH American Indian or Alaska Native females, and 59.1 for Hispanic females (unpublished NHLBI tabulation using CDC WONDER[81]).

### *Rural-Urban Disparities*

- Among Medicare fee-for-service beneficiaries, 30-day mortality was higher among patients with HF presenting to rural versus urban hospitals (HR, 1.15 [95% CI, 1.13–1.16]).[82]

## *Health Care Use: Hospital Utilization*

- In 2019, there were 8 054 000 physician office visits with a primary diagnosis of HF (NAMCS,[83] unpublished NHLBI tabulation). In 2020, there were 1 361 493 ED visits for HF (HCUP,[1] unpublished NHLBI tabulation). In 2020, there were 1 111 500 principal diagnosis hospital discharges for HF (HCUP,[1] unpublished NHLBI tabulation).
- In the NCDR PINNACLE, 1 in 6 patients with HFrEF developed worsening HF within 18 months of diagnosis and was more likely to be Black, to be >80 years of age, and to have greater comorbidity burden; overall, the 2-year mortality rate was 22.5%.[84]
- Outcomes remain poor after hospitalization for HF. In a pragmatic trial of 2494 patients discharged alive after hospitalization for HF in Canada in 2015 to 2016, 49.1% of patients were rehospitalized (47.4% of these for HF), an additional 34.1% visited the ED without being rehospitalized, and 15.5% died within 6 months of discharge.[85]

### *Secular Trends*

- In the NIS, hospitalizations for HF increased from 1 060 540 in 2008 to 1 270 360 in 2018 with a greater proportion among individuals from underrepresented racial and ethnic groups (Black individuals: 18.4% in 2008, 21.2% in 2018; Hispanic individuals: 7.1% in 2008, 9.0% in 2018; $P<0.001$ for all).[86]
- In the NIS, hospitalizations by HF subtype increased from 2008 to 2018 for both HFrEF (n=283 193 to n=679 815) and HFpEF (n=189 260 to n=495 095).[86] A greater proportion of HFrEF

hospitalizations occurred in males (60.5%), and a greater proportion of HFpEF hospitalizations occurred in females (62.5%; $P<0.001$ for sex difference).

### *Age, Sex, Race, and Socioeconomic Differences*

- Among 4 287 478 weighted hospitalizations in the US NIS data set, the median age was 73.4 years (IQR, 62.4–82.9 years), 51.3% of hospitalizations occurred in male patients, and race and ethnicity composition included White (70.0%), Black (17.5%), Hispanic (7.6%), Asian or Pacific Islander (2.2%), and Native American (0.5%) patients. Among the hospitalizations, 33.1% comprised patients from zip codes in the lowest quartile of national household income (including 0.6% homeless).[87] In models adjusted for baseline characteristics, male sex (RR, 1.09 [95% CI, 1.07–1.11]), and low SES (RR, 1.02 [95% CI, 1.00–1.05]) were associated with a higher risk of in-hospital mortality relative to female sex and high SES, whereas Black (RR, 0.79 [95% CI, 0.76–0.81]) and Hispanic (RR, 0.90 [95% CI, 0.86–0.93]) race or ethnicity was associated with a lower risk of in-hospital mortality than White race.
- Among 767 180 weighted hospitalizations for HF among young adults <50 years of age in the United States in the NIS, Black adults (50.1%) accounted for disproportionately higher HF hospitalizations compared with White (31.9%) and Hispanic (12.2%) adults. Nearly half of hospitalizations (45.8%) represented patients from the lowest quartile of national household income.[88]
- Data from a pragmatic clinical trial of 2494 patients hospitalized for HF indicate that females are on average 5 years older (mean±SD age, 80.0±10.9 years versus 75.4±12.8 years), more commonly reside in a nursing home (16.2% versus 8.2%), and experience worse quality of life, as measured by the EQ-5D-5L scores (range 0–1; 0.37 [95% CI, 0.30–0.44] females versus 0.62 [95% CI, 0.57–0.67] males).[85,89]
- Data from the 2005 to 2014 ARIC Community Surveillance study have shown that HF hospitalization rates are increasing over time with the average annual percentage change ranging from 1.9% (95% CI, 0.7%–3.1%) in White females to 4.3% (95% CI, 2.7%–5.9%) in Black females from 2005 to 2014. This increase in HF hospitalizations is driven largely by HFpEF events. For example, the annual percentage change among Black females was 8.2% (95% CI, 5.2%–11.3%) for HFpEF and 2.0% (95% CI, −0.7% to 4.7%) for HFrEF.[90] Age-adjusted 28-day and 1-year case fatality rates after first-time hospitalized HF were higher among White versus Black individuals. Specifically, 28-day age-adjusted case fatality was 12.1% (White males), 11.7% (White females), 10.2% (Black females), and 9.2% (Black males).[90]

### *Noncardiovascular Hospitalizations*

- In the CHARM Program, rates of cardiovascular hospitalization were higher among those with LVEF ≤40% (23.6 [95% CI, 22.6–24.7] per 100 patient-years) versus LVEF >40% (19.3 [95% CI, 18.2–20.5] per 100 patient-years; $P<0.001$ for difference), whereas rates of noncardiovascular hospitalization were similar (14.3 [95% CI, 13.5–15.2] versus 14.3 [95% CI, 13.3–15.3] per 100 patient-years, respectively).[91]

## Orthotopic Heart Transplantation and Mechanical Circulatory Support Device Placement in the United States

### *Heart Transplantation*

***(See Chapter 27 [Medical Procedures] for additional heart transplantation data.)***

- According to United Network for Organ Sharing data from 1988 to 2020, a total of 79 562 heart transplantations were performed, with the annual number of transplantations more than doubling over this period from 1676 to 3658.[92] Among the 3658 recipients in 2020, the primary diagnosis was cardiomyopathy (59.3%), CAD (23.0%), congenital HD (8.9%), and retransplantation (3.3%). A ventricular assist device was present in 34.5% at the time of transplantation.

### *Secular Trends*

- The 2020 Annual Data Report from the Organ Procurement Transplant Network shows a 32.5% increase in new listings for adult heart transplantation from 3019 in 2009 to 4000 in 2020.[93] Heart transplantation rates have increased steadily since 2015 (101 per 100 wait-list years in 2020 from 61 per 100 wait-list years in 2015) with a concomitant decline in median wait time (2.7 months for candidates in 2019–2020 from a peak of 11.9 months in 2013–2014). Mortality after transplantation has declined since 2009 with 1-year survival of 90.6% among adult recipients who underwent heart transplantation in 2019. The overall impact of the new adult heart allocation policy implemented in 2018 remains to be seen.

### *Sex, Racial and Ethnic, and Geographic Differences*

- Among 34 198 heart transplant recipients in the International Society for Heart and Lung Transplantation registry between 2004 and 2014, 23.7% were female and 76.3% were male.[94] When matched for recipient and donor characteristics, there was no significant difference in survival between male and female recipients ($P=0.57$).
- Among 32 353 adult heart transplant recipients in the United Network for Organ Sharing database,

the proportion of Black and Hispanic individuals listed increased from 2011 to 2020 (21.7% to 28.2% [*P*=0.003] and 7.7% to 9.0% [*P*=0.002], respectively).[95] Black individuals were less likely to undergo heart transplantation (aHR, 0.87 [95% CI, 0.84–0.90]; *P*<0.001) and had a higher risk of death after transplantation (aHR, 1.14 [95% CI, 1.04–1.24]; *P*=0.004) compared with White individuals.

- Among 8747 US adults listed for heart transplantation in the Scientific Registry of Transplant Recipients from January 2017 to September 2019, 84.7% were from metropolitan, 8.6% were from micropolitan, and 6.6% were from rural settings; and >70% were male candidates.[96]
- Among 15 036 adult candidates for heart transplantation between 2011 and 2016 in the United States, there was significant state-level variation in outcomes, ranging from 1.0 to 7.8 deaths per 1000 wait-list person-days for wait-list mortality.[97] One-year risk-adjusted graft survival ranged from 87% to 92%.

### *Mechanical Circulatory Support*

- INTERMACS reported outcomes on 25 551 patients undergoing primary isolated continuous-flow LVAD implantation between 2010 and 2019.[98] Mechanical circulatory support volumes have grown from 1558 in 2010 to 3198 in 2019 with increasing use of full magnetic levitation devices accounting for 77.7% of LVAD implantations in 2019, hybrid levitation continuous-flow devices accounting for 20.5%, and axial design accounting for 1.8%.
- Survival after primary continuous-flow LVAD implantation improved from 1-year survival of 80.5% in 2010 to 2014 to 82.3% in 2015 to 2019 (*P*<0.0001 for difference).[98] When stratified by LVAD strategy, 1-year survival was 86.8% for bridge to transplantation, 83.8% for bridge to candidacy, and 80.1% for destination therapy in 2015 to 2019.
- Device strategy has changed over time, with the majority of LVADs now implanted as destination therapy (73.1%) in 2019, 18% as bridge to candidacy, and 8.9% as bridge to transplantation (listed).[98] In contrast, in 2009, 34.9% were implanted as destination therapy, 36.5% as bridge to candidacy, and 28.6% as bridge to transplantation. In 2019, INTERMACS profiles of LVAD recipients were as follows: 1 (critical cardiogenic shock, 17.0%), 2 (progressive decline, 32.9%), 3 (stable but inotrope dependent, 37.3%), and 4 to 7 (resting symptoms or less sick, 12.9%).
- In a study that used the United Network for Organ Sharing registry between 2006 and 2015 and addressed insurance status, among those with bridge-to-transplantation LVADs, Medicaid insurance was associated with worse survival of patients on the heart transplantation wait list compared with patients with private insurance (subdistribution HR, 1.57 [95% CI, 1.15–2.16]), although access to transplantation was not different.[99]

### *Sex Differences*

- According to INTERMACS data from 2017 to 2019, for patients receiving contemporary centrifugal LVADs, the risk of death appeared to be higher in males (HR, 1.63; *P*=0.01) relative to females.[100]

## Cost

### *Overall Costs*

The overall cost of HF continues to rise. See Chapter 28 (Economic Cost of Cardiovascular Disease) for further statistics.

- In 2012, total cost for HF was estimated to be $30.7 billion (2010 dollars), of which more than two-thirds was attributable to direct medical costs.[101] Projections suggest that by 2030 the total cost of HF will increase by 127% to $69.8 billion, amounting to ≈$244 for every US adult.
- In a systematic review of HF-associated medical costs in the United States from 2014 to 2020, the annual median total cost was estimated at $24 383 per patient, with HF hospitalizations accounting for the majority ($15 879 per patient).[102]
- Data from the US NIS for 4 287 478 primary HF hospitalizations 2014 to 2017 highlight differences in cost of care across demographic groups.[87] The median direct cost of admission was higher in high than in low SES groups ($10 940.40 versus $9324.60), male versus female patients ($10 217.10 versus $9866.60), and White versus Black individuals ($10 019.80 versus $9077.20). The median costs increased with SES in all demographic groups, related to greater procedural use.
- Data from the US Nationwide Readmission Database for 2 645 336 patients with a primary HF admission between 2010 and 2014 show that major contributors to inpatient HF care are associated with comorbidities, invasive procedures, and readmissions.[103] The mean cost for patients without invasive care was $10 995 compared with $129 547 for receipt of circulatory support, $251 110 for LVAD implantation, and $293 575 for heart transplantation.
- On the basis of NIS data from 2009 to 2014, regional differences across the United States were noted in length of stay and cost after ventricular assist device implantation: In the Northeast, median length of stay was 32 days and median cost was $192 604; in the South, median length of stay was 27 days and median cost was $198 884; and in the West, median length of stay was 29 days and median cost was $246 292.[104]

- The costs associated with treating HF comorbidities and HF exacerbations in youths are significant, totaling nearly $1 billion in inpatient costs, and may be rising. The associated cost burden of HF is anticipated to constitute a large portion of total pediatric health care costs.[105]

## Global Burden of HF

- In 2019:
  - Across 204 countries and territories, there were an estimated 56.2 (95% UI 46.4–67.8) million people living with left HF, although these estimates likely underrepresent the true burden of HF, particularly in low-resource regions, because of data gaps.[106]
  - Adults >70 years of age accounted for 62.2% of the world's HF cases, with female predominance in this age group and male predominance in younger adults; 50.3% of those living with HF were females, but age-standardized prevalence was greater in males.[106]
  - 69.2% lived in low- and middle-income countries, although the highest age-standardized prevalence was highest in North America and lowest in South Asia.[106] Age-standardized HF prevalence in 2019 was highest in high-income North America (993.84 [95% CI, 866.22–1140.37] per 100 000 in females; 1344.62 [95% CI, 1159.53–1556.54] per 100 000 in males) and East Asia (1001.01 [95% CI, 819.06–1245.62] per 100 000 in females; 991.23 [95% CI, 808.02–1228.71] per 100 000 in males), followed by Oceania and eastern Sub-Saharan Africa.[107]
  - There were 5.1 (95% UI, 3.3–7.3) million years lived with disability from HF, distributed equally between the sexes.[106]
  - In sequence, ischemic, hypertensive, and rheumatic HDs were the most common causes of HF in the world. IHD and hypertensive HD were the top causes of HF in males and females, respectively.[106]
- Between 1990 and 2019[106]:
  - There was a doubling in the global number of HF cases from 27.2 (95% UI, 22.2–33.4) million to 56.2 (95% UI, 46.4–67.8) million, with a doubling in both males and females.
  - Accounting for population growth, the age-standardized rate of HF per 100 000 people decreased by 7.1% worldwide, from 766.0 (95% UI, 626.3–936.0) in 1990 to 711.9 (95% UI, 591.1–858.3) in 2019. There were 9.1% (from 864.2 to 785.7) and 5.8% (from 686.0 to 646.1) decreases in age-standardized rates per 100 000 in males and females, respectively.
  - High-income regions experienced a 16.0% decrease in age-standardized rates (from 877.5 to 736.8), whereas low-income regions experienced a 3.9% increase (from 612.1 to 636.0), largely consistent across sexes.
  - There was a temporal increase in age-standardized HF from hypertensive, rheumatic, and calcific aortic valvular HD, as well as a temporal decrease from IHD, with some regional and sex differences. Age-standardized HF rates from hypertensive HD were largely stable but increased by as much as 22.3% in females in high-middle–SDI regions. Age-standardized prevalence of HF from rheumatic HD increased over time; this was driven by increasing rates in males in low- (5% increase) and low-middle– (9.2% increase) SDI regions and most notably in Andean Latin America (16.7% increase). Despite an overall decrease in the age-standardized HF attributable to IHD, low- and low-middle–SDI regions (including South and Southeast Asia and eastern and western sub-Saharan Africa) experienced increases ranging from 5% to 25% over time; this trend was consistent in both sexes.

**Table 22-1. Global Prevalence and Mortality of Cardiomyopathy and Myocarditis, by Sex, 2021**

| | Both sexes | | Male | | Female | |
|---|---|---|---|---|---|---|
| | Deaths (95% UI) | Prevalence (95% UI) | Deaths (95% UI) | Prevalence (95% UI) | Deaths (95% UI) | Prevalence (95% UI) |
| Total number (millions), 2021 | 0.41 (0.38 to 0.44) | 5.70 (4.94 to 6.65) | 0.25 (0.23 to 0.27) | 3.31 (2.85 to 3.86) | 0.16 (0.14 to 0.17) | 2.40 (2.08 to 2.80) |
| Percent change in total number, 1990–2021 | 48.44 (35.91 to 63.50) | 80.85 (73.43 to 88.90) | 66.22 (49.04 to 83.32) | 84.90 (76.99 to 93.19) | 27.32 (16.88 to 42.11) | 75.54 (67.95 to 84.37) |
| Percent change in total number, 2010–2021 | 1.66 (−4.41 to 7.79) | 22.57 (17.25 to 29.22) | 2.80 (−6.24 to 9.11) | 22.56 (17.04 to 29.37) | −0.06 (−6.22 to 7.37) | 22.58 (16.69 to 29.22) |
| Rate per 100 000, age standardized, 2021 | 4.95 (4.59 to 5.29) | 71.45 (62.08 to 83.09) | 6.48 (5.91 to 7.05) | 85.23 (73.91 to 99.97) | 3.55 (3.21 to 3.85) | 58.41 (50.36 to 68.38) |
| Percent change in rate, age standardized, 1990–2021 | −38.03 (−42.46 to −32.55) | 5.30 (−0.14 to 10.80) | −31.56 (−37.46 to −25.47) | 7.45 (2.37 to 13.13) | −46.65 (−50.52 to −41.56) | 2.52 (−3.84 to 8.73) |
| Percent change in rate, age standardized, 2010–2021 | −25.09 (−29.38 to −20.50) | 1.60 (−2.82 to 6.17) | −23.01 (−29.25 to −18.64) | 1.54 (−2.83 to 6.44) | −27.78 (−31.94 to 22.51) | 1.57 (−3.17 to 6.36) |

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Disease; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[45]

**Table 22-2. HF in the United States**

| Population group | Prevalence, 2017–2020, ≥20 y of age | Mortality, 2021, all ages* | Hospital discharges, 2020, all ages | Cost, 2012† |
|---|---|---|---|---|
| Both sexes | 6 700 000 (2.3%) [95% CI, 1.9%–2.8%] | 85 037 | 1 111 500 | $30.7 billion |
| Males | 3 700 000 (2.7%) | 40 344 (47.4%)‡ | | … |
| Females | 3 000 000 (1.9%) | 44 693 (52.6%)‡ | | … |
| NH White males | 2.9% | 31 993 | … | … |
| NH White females | 1.6% | 35 873 | … | … |
| NH Black males | 3.8% | 4902 | … | … |
| NH Black females | 3.3% | 5208 | … | … |
| Hispanic males | 1.8% | 2249 | … | … |
| Hispanic females | 1.6% | 2398 | … | … |
| NH Asian males | 1.4% | 734§ | … | … |
| NH Asian females | 0.5% | 869§ | … | … |
| NH American Indian or Alaska Native | … | 363 | … | … |
| NH Native Hawaiian or Pacific Islander | | 82 | | |

HF includes people who answered "yes" to the question of ever having congestive HF. CIs have been added for overall prevalence estimates in key chapters. CIs have not been included in this table for all subcategories of prevalence for ease of reading. In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.[108]

COVID-19 indicates coronavirus disease 2019; ellipses (…), data not available; HF, heart failure; NH, non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

*Mortality data for underlying cause of death listed as HF on death certificates for Hispanic, NH American Indian or Alaska Native, and NH Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting Hispanic origin or race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native, Asian and Pacific Islander, and Hispanic decedents, as well as undercounts of these groups in censuses. For reference to all-cause mortality in setting of prevalent HF, please see the Mortality section.

†Cost data are from Heidenreich et al.[101]

‡These percentages represent the portion of total mortality attributable to HF that is for males vs females.

§Includes Chinese, Filipino, Japanese, and other Asian people.

Sources: Prevalence: Unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using NHANES.[109] Percentages are age adjusted for Americans ≥20 years of age. Age-specific percentages are extrapolated to the 2020 US population estimates. These data are based on self-reports. Mortality (for underlying cause of HF): Unpublished NHLBI tabulation using National Vital Statistics System.[78] Hospital discharges (with a principal diagnosis of HF): Unpublished NHLBI tabulation using Healthcare Cost and Utilization Project (data include those inpatients discharged alive, dead, or status unknown).[1]

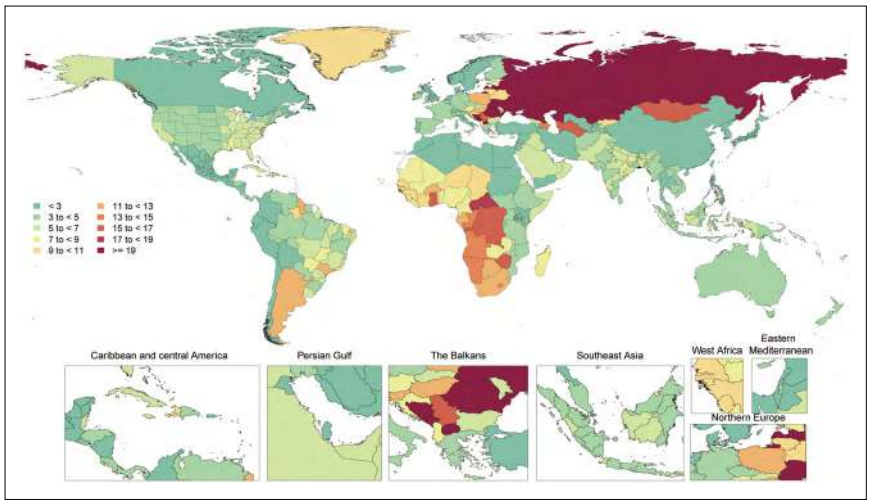



**Chart 22-1. Age-standardized global mortality rates of cardiomyopathy and myocarditis per 100 000, both sexes, 2021.**
During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.
GBD indicates Global Burden of Disease.
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[45]

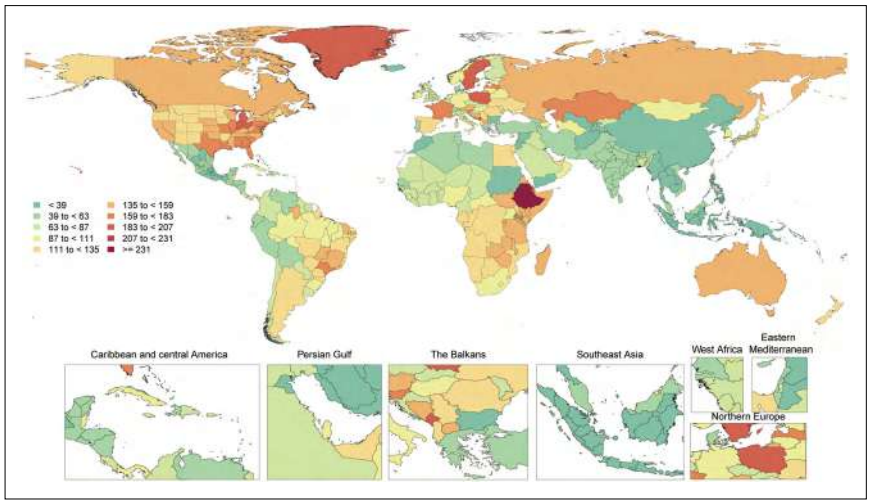



**Chart 22-2. Age-standardized global prevalence rates of cardiomyopathy and myocarditis per 100 000, both sexes, 2021.**
During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.
GBD indicates Global Burden of Disease.
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[45]

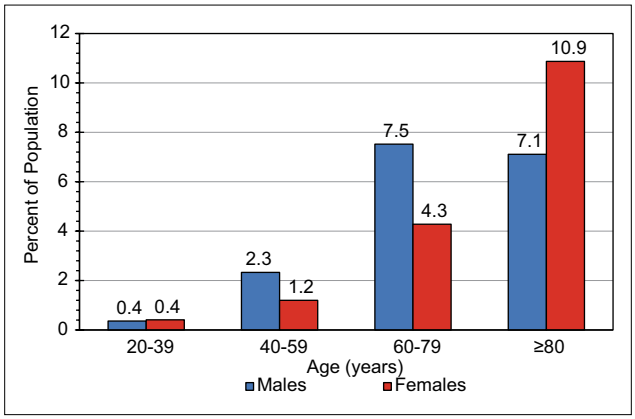



**Chart 22-3. Prevalence of HF among US adults ≥20 years of age, by sex and age (NHANES, 2017–2020).**
HF indicates heart failure; and NHANES, National Health and Nutrition Examination Survey.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.[109]

## REFERENCES


1. Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project (HCUP). Accessed April 1, 2023. http://hcupnet.ahrq.gov/
2. Hershberger RE, Givertz MM, Ho CY, Judge DP, Kantor PF, McBride KL, Morales A, Taylor MRG, Vatta M, Ware SM. Genetic Evaluation of cardiomyopathy: a Heart Failure Society of America practice guideline. *J Card Fail*. 2018;24:281–302. doi: 10.1016/j.cardfail.2018.03.004
3. Jaaskelainen P, Vangipurapu J, Raivo J, Kuulasmaa T, Helio T, Aalto-Setala K, Kaartinen M, Ilveskoski E, Vanninen S, Hamalainen L, et al. Genetic basis and outcome in a nationwide study of Finnish patients with hypertrophic cardiomyopathy. *ESC Heart Fail*. 2019;6:436–445. doi: 10.1002/ehf2.12420
4. Watkins H, Ashrafian H, Redwood C. Inherited cardiomyopathies. *N Engl J Med*. 2011;364:1643–1656. doi: 10.1056/NEJMra0902923
5. Tadros R, Francis C, Xu X, Vermeer AMC, Harper AR, Huurman R, Kelu Bisabu K, Walsh R, Hoorntje ET, Te Rijdt WP, et al. Shared genetic pathways contribute to risk of hypertrophic and dilated cardiomyopathies with opposite directions of effect. *Nat Genet*. 2021;53:128–134. doi: 10.1038/s41588-020-00762-2
6. Ho CY, Day SM, Ashley EA, Michels M, Pereira AC, Jacoby D, Cirino AL, Fox JC, Lakdawala NK, Ware JS, et al. Genotype and lifetime burden of disease in hypertrophic cardiomyopathy: insights from the Sarcomeric Human Cardiomyopathy Registry (SHaRe). *Circulation*. 2018;138:1387–1398. doi: 10.1161/CIRCULATIONAHA.117.033200
7. Abdelfattah OM, Martinez M, Sayed A, ElRefaei M, Abushouk AI, Hassan A, Masri A, Winters SL, Kapadia SR, Maron BJ, et al. Temporal and global trends of the incidence of sudden cardiac death in hypertrophic cardiomyopathy. *JACC Clin Electrophysiol*. 2022;8:1417–1427. doi: 10.1016/j.jacep.2022.07.012
8. Butzner M, Leslie D, Cuffee Y, Hollenbeak CS, Sciamanna C, Abraham TP. Sex differences in clinical outcomes for obstructive hypertrophic cardiomyopathy in the USA: a retrospective observational study of administrative claims data. *BMJ Open*. 2022;12:e058151. doi: 10.1136/bmjopen-2021-058151
9. Ingles J, Goldstein J, Thaxton C, Caleshu C, Corty EW, Crowley SB, Dougherty K, Harrison SM, McGlaughon J, Milko LV, et al. Evaluating the clinical validity of hypertrophic cardiomyopathy genes. *Circ Genom Precis Med*. 2019;12:e002460. doi: 10.1161/CIRCGEN.119.002460
10. Page SP, Kounas S, Syrris P, Christiansen M, Frank-Hansen R, Andersen PS, Elliott PM, McKenna WJ. Cardiac myosin binding protein-C mutations in families with hypertrophic cardiomyopathy: disease expression in relation to age, gender, and long term outcome. *Circ Cardiovasc Genet*. 2012;5:156–166. doi: 10.1161/CIRCGENETICS.111.960831
11. Lorenzini M, Norrish G, Field E, Ochoa JP, Cicerchia M, Akhtar MM, Syrris P, Lopes LR, Kaski JP, Elliott PM. Penetrance of hypertrophic cardiomyopathy in sarcomere protein mutation carriers. *J Am Coll Cardiol*. 2020;76:550–559. doi: 10.1016/j.jacc.2020.06.011
12. Hershberger RE, Hedges DJ, Morales A. Dilated cardiomyopathy: the complexity of a diverse genetic architecture. *Nat Rev Cardiol*. 2013;10:531–547. doi: 10.1038/nrcardio.2013.105
13. Hershberger RE, Siegfried JD. Update 2011: clinical and genetic issues in familial dilated cardiomyopathy. *J Am Coll Cardiol*. 2011;57:1641–1649. doi: 10.1016/j.jacc.2011.01.015
14. Huggins GS, Kinnamon DD, Haas GJ, Jordan E, Hofmeyer M, Kransdorf E, Ewald GA, Morris AA, Owens A, Lowes B, et al; DCM Precision Medicine Study of the DCM Consortium. Prevalence and cumulative risk of familial idiopathic dilated cardiomyopathy. *JAMA*. 2022;327:454–463. doi: 10.1001/jama.2021.24674
15. Hastings R, de Villiers CP, Hooper C, Ormondroyd L, Pagnamenta A, Lise S, Salatino S, Knight SJ, Taylor JC, Thomson KL, et al. Combination of whole genome sequencing, linkage, and functional studies implicates a missense mutation in titin as a cause of autosomal dominant cardiomyopathy with features of left ventricular noncompaction. *Circ Cardiovasc Genet*. 2016;9:426–435. doi: 10.1161/CIRCGENETICS.116.001431
16. Walsh R, Thomson KL, Ware JS, Funke BH, Woodley J, McGuire KJ, Mazzarotto F, Blair E, Seller A, Taylor JC, et al. Reassessment of mendelian gene pathogenicity using 7,855 cardiomyopathy cases and 60,706 reference samples. *Genet Med*. 2017;19:192–203. doi: 10.1038/gim.2016.90
17. Schultheiss HP, Fairweather D, Caforio ALP, Escher F, Hershberger RE, Lipshultz SE, Liu PP, Matsumori A, Mazzanti A, McMurray J, et al. Dilated cardiomyopathy. *Nat Rev Dis Primers*. 2019;5:32. doi: 10.1038/s41572-019-0084-1
18. Givertz MM, Mann DL. Epidemiology and natural history of recovery of left ventricular function in recent onset dilated cardiomyopathies. *Curr Heart Fail Rep*. 2013;10:321–330. doi: 10.1007/s11897-013-0157-5
19. Yeboah J, Rodriguez CJ, Stacey B, Lima JA, Liu S, Carr JJ, Hundley WG, Herrington DM. Prognosis of individuals with asymptomatic left ventricular systolic dysfunction in the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation*. 2012;126:2713–2719. doi: 10.1161/CIRCULATIONAHA.112.112201
20. Dec WG, Fuster V. Idiopathic dilated cardiomyopathy. *N Engl J Med*. 1994;331:1564–1575.
21. Shetty NS, Parcha V, Hasnie A, Pandey A, Arora G, Arora P. Mechanical circulatory support devices among patients with familial dilated cardiomyopathy: insights from the INTERMACS. *Circulation*. 2022;146:1486–1488. doi: 10.1161/CIRCULATIONAHA.122.061143
22. Vissing CR, Espersen K, Mills HL, Bartels ED, Jurlander R, Skriver SV, Ghouse J, Thune JJ, Axelsson Raja A, Christensen AH, et al. Family screening in dilated cardiomyopathy: prevalence, incidence, and potential for limiting follow-up. *JACC Heart Fail*. 2022;10:792–803. doi: 10.1016/j.jchf.2022.07.009
23. Jordan E, Peterson L, Ai T, Asatryan B, Bronicki L, Brown E, Celeghin R, Edwards M, Fan J, Ingles J, et al. Evidence-based assessment of genes in dilated cardiomyopathy. *Circulation*. 2021;144:7–19. doi: 10.1161/circulationaha.120.053033
24. Harper AR, Goel A, Grace C, Thomson KL, Petersen SE, Xu X, Waring A, Ormondroyd E, Kramer CM, Ho CY, et al. Common genetic variants and modifiable risk factors underpin hypertrophic cardiomyopathy susceptibility and expressivity. *Nat Genet*. 2021;53:135–142. doi: 10.1038/s41588-020-00764-0
25. Isogai T, Kamiya CA. Worldwide incidence of peripartum cardiomyopathy and overall maternal mortality. *Int Heart J*. 2019;60:503–511. doi: 10.1536/ihj.18-729
26. Honigberg MC, Givertz MM. Peripartum cardiomyopathy. *BMJ*. 2019;364:k5287. doi: 10.1136/bmj.k5287
27. Sliwa K, Mebazaa A, Hilfiker-Kleiner D, Petrie MC, Maggioni AP, Laroche C, Regitz-Zagrosek V, Schaufelberger M, Tavazzi L, van der Meer P, et al. Clinical characteristics of patients from the worldwide registry on peripartum cardiomyopathy (PPCM): EURObservational Research Programme in conjunction with the Heart Failure Association of the European Society of Cardiology Study Group on PPCM. *Eur J Heart Fail*. 2017;19:1131–1141. doi: 10.1002/ejhf.780
28. Fett JD, Christie LG, Carraway RD, Murphy JG. Five-year prospective study of the incidence and prognosis of peripartum cardiomyopathy at a single institution. *Mayo Clin Proc*. 2005;80:1602–1606. doi: 10.4065/80.12.1602
29. Kolte D, Khera S, Aronow WS, Palaniswamy C, Mujib M, Ahn C, Jain D, Gass A, Ahmed A, Panza JA, et al. Temporal trends in incidence and outcomes of peripartum cardiomyopathy in the United States: a nationwide population-based study. *J Am Heart Assoc*. 2014;3:e001056. doi: 10.1161/JAHA.114.001056
30. Ware JS, Li J, Mazaika E, Yasso CM, DeSouza T, Cappola TP, Tsai EJ, Hilfiker-Kleiner D, Kamiya CA, Mazzarotto F, et al; IMAC-2 and IPAC Investigators. Shared genetic predisposition in peripartum and dilated cardiomyopathies. *N Engl J Med*. 2016;374:233–241. doi: 10.1056/NEJMoa1505517
31. Kerpen K, Koutrolou-Sotiropoulou P, Zhu C, Yang J, Lyon JA, Lima FV, Stergiopoulos K. Disparities in death rates in women with peripartum cardiomyopathy between advanced and developing countries: a systematic review and meta-analysis. *Arch Cardiovasc Dis*. 2019;112:187–198. doi: 10.1016/j.acvd.2018.10.002
32. Olanipekun T, Abe T, Effoe V, Egbuche O, Mather P, Echols M, Adedinsewo D. Racial and ethnic disparities in the trends and outcomes of cardiogenic shock complicating peripartum cardiomyopathy. *JAMA Netw Open*. 2022;5:e2220937. doi: 10.1001/jamanetworkopen.2022.20937
33. McNamara DM, Elkayam U, Alharethi R, Damp J, Hsich E, Ewald G, Modi K, Alexis JD, Ramani GV, Semigran MJ, et al; IPAC Investigators. Clinical outcomes for peripartum cardiomyopathy in North America: results of the IPAC Study (Investigations of Pregnancy-Associated Cardiomyopathy). *J Am Coll Cardiol*. 2015;66:905–914. doi: 10.1016/j.jacc.2015.06.1309
34. Elkayam U, Akhter MW, Singh H, Khan S, Bitar F, Hameed A, Shotan A. Pregnancy-associated cardiomyopathy: clinical characteristics and a comparison between early and late presentation. *Circulation*. 2005;111:2050–2055. doi: 10.1161/01.CIR.0000162478.36652.7E

35. Irizarry OC, Levine LD, Lewey J, Boyer T, Riis V, Elovitz MA, Arany Z. Comparison of clinical characteristics and outcomes of peripartum cardiomyopathy between African American and non-African American Women. *JAMA Cardiol*. 2017;2:1256–1260. doi: 10.1001/jamacardio.2017.3574
36. Amos AM, Jaber WA, Russell SD. Improved outcomes in peripartum cardiomyopathy with contemporary. *Am Heart J*. 2006;152:509–513. doi: 10.1016/j.ahj.2006.02.008
37. Wilkinson JD, Landy DC, Colan SD, Towbin JA, Sleeper LA, Orav EJ, Cox GF, Canter CE, Hsu DT, Webber SA, et al. The Pediatric Cardiomyopathy Registry and heart failure: key results from the first 15 years. *Heart Fail Clin*. 2010;6:401–413, vii. doi: 10.1016/j.hfc.2010.05.002
38. Colan SD, Lipshultz SE, Lowe AM, Sleeper LA, Messere J, Cox GF, Lurie PR, Orav EJ, Towbin JA. Epidemiology and cause-specific outcome of hypertrophic cardiomyopathy in children: findings from the Pediatric Cardiomyopathy Registry. *Circulation*. 2007;115:773–781. doi: 10.1161/CIRCULATIONAHA.106.621185
39. Ziolkowska L, Turska-Kmiec A, Petryka J, Kawalec W. Predictors of long-term outcome in children with hypertrophic cardiomyopathy. *Pediatr Cardiol*. 2016;37:448–458. doi: 10.1007/s00246-015-1298-y
40. Sakai-Bizmark R, Webber EJ, Marr EH, Mena LA, Chang RR. Patient characteristics and incidence of childhood hospitalisation due to hypertrophic cardiomyopathy in the United States of America 2001-2014. *Cardiol Young*. 2019;29:344–354. doi: 10.1017/S1047951118002421
41. Towbin JA, Lowe AM, Colan SD, Sleeper LA, Orav EJ, Clunie S, Messere J, Cox GF, Lurie PR, Hsu D, et al. Incidence, causes, and outcomes of dilated cardiomyopathy in children. *JAMA*. 2006;296:1867–1876. doi: 10.1001/jama.296.15.1867
42. Pahl E, Sleeper LA, Canter CE, Hsu DT, Lu M, Webber SA, Colan SD, Kantor PF, Everitt MD, Towbin JA, et al; Pediatric Cardiomyopathy Registry Investigators. Incidence of and risk factors for sudden cardiac death in children with dilated cardiomyopathy: a report from the Pediatric Cardiomyopathy Registry. *J Am Coll Cardiol*. 2012;59:607–615. doi: 10.1016/j.jacc.2011.10.878
43. Choudhry S, Puri K, Denfield SW. An update on pediatric cardiomyopathy. *Curr Treat Options Cardiovasc Med*. 2019;21:36. doi: 10.1007/s11936-019-0739-y
44. Mulrooney DA, Yeazel MW, Kawashima T, Mertens AC, Mitby P, Stovall M, Donaldson SS, Green DM, Sklar CA, Robison LL, et al. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. *BMJ*. 2009;339:b4606. doi: 10.1136/bmj.b4606
45. *Global Burden of Disease Study and Institute for Health Metrics and Evaluation*. University of Washington. Accessed August 2, 2023. http://ghdx.healthdata.org/
46. Khera R, Kondamudi N, Zhong L, Vaduganathan M, Parker J, Das SR, Grodin JL, Halm EA, Berry JD, Pandey A. Temporal trends in heart failure incidence among Medicare beneficiaries across risk factor strata, 2011 to 2016. *JAMA Netw Open*. 2020;3:e2022190. doi: 10.1001/jamanetworkopen.2020.22190
47. Dunlay SM, Weston SA, Jacobsen SJ, Roger VL. Risk factors for heart failure: a population-based case-control study. *Am J Med*. 2009;122:1023–1028. doi: 10.1016/j.amjmed.2009.04.022
48. Kovell LC, Juraschek SP, Russell SD. Stage A heart failure is not adequately recognized in US Adults: analysis of the National Health and Nutrition Examination Surveys, 2007-2010. *PLoS One*. 2015;10:e0132228. doi: 10.1371/journal.pone.0132228
49. Ho JE, Enserro D, Brouwers FP, Kizer JR, Shah SJ, Psaty BM, Bartz TM, Santhanakrishnan R, Lee DS, Chan C, et al. Predicting heart failure with preserved and reduced ejection fraction: the International Collaboration on Heart Failure Subtypes. *Circ Heart Fail*. 2016;9:e003116. doi: 10.1161/CIRCHEARTFAILURE.115.003116
50. Tromp J, Paniagua SMA, Lau ES, Allen NB, Blaha MJ, Gansevoort RT, Hillege HL, Lee DE, Levy D, Vasan RS, et al. Age dependent associations of risk factors with heart failure: pooled population based cohort study. *BMJ*. 2021;372:n461. doi: 10.1136/bmj.n461
51. Pandey A, LaMonte M, Klein L, Ayers C, Psaty BM, Eaton CB, Allen NB, de Lemos JA, Carnethon M, Greenland P, et al. Relationship between physical activity, body mass index, and risk of heart failure. *j Am Coll Cardiol*. 2017;69:1129–1142. doi: 10.1016/j.jacc.2016.11.081
52. Folsom AR, Shah AM, Lutsey PL, Roetker NS, Alonso A, Avery CL, Miedema MD, Konety S, Chang PP, Solomon SD. American Heart Association's Life's Simple 7: avoiding heart failure and preserving cardiac structure and function. *Am J Med*. 2015;128:970–976.e2. doi: 10.1016/j.amjmed.2015.03.027
53. Sinha A, Ning H, Carnethon MR, Allen NB, Wilkins JT, Lloyd-Jones DM, Khan SS. Race- and sex-specific population attributable fractions of incident heart failure: a population-based cohort study from the Lifetime Risk Pooling Project. *Circ Heart Fail*. 2021;14:e008113. doi: 10.1161/CIRCHEARTFAILURE.120.008113
54. Sullivan K, Doumouras BS, Santema BT, Walsh MN, Douglas PS, Voors AA, Van Spall HGC. Sex-specific differences in heart failure: pathophysiology, risk factors, management, and outcomes. *Can J Cardiol*. 2021;37:560–571. doi: 10.1016/j.cjca.2020.12.025
55. Lee DS, Pencina MJ, Benjamin EJ, Wang TJ, Levy D, O'Donnell CJ, Nam BH, Larson MG, D'Agostino RB, Vasan RS. Association of parental heart failure with risk of heart failure in offspring. *N Engl J Med*. 2006;355:138–147. doi: 10.1056/NEJMoa052948
56. Cappola TP, Li M, He J, Ky B, Gilmore J, Qu L, Keating B, Reilly M, Kim CE, Glessner J, et al. Common variants in *HSPB7* and *FRMD4B* associated with advanced heart failure. *Circ Cardiovasc Genet*. 2010;3:147–154. doi: 10.1161/CIRCGENETICS.109.898395
57. Matkovich SJ, Van Booven DJ, Hindes A, Kang MY, Druley TE, Vallania FL, Mitra RD, Reilly MP, Cappola TP, Dorn GW. Cardiac signaling genes exhibit unexpected sequence diversity in sporadic cardiomyopathy, revealing *HSPB7* polymorphisms associated with disease. *J Clin Invest*. 2010;120:280–289. doi: 10.1172/JCI39085
58. Stark K, Esslinger UB, Reinhard W, Petrov G, Winkler T, Komajda M, Isnard R, Charron P, Villard E, Cambien F, et al. Genetic association study identifies *HSPB7* as a risk gene for idiopathic dilated cardiomyopathy. *PLoS Genet*. 2010;6:e1001167. doi: 10.1371/journal.pgen.1001167
59. Xu H, Dorn Ii GW, Shetty A, Parihar A, Dave T, Robinson SW, Gottlieb SS, Donahue MP, Tomaselli GF, Kraus WE, et al. A genome-wide association study of idiopathic dilated cardiomyopathy in African Americans. *J Pers Med*. 2018;8:E11. doi: 10.3390/jpm8010011
60. Shah S, Henry A, Roselli C, Lin H, Sveinbjornsson G, Fatemifar G, Hedman AK, Wilk JB, Morley MP, Chaffin MD, et al. Genome-wide association and mendelian randomisation analysis provide insights into the pathogenesis of heart failure. *Nat Commun*. 2020;11:163. doi: 10.1038/s41467-019-13690-5
61. Aung N, Vargas JD, Yang C, Cabrera CP, Warren HR, Fung K, Tzanis E, Barnes MR, Rotter JI, Taylor KD, et al. Genome-wide analysis of left ventricular image-derived phenotypes identifies fourteen loci associated with cardiac morphogenesis and heart failure development. *Circulation*. 2019;140:1318–1330. doi: 10.1161/CIRCULATIONAHA.119.041161
62. Mosley JD, Levinson RT, Farber-Eger E, Edwards TL, Hellwege JN, Hung AM, Giri A, Shuey MM, Shaffer CM, Shi M, et al. The polygenic architecture of left ventricular mass mirrors the clinical epidemiology. *Sci Rep*. 2020;10:7561. doi: 10.1038/s41598-020-64525-z
63. Levin MG, Tsao NL, Singhal P, Liu C, Vy HMT, Paranjpe I, Backman JD, Bellomo TR, Bone WP, Biddinger KJ, et al. Genome-wide association and multi-trait analyses characterize the common genetic architecture of heart failure. *Nat Commun*. 2022;13:6914. doi: 10.1038/s41467-022-34216-6
64. Chaffin M, Papangeli I, Simonson B, Akkad AD, Hill MC, Arduini A, Fleming SJ, Melanson M, Hayat S, Kost-Alimova M, et al. Single-nucleus profiling of human dilated and hypertrophic cardiomyopathy. *Nature*. 2022;608:174–180. doi: 10.1038/s41586-022-04817-8
65. Merlo M, Pivetta A, Pinamonti B, Stolfo D, Zecchin M, Barbati G, Di Lenarda A, Sinagra G. Long-term prognostic impact of therapeutic strategies in patients with idiopathic dilated cardiomyopathy: changing mortality over the last 30 years. *Eur J Heart Fail*. 2014;16:317–324. doi: 10.1002/ejhf.16
66. Vaduganathan M, Claggett BL, Jhund PS, Cunningham JW, Pedro Ferreira J, Zannad F, Packer M, Fonarow GC, McMurray JJV, Solomon SD. Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials. *Lancet*. 2020;396:121–128. doi: 10.1016/S0140-6736(20)30748-0
67. Gevaert AB, Kataria R, Zannad F, Sauer AJ, Damman K, Sharma K, Shah SJ, Van Spall HGC. Heart failure with preserved ejection fraction: recent concepts in diagnosis, mechanisms and management. *Heart*. 2022;108:1342–1350. doi: 10.1136/heartjnl-2021-319605
68. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, Deswal A, Drazner MH, Dunlay SM, Evers LR, et al. AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines [published corrections appear in *Circulation*. 2022;145:e1033, *Circulation*. 2022;146:e185, and *Circulation*. 2023;147:e674]. *Circulation*. 2022;145:e895–e1032. doi: 10.1161/CIR.0000000000001063

69. Greene SJ, Butler J, Albert NM, DeVore AD, Sharma PP, Duffy CI, Hill CL, McCague K, Mi X, Patterson JH, et al. Medical therapy for heart failure with reduced ejection fraction: the CHAMP-HF Registry. *J Am Coll Cardiol.* 2018;72:351–366. doi: 10.1016/j.jacc.2018.04.070
70. Siddiqi TJ, Khan Minhas AM, Greene SJ, Van Spall HGC, Khan SS, Pandey A, Mentz RJ, Fonarow GC, Butler J, Khan MS. Trends in heart failure-related mortality among older adults in the United States from 1999-2019. *JACC Heart Fail.* 2022;10:851–859. doi: 10.1016/j.jchf.2022.06.012
71. Shoaib A, Van Spall HGC, Wu J, Cleland JGF, McDonagh TA, Rashid M, Mohamed MO, Ahmed FZ, Deanfield J, de Belder M, et al. Substantial decline in hospital admissions for heart failure accompanied by increased community mortality during COVID-19 pandemic. *Eur Heart J Qual Care Clin Outcomes.* 2021;7:378–387. doi: 10.1093/ehjqcco/qcab040
72. Keshvani N, Mehta A, Alger HM, Rutan C, Williams J, Zhang S, Young R, Alhanti B, Chiswell K, Greene SJ, et al. Heart failure quality of care and in-hospital outcomes during the COVID-19 pandemic: findings from the Get With The Guidelines-Heart Failure registry. *Eur J Heart Fail.* 2022;24:1117–1128. doi: 10.1002/ejhf.2484
73. Bhambhani V, Kizer JR, Lima JAC, van der Harst P, Bahrami H, Nayor M, de Filippi CR, Enserro D, Blaha MJ, Cushman M, et al. Predictors and outcomes of heart failure with mid-range ejection fraction. *Eur J Heart Fail.* 2018;20:651–659. doi: 10.1002/ejhf.1091
74. Gevaert AB, Tibebu S, Mamas MA, Ravindra NG, Lee SF, Ahmad T, Ko DT, Januzzi JL Jr, Van Spall HGC. Clinical phenogroups are more effective than left ventricular ejection fraction categories in stratifying heart failure outcomes. *ESC Heart Fail.* 2021;8:2741–2754. doi: 10.1002/ehf2.13344
75. Desai AS, Jhund PS, Claggett BL, Vaduganathan M, Miao ZM, Kondo T, Barkoudah E, Brahimi A, Connolly E, Finn P, et al. Effect of dapagliflozin on cause-specific mortality in patients with heart failure across the spectrum of ejection fraction: a participant-level pooled analysis of DAPA-HF and DELIVER. *JAMA Cardiol.* 2022;7:1227–1234. doi: 10.1001/jamacardio.2022.3736
76. Glynn P, Lloyd-Jones DM, Feinstein MJ, Carnethon M, Khan SS. Disparities in cardiovascular mortality related to heart failure in the United States. *J Am Coll Cardiol.* 2019;73:2354–2355. doi: 10.1016/j.jacc.2019.02.042
77. Glynn PA, Molsberry R, Harrington K, Shah NS, Petito LC, Yancy CW, Carnethon MR, Lloyd-Jones DM, Khan SS. Geographic variation in trends and disparities in heart failure mortality in the United States, 1999 to 2017. *J Am Heart Assoc.* 2021;10:e020541. doi: 10.1161/JAHA.120.020541
78. Centers for Disease Control and Prevention and National Center for Health Statistics. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death micro-data files. Accessed April 8, 2023. https://cdc.gov/nchs/nvss/mortality_public_use_data.htm
79. Akwo EA, Kabagambe EK, Wang TJ, Harrell FE Jr, Blot WJ, Mumma M, Gupta DK, Lipworth L. Heart failure incidence and mortality in the Southern Community Cohort Study. *Circ Heart Fail.* 2017;10:e003553. doi: 10.1161/CIRCHEARTFAILURE.116.003553
80. Loehr LR, Rosamond WD, Chang PP, Folsom AR, Chambless LE. Heart failure incidence and survival (from the Atherosclerosis Risk in Communities study). *Am J Cardiol.* 2008;101:1016–1022. doi: 10.1016/j.amjcard.2007.11.061
81. Centers for Disease Control and Prevention and National Center for Health Statistics. Multiple cause of death, CDC WONDER online database. Accessed April 1, 2023. https://wonder.cdc.gov/mcd-icd10.html.
82. Loccoh EC, Joynt Maddox KE, Wang Y, Kazi DS, Yeh RW, Wadhera RK. Rural-urban disparities in outcomes of myocardial infarction, heart failure, and stroke in the United States. *J Am Coll Cardiol.* 2022;79:267–279. doi: 10.1016/j.jacc.2021.10.045
83. Centers for Disease Control and Prevention and National Center for Health Statistics. National Ambulatory Medical Care Survey (NAMCS) public use data files. Accessed April 1, 2023. https://www.cdc.gov/nchs/ahcd/datasets_documentation_related.htm#data
84. Butler J, Yang M, Manzi MA, Hess GP, Patel MJ, Rhodes T, Givertz MM. Clinical course of patients with worsening heart failure with reduced ejection fraction. *J Am Coll Cardiol.* 2019;73:935–944. doi: 10.1016/j.jacc.2018.11.049
85. Van Spall HGC, DeFilippis EM, Lee SF, Oz UE, Perez R, Healey JS, Allen LA, Voors AA, Ko DT, Thabane L, et al. Sex-specific clinical outcomes of the PACT-HF randomized trial. *Circ Heart Fail.* 2021;14:e008548. doi: 10.1161/CIRCHEARTFAILURE.121.008548
86. Clark KAA, Reinhardt SW, Chouairi F, Miller PE, Kay B, Fuery M, Guha A, Ahmad T, Desai NR. Trends in heart failure hospitalizations in the US from 2008 to 2018. *J Card Fail.* 2022:171–180. doi: 10.1016/j.cardfail.2021.08.020
87. Averbuch T, Mohamed MO, Islam S, Defilippis EM, Breathett K, Alkhouli MA, Michos ED, Martin GP, Kontopantelis E, Mamas MA, et al. The association between socioeconomic status, sex, race/ethnicity and in-hospital mortality among patients hospitalized for heart failure. *J Card Fail.* 2022;28:697–709. doi: 10.1016/j.cardfail.2021.09.012
88. Jain V, Minhas AMK, Khan SU, Greene SJ, Pandey A, Van Spall HGC, Fonarow GC, Mentz RJ, Butler J, Khan MS. Trends in HF hospitalizations among young adults in the United States from 2004 to 2018. *JACC Heart Fail.* 2022;10:350–362. doi: 10.1016/j.jchf.2022.01.021
89. Blumer V, Gayowsky A, Xie F, Greene SJ, Graham MM, Ezekowitz JA, Perez R, Ko DT, Thabane L, Zannad F, et al. Effect of patient-centered transitional care services on patient-reported outcomes in heart failure: sex-specific analysis of the PACT-HF randomized controlled trial. *Eur J Heart Fail.* 2021;23:1488–1498. doi: 10.1002/ejhf.2312
90. Chang PP, Wruck LM, Shahar E, Rossi JS, Loehr LR, Russell SD, Agarwal SK, Konety SH, Rodriguez CJ, Rosamond WD. Trends in hospitalizations and survival of acute decompensated heart failure in four US communities (2005-2014): ARIC Study Community Surveillance. *Circulation.* 2018;138:12–24. doi: 10.1161/CIRCULATIONAHA.117.027551
91. Desai AS, Claggett B, Pfeffer MA, Bello N, Finn PV, Granger CB, McMurray JJ, Pocock S, Swedberg K, Yusuf S, et al. Influence of hospitalization for cardiovascular versus noncardiovascular reasons on subsequent mortality in patients with chronic heart failure across the spectrum of ejection fraction. *Circ Heart Fail.* 2014;7:895–902. doi: 10.1161/CIRCHEARTFAILURE.114.001567
92. US Department of Health and Human Services. Organ Procurement and Transplantation Network website. Accessed April 18, 2023. https://optn.transplant.hrsa.gov/data/
93. Colvin M, Smith JM, Ahn Y, Skeans MA, Messick E, Bradbrook K, Gauntt K, Israni AK, Snyder JJ, Kasiske BL. OPTN/SRTR 2020 annual data report: heart. *Am J Transplant.* 2022;22:350–437. doi: 10.1111/ajt.16977
94. Moayedi Y, Fan CPS, Cherikh WS, Stehlik J, Teuteberg JJ, Ross HJ, Khush KK. Survival outcomes after heart transplantation: does recipient sex matter? *Circ Heart Fail.* 2019;12:e006218. doi: 10.1161/CIRCHEARTFAILURE.119.006218
95. Chouairi F, Fuery M, Clark KA, Mullan CW, Stewart J, Caraballo C, Clarke JD, Sen S, Guha A, Ibrahim NE, et al. Evaluation of racial and ethnic disparities in cardiac transplantation. *J Am Heart Assoc.* 2021;10:e021067. doi: 10.1161/JAHA.120.021067
96. Breathett K, Knapp SM, Addison D, Johnson A, Shah RU, Flint K, Van Spall HGC, Sweitzer NK, Mazimba S. Relationships between 2018 UNOS heart policy and transplant outcomes in metropolitan, micropolitan, and rural settings. *J Heart Lung Transplant.* 2022;41:1228–1236. doi: 10.1016/j.healun.2022.06.015
97. Akintoye E, Shin D, Alvarez P, Briasoulis A. State-level variation in waitlist mortality and transplant outcomes among patients listed for heart transplantation in the US from 2011 to 2016. *JAMA Netw Open.* 3:e2028459. doi: 10.1001/jamanetworkopen.2020.28459
98. Molina EJ, Shah P, Kiernan MS, Cornwell WK 3rd, Copeland H, Takeda K, Fernandez FG, Badhwar V, Habib RH, Jacobs JP, et al. The Society of Thoracic Surgeons Intermacs 2020 annual report. *Ann Thorac Surg.* 2021;111:778–792. doi: 10.1016/j.athoracsur.2020.12.038
99. Emani S, Tumin D, Foraker RE, Hayes D Jr, Smith SA. Impact of insurance status on heart transplant wait-list mortality for patients with left ventricular assist devices. *Clin Transplant.* 2017;31:10.1111/ctr.12875. doi: 10.1111/ctr.12875
100. Teuteberg JJ, Cleveland JC Jr, Cowger J, Higgins RS, Goldstein DJ, Keebler M, Kirklin JK, Myers SL, Salerno CT, Stehlik J, et al. The Society of Thoracic Surgeons Intermacs 2019 annual report: the changing landscape of devices and indications. *Ann Thorac Surg.* 2020;109:649–660. doi: 10.1016/j.athoracsur.2019.12.005
101. Heidenreich PA, Albert NM, Allen LA, Bluemke DA, Butler J, Fonarow GC, Ikonomidis JS, Khavjou O, Konstam MA, Maddox TM, et al; on behalf of the American Heart Association Advocacy Coordinating Committee, Council on Arteriosclerosis, Thrombosis, and Vascular Biology, Council on Cardiovascular Radiology and Intervention, Council on Clinical Cardiology, Council on Epidemiology and Prevention and Stroke Council. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circ Heart Fail.* 2013;6:606–619. doi: 10.1161/HHF.0b013e318291329a
102. Urbich M, Globe G, Pantiri K, Heisen M, Bennison C, Wirtz HS, Di Tanna GL. A systematic review of medical costs associated with heart failure in the USA (2014-2020). *PharmacoEcon.* 2020;38:1219–1236. doi: 10.1007/s40273-020-00952-0

103. Kwok CS, Abramov D, Parwani P, Ghosh RK, Kittleson M, Ahmad FZ, Al Ayoubi F, Van Spall HGC, Mamas MA. Cost of inpatient heart failure care and 30-day readmissions in the United States. *Int J Cardiol*. 2021;329:115–122. doi: 10.1016/j.ijcard.2020.12.020
104. Briasoulis A, Inampudi C, Akintoye E, Adegbala O, Asleh R, Alvarez P, Bhama J. Regional variation in mortality, major complications, and cost after left ventricular assist device implantation in the United States (2009 to 2014). *Am J Cardiol*. 2018;121:1575–1580. doi: 10.1016/j.amjcard.2018.02.047
105. Nandi D, Rossano JW. Epidemiology and cost of heart failure in children. *Cardiol Young*. 2015;25:1460–1468. doi: 10.1017/S1047951115002280
106. Wei S, Miranda JJ, Mamas MA, Zuhlke LJ, Kontopantelis E, Thabane L, Van Spall HGC. Sex differences in the etiology and burden of heart failure across country income level: analysis of 204 countries and territories 1990-2019 [published online December 28, 2022]. *Eur Heart J Qual Care Clin Outcomes*. doi: 10.1093/ehjqcco/qcac088. https://academic.oup.com/ehjqcco/advance-article/doi/10.1093/ehjqcco/qcac088/6964647?login=false
107. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. 2020;396:1204–1222. doi: 10.1016/S0140-6736(20)30925-9
108. Stierman B, Afful J, Carroll M, Chen T, Davy O, Fink S, Fryar C, Gu Q, Hales C, Hughes J, et al. National Health and Nutrition Examination Survey 2017-March 2020 prepandemic data files: development of files and prevalance estmates for selected health outcomes. *Natl Health Stat Rep*. 2021;158:1–9.
109. Centers for Disease Control and Prevention and National Center for Health Statistics. National Health and Nutrition Examination Survey (NHANES) public use data files. Accessed April 1, 2023. https://www.cdc.gov/nchs/nhanes/

# 23. VALVULAR DISEASES

*See Tables 23-1 through 23-3 and Charts 23-1 through 23-10*

Click here to return to the Table of Contents

Click here to return to the Abbreviations

Mortality and any-mention mortality in this section are for 2021 and based on unpublished NHLBI tabulations using the NVSS and CDC WONDER.[1,2] Mortality is the number of deaths in 2021 for the given underlying cause according to *ICD-10*. Prevalence data are for 2016 and 2017. Hospital discharge data are from HCUP[3] 2020; data included are for inpatients discharged alive, dead, or status unknown. Hospital discharge data for 2020 are based on *ICD-10* codes.

## Valvular HD

### *ICD-9* 424; *ICD-10* I34 to I38.

2021, United States: Underlying cause mortality—23 143. Any-mention mortality—57 451.

2020, United States: Hospital discharges—128 910.

#### *Prevalence*

- The global prevalence of nonrheumatic valvular HD is 32.6 million with an 95% UI of 30.9 million to 34.3 million.[4]
- In a prospective cross-sectional study across all 31 provinces in China between 2012 and 2015, the weighted prevalence of valvular HD based on an analysis of 31 499 adults ≥35 years of age was 3.8% (95% CI, 2.6%–5.6%) or an estimated 25 621 503 people. Of those with valvular HD, 55.1% had rheumatic disease and 21.3% had degenerative disease. The prevalence of valvular HD increased with age ($P$<0.001) and was not different between males and females ($P$=0.308). Valvular HD was more prevalent in participants with hypertension (5.6% versus 2.8%; $P$<0.001) or CKD (9.2% versus 3.5%; $P$<0.001).
- Older adults in the ARIC study, a prospective community-based cohort study, underwent protocol echocardiography to classify their aortic and mitral stenotic or regurgitant lesions classified according to ACC/AHA guidelines.[5] Among 6118 ARIC participants with mean±SD age of 76±5 years (42% male, 22% Black race), at-risk (stage A) left-sided valvular HD was present in 39%, progressive (stage B) in 17%, and advanced (stage C/D) in 1.1%; 0.7% had previously undergone valve replacement or repair. A graded association was observed between stage A, B, and C/D valvular HD and risk of all-cause mortality, incident HF, incident AF, and incident CHD but not incident stroke. During the 6.6 years of follow-up, the prevalence of stage C/D valvular HD increased from 1% to 7%.
- In a US population-based study conducted between October 2011 and June 2014, the prevalence of valvular HD in 1818 Hispanic/Latino people (mean age, 55 years; 57% female) was 3.1%. Regurgitant lesions of moderate or greater severity were present in 2.4% of the population, and stenotic lesions of moderate or greater severity were present in 0.2%.[6]

#### *Incidence*

- In a report using a Swedish nationwide register to identify all patients with a first diagnosis of valvular HD at Swedish hospitals between 2003 and 2010 (N=10 164 211), the incidence of valvular HD was 63.9 per 100 000 person-years, with aortic stenosis (47.2%), MR (24.2%), and aortic regurgitation (18.0%) contributing most of the valvular diagnoses.[7] The majority of valvulopathies were diagnosed in the older adults (68.9% in individuals ≥65 years of age). Incidences of aortic regurgitation, aortic stenosis, and MR were higher in males, who were also more frequently diagnosed at an earlier age. Mitral stenosis incidence was higher in females. Incidences of aortic regurgitation (incidence rate, 20.2 versus 10.8), aortic stenosis (incidence rate, 37.8 versus 24.2), and MR (incidence rate, 21.3 versus 16) were higher in males, who were also more frequently diagnosed at an earlier age (70 years versus 76 years). Mitral stenosis incidence was higher in females (incidence rate, 2.3 versus 1.5).

## Aortic Valve Disorders

### *ICD-9* 424.1; *ICD-10* I35.

2021, United States: Underlying cause mortality—15 239. Any-mention mortality—37 574.

2020, United States: Hospital discharges—98 220.

#### *Prevalence*

- Data from the GBD Study revealed that the global prevalence of calcific aortic valve disease in 2019 was 9 404 080 (95% CI, 8 079 600–10 889 730) and the prevalence of calcific aortic valve disease

The 2024 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2024. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

in the United States was 327 978 730 (95% CI, 285 959 303–369 324 168).[8]
- Globally, there was a 443% increase in the prevalence of calcific aortic valve disease from 1 732 988 (95% CI, 1 431 470–2 074 810) in 1990 to 9 404 080 (95% CI, 8 079 600–10 889 730) in 2019.[9]
- In a random sample of Swedish males from the general population born in 1943 (n=798) and followed up for 21 years, prevalence of aortic stenosis was 2.6%.[10]
- In younger age groups, the most prevalent cause of aortic stenosis is bicuspid aortic valve, the most common form of congenital HD:
  - In the Copenhagen Baby Heart Study, which involved 25 556 newborns (51.7% male; mean±SD age, 12±8 days) in Denmark born between 2016 and 2018 who underwent transthoracic echocardiography, the prevalence of bicuspid aortic valve was 0.77% (95% CI, 0.67%–0.88%), with a male-to-female ratio of 2.1:1.[11]
  - A meta-analysis of 11 observational studies revealed that among 1177 patients with Turner syndrome, the prevalence of bicuspid aortic valve identified by cardiac MRI or CT was 23.7% (95% CI, 21.3%–26.1%).[12]
- In the MESA study of 6814 participants 45 to 84 years of age free of known CVD in the United States,[13] 77 participants (1.1%) had aortic stenosis on echocardiography; the age-adjusted prevalence of aortic stenosis was highest in White (3.5% [95% CI, 2.6%–4.7%]) and Hispanic (3.7% [95% CI, 2.5%–5.6%]) participants with lower prevalence in Black (1.8% [95% CI, 1.1%–3.1%]) and Chinese (0.3% [95% CI, 0.04%–2.0%]) participants.

### Incidence

- Globally, the incident cases of calcific aortic valve disease have increased by 351% from 130 821 cases (95% CI, 110 700–156 020) in 1990 to 589 637 cases (95% CI, 512 900–677 060) in 2019.[9]
- In a population-based cohort study of inpatient, outpatient, and professional claims from a 20% sample of Medicare beneficiaries in the United States between 2010 and 2018, 1 513 455 patients were diagnosed with aortic stenosis.[14]
  - The aortic stenosis incidence rate for the overall group increased from 13.5 to 17.0 per 1000 between 2010 and 2018 ($P<0.001$).
  - In addition, beneficiaries from underrepresented racial and ethnic groups had significantly lower incidence rates compared with White beneficiaries throughout the study period (91.3% White, 4.5% Black, 1.1% Hispanic, and 3.1% Asian and North American Native).
- Nationally representative data from Sweden demonstrate an age-adjusted incidence of aortic stenosis from 15.0 to 11.4 per 100 000 males and from 9.8 to 7.1 per 100 000 females between 1989 to 1991 and 2007 to 2009.[15]
- In the Norwegian Tromsø study, the incidence of new aortic stenosis was 4.9 per 1000 per year, with the initial mean age of participants being 60 years.[16]
- In the Canadian CANHEART aortic stenosis study, the absolute incidence of severe aortic stenosis among individuals >65 years of age was 144 per 100 000 person-years (169 and 127 per 100 000 person-years in males and females, respectively).[17]
- In a retrospective cohort study of 1507 patients from 9 institutions in Japan undergoing hemodialysis, 251 or 17% of patients developed aortic stenosis within a median follow-up period of 3.2 years.[18]
- A prospective cross-sectional study of 31 499 people across all 31 provinces in China between 2012 and 2015 reported an aortic regurgitation incidence of 1.2% (95% CI, 0.7%–2.1%) and an aortic stenosis incidence of 0.7% (95% CI, 0.4%–1.1%).[19]

### Lifetime Risk and Cumulative Incidence

- Global incidence and prevalence of calcific aortic valve disease are positively correlated with age. There are 2 peaks in incidence: 1 peak at 70 to 74 years of age and the other at >95 years of age. The prevalence of calcific aortic valve disease peaks at 90 to 94 years of age globally.[9]
- The number of older adults with calcific aortic stenosis is projected to more than double by 2050 in both the United States and Europe according to a simulation model in 7 decision analysis studies.[20]
- The pooled prevalence of all aortic stenosis in the elderly was 12.4% (95% CI, 6.6%–18.2%), and the prevalence of severe aortic stenosis was 3.4% (95% CI, 1.1%–5.7%).[20]
- In the Icelandic AGES-Reykjavik study alone, in both males and females, the prevalence of severe aortic stenosis, defined as an aortic valve area index of <0.6 $cm^2/m^2$, in the groups <70, 70 to 79, and ≥80 years of age were 0.92%, 2.4%, and 7.3%, respectively. Projections suggest a doubling in prevalence among those with severe aortic stenosis who are ≥70 years of age by 2040 and a tripling by 2060.[21]
- In a randomly selected group of male participants (N=9998) born from 1915 to 1925 in Gothenburg, Sweden, 7494 were examined and followed up until a diagnosis of aortic stenosis or death (maximum follow-up time, 42.8 years).[22] The lifetime cumulative incidence of aortic stenosis in the middle-aged male population was 3.2%.

### Risk Factors

- In the Canadian CANHEART study, among 1.12 million individuals >65 years of age followed up for

a median of 13 years, 20 995 subjects developed severe aortic stenosis.[17] Hypertension (aHR, 1.71 [95% CI, 1.66–1.76]), diabetes (HR, 1.49 [95% CI, 1.44–1.54]), and dyslipidemia (HR, 1.17 [95% CI, 1.14–1.21]) were the strongest predictors of the development of severe aortic stenosis (all $P<0.001$).

- In the CGPS, among 108 275 individuals, the risk of developing aortic stenosis was particularly high if BMI was ≥35.0 kg/m$^2$ (HR, 2.6 [95% CI, 2.0–3.5]).[23]
- In the Swedish General Population Study, higher BMI, obesity, cholesterol, hypertension, AF, smoking, and heredity for stroke were associated with aortic stenosis.[22] The HRs of being diagnosed with aortic stenosis for males with a baseline BMI of 25 to 27.5, 27.5 to 30, and >30 kg/m$^2$ were 1.99 (95% CI, 1.12–3.55), 2.98 (95% CI, 1.65–5.40), and 3.55 (95% CI, 1.84–6.87), respectively, with BMI of 20 to 22.5 kg/m$^2$ used as reference.
- In a prospective cohort study of 361 930 people with genetic data in the UK Biobank, a total of 1602 participants developed aortic valve stenosis during an 8.4-year follow-up.[24] Cox proportional risk regression models were used to estimate the HRs between 28 modifiable risk factors and aortic valve stenosis.
  - Modifiable risk factors associated with a higher risk of aortic valve stenosis included the following: adiposity (HR, 1.04 [95% CI, 1.05–1.07]), waist-to-hip ratio (HR,1.03 [95% CI, 1.03–1.04]), BP (HR, 1.10 [95% CI, 1.07–1.14]), pulse pressure (HR, 1.23 [95% CI, 1.19–1.26]), resting heart rate (HR, 1.06 [95% CI, 1.02–1.10]), LDL (HR, 1.10 [95% CI, 1.03–1.18]), urate (HR, 1.02 [95% CI, 1.02–1.03]), CRP (HR, 1.03 [95% CI, 1.02–1.04]), creatinine (HR, 1.04 [95% CI, 1.03–1.05]), glycated hemoglobin (HR, 1.07 [95% CI, 1.06–1.08]), smoking (HR, 1.35 [95% CI, 1.21–1.50]), and insomnia (HR, 1.19 [95% CI, 1.05–1.35]).
  - Genetically predicted 1-SD-higher levels of BMI (HR, 1.09 [95% CI, 1.03–1.16]), body fat percentage (HR, 1.17 [95% CI, 1.03–1.33]), LDL (HR, 1.15 [95% CI, 1.08–1.21]), and serum TC (HR, 1.13 [95% CI, 1.02–1.25]) were associated with a higher risk of aortic valve stenosis.
- The CGPS recruited 69 988 randomly selected individuals between 2003 to 2015 to evaluate the association between high lipoprotein(a) and high BMI with risk of calcific aortic valve disease.[25]
  - Compared with individuals in the 1st to 49th percentiles for both lipoprotein(a) and BMI, the aHRs for calcific aortic valve disease were 1.6 (95% CI, 1.3–1.9) for the 50th to 89th percentiles of both and 3.5 (95% CI, 2.5–5.1) for the 90th to 100th percentiles of both.
  - The 10-year absolute risk of calcific aortic valve disease was higher in males than in females. The 10-year absolute risk of calcific aortic valve disease in females 70 to 79 years of age with BMI ≥30.0 kg/m$^2$ was 5% for lipoprotein(a) ≤42 mg/dL, 7% for lipoprotein(a) 42 to 79 mg/dL, and 9% for lipoprotein(a) ≥80 mg/dL.
  - The 10-year absolute risk of calcific aortic valve disease in males 70 to 79 years of age with BMI ≥30.0 kg/m$^2$ was: 8% for lipoprotein(a) ≤42 mg/dL, 11% for lipoprotein(a) 42 to 79 mg/dL, and 14% for lipoprotein(a) ≥80 mg/dL.
- In a retrospective registry based observational study comprising 23 298 individuals who had their lipoprotein(a) measured between 2003 and 2017 at Karolinska University Laboratory in Stockholm, 489 participants developed calcific aortic valve stenosis.[26] The cohort was divided into deciles of lipoprotein(a) levels.
  - At the 90th percentile, those with calcific aortic stenosis had significantly higher lipoprotein(a) (117 mg/dL) than those without calcific aortic stenosis (89 mg/dL; $P<0.001$).
  - For individuals at the 90th percentile for lipoprotein(a) levels, the sex- and age-adjusted HR for development of calcific aortic stenosis was 1.53 (95% CI, 1.08–2.15; $P=0.016$) compared with those below the 50th percentile.
- A comparison of 2786 patients on dialysis with and without aortic stenosis from 58 hospitals in the Tokai region of Japan between 2017 and 2018 was conducted.[27]
  - Multivariable logistic regression analysis revealed that age (aOR, 1.93 [95% CI, 1.71–2.19]; $P<0.001$), long-term dialysis (aOR, 1.41 [95% CI, 1.21–1.64]; $P<0.001$), and elevated serum phosphorus levels (aOR, 1.16 [95% CI, 1.06–1.28]; $P=0.001$) were associated with mild aortic stenosis.
  - Similarly, age (aOR, 2.51 [95% CI, 2.02–3.12]; $P<0.001$), long-term dialysis (aOR, 1.35 [95% CI, 1.06–1.71]; $P=0.01$), and elevated serum phosphorus levels (aOR, 1.24 [95% CI, 1.07–1.44]; $P=0.005$) were associated with moderate to severe aortic stenosis.

### Genetics and Family History

- Bicuspid aortic valve is thought to be highly heritable with 47% of the phenotypic variance being explained by genetic variation.[28] Variants in *NOTCH1*, *GATA4*, *GATA5*, *GATA6*, *EXOC4*, *PALMD*, *TEX41*, *FBN1*, *ROBO4*, *MYH6*, and *SMAD6* have been associated with bicuspid aortic valve.[29–36]
- In a nationwide Swedish study comprising 6 117 263 siblings (13 442 with aortic stenosis), having at least 1 sibling with aortic stenosis was associated with an HR of 3.41 (95% CI, 2.23–5.21) for being diagnosed with aortic stenosis. These findings

indicate an overall familial aggregation of this disease beyond bicuspid aortic valve alone.[37]

- A GWAS in 6942 individuals identified an SNP located in an intron of the lipoprotein(a) gene that was significantly associated with the presence of aortic calcification (OR per allele, 2.05), circulating lipoprotein(a) levels, and the development of aortic stenosis.[38]
- In a GWAS of 1009 individuals undergoing cardiac surgery in Quebec and across Europe between 1993 and 2018,[39] a weighted GRS in each individual, estimated by adding the number of lipoprotein(a)-raising alleles weighted by the effect of each variant on lipoprotein(a) levels, was associated with a higher risk of calcific aortic stenosis (OR, 1.35 [95% CI, 1.10–1.660]; *P*=0.003).
- To investigate the association of hepatic *LPA* expression with calcific aortic valve stenosis, 80 SNPs strongly associated with the expression of *LPA* were examined in 408 403 individuals in the UK Biobank.[40] Of the total cohort, 2574 had calcific aortic valve stenosis (1659 males and 915 females). There was a causal association between hepatic *LPA* expression and calcific aortic valve stenosis in males (OR, 1.27 [95% CI, 1.13–1.43]) and females (OR, 1.22 [95% CI, 1.04–1.44]).
- A GWAS meta-analysis of 5115 cases and 354 072 controls identified *IL6*, *ALPL*, and *NAV1* as susceptibility genes for calcific aortic valve stenosis,[41] adding to knowledge from previous GWASs and transcriptome studies of aortic valve stenosis that have established several loci, including *LPA*, *PALMD*, and *TEX41*.[38,39,42,43] A multiancestry GWAS for calcific aortic valve stenosis conducted in >400 000 individuals identified 6 novel loci (*SLMAP*, *CEL-SR2*, *CEP85L*, *MECOM*, *CDAN1*, and *FTO*).[44] Secondary analysis assessing the pathophysiology of calcific aortic valve stenosis highlighted the role of inflammation, lipid metabolism, calcification, adiposity, and cellular senescence.[44]
- Multiple SNPs that encode for LDL-C have been combined to form a GRS that has been associated with prevalent aortic valve calcification (OR, 1.38 [95% CI, 1.09–1.74] per GRS increment) and incident aortic valve stenosis (HR, 2.78 [95% CI, 1.22–6.37] per GRS increment) by use of a mendelian randomization design.[45]
- PCSK9, a key regulator of plasma LDL-C, binds to LDL receptors, leading to their degradation in the liver. Inhibition of PCSK9 leads to an increase in LDL receptors and a decrease in LDL in the blood. A meta-analysis of 10 studies found that the loss-of-function R46L variant in *PCSK9* is associated with a reduced risk of calcific aortic valve stenosis (OR, 0.80 [95% CI, 0.70–0.91]; *P*=0.0011).[46]
- To evaluate the association between SBP and risk of valvular disease, 502 602 individuals 40 to 96 years of age in the UK Biobank between 2006 and 2010 were evaluated through mendelian randomization.[47] Each genetically predicted 20–mm Hg increment in SBP was associated with an increased risk of aortic stenosis (OR, 3.26 [95% CI, 1.50–7.10]) and aortic regurgitation (OR, 2.59 [95% CI, 0.75–8.92]).
- To investigate the genetic association of obesity with incident aortic valve stenosis and aortic valve replacement, a mendelian randomization study using 5 genetic variants associated with obesity and including 108 211 individuals from the Copenhagen General Population Study was conducted. The study found that each 1–kg/m$^2$ increase in BMI was associated with causal risk ratios for aortic valve stenosis and replacement of 1.52 (95% CI, 1.23–1.87) and 1.49 (95% CI, 1.07–2.08), respectively.[23]

## Treatment
## (See Chart 23-1)

### *Randomized Controlled Trials*

- The AVATAR is prospective RCT that evaluated the safety and efficacy of early SAVR in the treatment of asymptomatic patients with severe aortic stenosis.[48] One hundred fifty-seven patients (mean age, 67 years of age; 57% men) across 7 European countries between 2015 and 2020 were randomly allocated to early surgery (n=78) or conservative treatment (n=79). At a median follow-up period of 32 months, patients randomized to early surgery had a significantly lower incidence of the primary composite end point of all-cause death, AMI, stroke, or unplanned hospitalization for HF than those in the conservative arm (HR, 0.46 [95% CI, 0.23–0.90]; *P*=0.02). Kaplan-Meier estimates of the individual end points of all-cause mortality and HF hospitalization tended to be higher in the conservative compared with the early surgery group but did not reach statistical significance.
- A propensity-matched comparison of pulmonary autograft (Ross procedure; n=434) and bioprosthetic and mechanical aortic valve replacement (n=434) was performed in individuals between 18 and 50 years of age in the mandatory California and New York databases between 1997 and 2014.[49] At 15 years, the actuarial survival after the Ross procedure was 93.1% (95% CI, 89.1%–95.7%), significantly higher than actuarial survival after bioprosthetic aortic valve replacement (HR, 0.42 [95% CI, 0.23–0.75]; *P*=0.003) or mechanical aortic valve replacement (HR, 0.45 [95% CI, 0.26–0.79]; *P*=0.006). At 15 years, the Ross procedure was associated with a lower cumulative risk of reintervention (*P*=0.008) and endocarditis (*P*=0.01) than bioprosthetic aortic valve replacement. In contrast, the Ross procedure was associated with a higher cumulative incidence of reoperation (*P*<0.001). At

15 years, the Ross procedure also had lower risks of stroke (*P*=0.03) and major bleeding (*P*=0.016) compared with mechanical aortic valve replacement.

- A meta-analysis examined mortality and morbidity in 4812 patients ≥16 years of age undergoing the Ross procedure (n=1991) or mechanical (n=2019) or bioprosthetic (n=802) aortic valve replacement.[50] At a mean follow-up period of 7.4 years, all-cause mortality was significantly lower in the Ross procedure group compared with the mechanical aortic valve replacement (HR, 0.58 [95% CI, 0.35–0.97]; *P*=0.035) and bioprosthetic aortic valve replacement (HR, 0.32 [95% CI, 0.18–0.59]; *P*<0.001) groups.
- The CAVIAAR prospective cohort study enrolled 130 patients who underwent aortic valve remodeling root repair with expansible aortic ring annuloplasty and 131 patients who underwent mechanical composite valve and graft replacement.[51] At 4 years, there was no statistically significant difference in the primary composite outcome of mortality, reoperation, thromboembolic or major bleeding events, endocarditis or operating site infections, pacemaker implantation, and HF between patients who underwent aortic valve repair or mechanical composite valve and graft replacement (HR, 0.66 [95% CI, 0.39–1.12)]. However, there were significantly fewer valve-related deaths (HR, 0.09 [95% CI, 0.02–0.34]) and major bleeding events (HR, 0.37 [95% CI, 0.16–0.85]) in patients who underwent aortic valve repair compared with those who underwent mechanical composite valve and graft replacement.
- SAVR can be performed through either a minimally invasive or full sternotomy approach. A total of 358 patients enrolled in the PARTNER 3 low-risk trial underwent isolated SAVR at 68 centers through either a minimally invasive or full sternotomy approach.[52] The composite end point of death, stroke, or rehospitalization was similar between both groups (16.9% for minimally invasive versus 14.9% for full sternotomy; HR, 1.15 [95% CI, 0.66–2.03]; *P*=0.618). At 1 year, there were no significant differences in mortality (2.8% in both minimally invasive and full sternotomy groups; *P*>0.05), stroke (1.9% for minimally invasive versus 3.6% for full sternotomy; *P*>0.05), or rehospitalization (13.3% for minimally invasive versus 10.6% for full sternotomy; *P*>0.05 for all). Quality of life, as assessed by the Kansas City Cardiomyopathy Questionnaire score at 30 days or 1 year, was comparable in both groups (*P*=0.351).
- Between 2014 and 2016, 270 patients from a single center in the United Kingdom were enrolled and randomized to undergo mini-sternotomy aortic valve replacement (n=135) or conventional median sternotomy aortic valve replacement (n=135).[53] At a median follow-up period of 6.1 years, the composite outcome of all-cause mortality and reoperation occurred in 25 patients (18.5%) in the conventional sternotomy group and in 23 patients (17%) in the mini-sternotomy group (*P*=0.72).
- The annual volume of TAVR has increased each year since 2011.[54] After the US FDA approval of TAVR for low-risk patients in 2019, the TAVR volume exceeded all forms of SAVR (n=72 991 versus 57 626).[54] From 2011 through 2018, extreme-risk and high-risk patients remained the largest cohort undergoing TAVI, but in 2019, intermediate-risk patients were the largest cohort, and the low-risk patients with a median of 75 years of age increased to 8395, making up 11.5% of all patients with TAVI.
- Between 2014 and 2018, 913 patients ≥70 years of age at 34 centers in the United Kingdom with severe, symptomatic aortic stenosis were randomized to either TAVR with any valve and any access route (n=458) or SAVR (n=455).[55] The median STS mortality risk score of all study participants was 2.6% (IQR, 2.0%–3.4%). At 1 year, there were 21 deaths (4.6%) in the TAVI group and 30 deaths (6.6%) in the SAVR group, with an adjusted absolute risk difference of −2.0% (1-sided 97.5% CI, −∞ to 1.2%; *P*<0.001 for noninferiority). At 1 year, there were significantly fewer major bleeding events after TAVI compared with surgery (aHR, 0.33 [95% CI, 0.24–0.45]) but significantly more vascular complications (aHR, 4.42 [95% CI, 2.54–7.71]), conduction disturbances requiring pacemaker implantation (aHR, 2.05 [95% CI, 1.43–2.94]), and aortic regurgitation (aHR, 4.89 [95% CI, 3.08–7.75]).
- Despite the increase in TAVR procedures, racial disparities observed in SAVR also exist with TAVR.[56] Among the 70 221 patients in the STS/ACC TVT Registry who underwent TAVR between 2011 and 2016, 91.3% were White, 3.8% were Black, 3.4% were Hispanic, and 1.5% were Asian/Native American/Pacific Islander. Among the 4 racial groups, no difference was noted in the rates of in-hospital mortality, MI, stroke, major bleeding, vascular complications, or new pacemaker requirements. Among the 29 351 Medicare and Medicaid patients in this cohort, 1-year adjusted mortality rates were similar in Black and Hispanic individuals compared with White individuals but lower among patients of Asian/Native American/Pacific Islander race (aHR, 0.71 [95% CI, 0.55–0.92]; *P*=0.028). Black and Hispanic individuals had more HF hospitalizations compared with White individuals (aHR, 1.39 [95% CI, 1.16–1.67]; *P*<0.001; and aHR, 1.37 [95% CI, 1.13–1.66]; *P*=0.004, respectively). These differences remained after further adjustment for SES.

- The 276 316 patients treated with TAVR who entered the STS/ACC TVT Registry between 2011 and 2019 demonstrated improved temporal trends, with 2018 or 2019 cohorts demonstrating lower event rates than more historic cohorts[54]:
  - Expected risk of 30-day operative mortality (STS Predicted Risk of Mortality score) is 2.5%.
  - The 1-year mortality is 12.6%, with mortality differing according to risk group and intermediate-risk patients experiencing in-hospital, 30-day, and 1-year mortality about half that of high- and extreme-risk patients.
  - Overall in-hospital and 30-day stroke rates are 1.6% and 2.3%, respectively.
  - Incidence of permanent pacemaker implantation at 30 days is 10.8%.
- In Germany, >15 000 TAVR procedures were performed in 2016, a number 3 times higher than in 2011.[57] Over the same period (2011–2016), the number of SAVR procedures remained relatively stable at ≈10 000 per year, a lower number than for TAVR (Chart 23-1). In the same European registry, mortality decreased continuously, with overall in-hospital mortality being similar for TAVR and SAVR (2.6% versus 2.9%, respectively; *P*=0.19) in 2016 despite the higher risk profile in patients undergoing TAVR (Chart 23-1).
- On the basis of a retrospective study of 8210 patients using the NIS (2012–2014), females with severe aortic stenosis undergoing TAVR experienced a mortality rate (4.7% versus 3.9%; *P*=0.15) similar to that of males; however, females had higher rates of stroke (3% versus 2%; *P*=0.04), hemorrhage requiring transfusion (28% versus 20%; *P*<0.0001), and pericardial complications (1.3% versus 0.5%; *P*=0.0009).[58]
- A study to determine the 5-year outcome in 18 010 patients treated by isolated TAVR or SAVR (8942 with TAVR and 9068 with SAVR) in the German Aortic Valve Registry between 2011 and 2012[59] showed that patients treated with TAVR were significantly older (80.9±6.1 years versus 68.5±11.1 years; *P*<0.001) and had a higher STS score (6.3±4.9 versus 2.6±3.0; *P*<0.001) and higher 5-year all-cause mortality (49.8% versus 16.5%; *P*<0.0001). There was no significant difference in in-hospital stroke, in-hospital MI, or dialysis. With the use of propensity score–matching methods, in a total sample size of 3640 patients, there were 763 deaths (41.9%) among 1820 patients treated with TAVR compared with 552 (30.3%) among 1820 treated with SAVR during the 5-year follow-up (HR, 1.51 [95% CI, 1.35–1.68]; *P*<0.0001).[59] The patients who received TAVR had a higher rate of new pacemaker implantation compared with those who received SAVR (448 [24.6%] versus 201 [11.0%]; *P*<0.0001, respectively).

### *High-Risk Patients*

- Two RCTs, PARTNER 1A and US CoreValve High Risk, using balloon-expandable and self-expanding devices, respectively, have shown that TAVR compares favorably with SAVR in terms of mortality in high-risk patients at 1 and 5 years.
  - In the PARTNER 1A trial, risk of death at 5 years was 67.8% in the TAVR group compared with 62.4% in the SAVR group (HR, 1.04 [95% CI, 0.86–1.24]; *P*=0.76).[60]
  - The 5-year follow-up results in the US CoreValve High Risk trial revealed similar midterm survival and stroke rates in high-risk patients after TAVR (55.3% all-cause mortality, 12.3% major stroke) and SAVR (55.4% all-cause mortality, 13.2% major stroke rates).[61]

### *Intermediate-Risk Patients*

- In a cohort of 1746 patients from 87 centers in Europe and North America with severe aortic stenosis at intermediate surgical risk in the SURTAVI trial, the estimated incidence of the primary end point (death attributable to any cause or debilitating stroke) was 12.6% in the TAVR group (using a self-expanding device) and 14.0% in the SAVR group (95% credible interval [Bayesian analysis] for difference, −5.2 to 2.3%; posterior probability of noninferiority >0.999) at 24 months.[62] At the 5-year follow up, the primary end point was 31.3% in the TAVR group and 30.8% in the SAVR group (HR, 1.02 [95% CI, 0.85–1.22]; *P*=0.85).[63] Moderate to severe paravalvular leak was more common with TAVR than surgery (11 [3.0%] versus 2 [0.7%]; risk difference, 2.37% [95% CI, 0.17%–4.85%]; *P*=0.05). Pacemaker implantation rates were higher after TAVR (289 [39.1%] versus 94 [15.1%]; HR, 3.30 [95% CI, 2.61–4.17]; *P*<0.001). Last, valve reintervention rates were higher after TAVR (27 [3.5%] versus 11 [1.9%]; HR, 2.21 [95% CI, 1.10–4.45]; *P*=0.02).
- In the PARTNER 2 trial using a balloon-expandable device, the Kaplan-Meier event rates of the same end point were 19.3% in the TAVR group and 21.1% in the SAVR group (HR in the TAVR group, 0.89 [95% CI, 0.73–1.09]; *P*=0.25) at the 2-year follow-up. At 5 years, the incidence of death resulting from any cause or disabling stroke in the PARTNER 2 trial was 47.9% and 43.4% in the TAVR (transfemoral access) group and SAVR group, respectively (HR, 1.09 [95% CI, 0.95–1.25]; *P*=0.21).[64] Overall, these findings demonstrate that TAVR is a noninferior alternative to SAVR in patients with severe aortic stenosis at intermediate surgical risk.[64,65]

### *Low-Risk Patients*

- In 1000 patients with severe aortic stenosis at low surgical risk randomized in the PARTNER 3 trial to

either balloon-expandable TAVR or SAVR, the primary composite end point (death, stroke, or rehospitalization) rate was significantly lower in the TAVR than the SAVR group (8.5% versus 15.1%; absolute difference, −6.6 percentage points [95% CI, −10.8 to −2.5]; $P<0.001$ for noninferiority; HR, 0.54 [95% CI, 0.37–0.79]; $P=0.001$ for superiority).[66] At 2 years, the primary end point was significantly reduced after TAVR compared with SAVR (11.5% versus 17.4%; HR, 0.63 [95% CI, 0.45–0.88]; $P=0.007$), although TAVR valve thrombosis at 2 years was increased (2.6%; 13 events) compared with surgery (0.7%; 3 events; $P=0.02$). In the Medtronic Evolut Transcatheter Aortic Valve Replacement in Low Risk Patients, a total of 1414 patients with severe aortic stenosis at low surgical risk were randomized to receive either TAVR (n=730) or SAVR (n=684) between 2016 and 2019.[67] After 1 year of follow-up, Bayesian statistical inference was used to predict that the 2-year incidence of composite death or disabling stroke was 5.3% in the TAVR group and 6.7% in the SAVR group (difference, −1.4 percentage points [95% Bayesian credible interval for difference, −4.9 to 2.1]; posterior probability of noninferiority >0.999). After the 2-year follow-up, the primary end point of death or disabling stroke was 4.3% in the TAVR group and 6.3% in the surgery group ($P=0.084$).[68]

- Noninferiority of TAVR versus SAVR in low-surgical-risk patients with severe aortic stenosis was confirmed at the 5-year follow-up in the European NOTION study.[69]
- Although TAVR and SAVR are comparable in terms of mortality and disabling stroke in patients with severe aortic stenosis at low and intermediate risk, a meta-analysis of RCTs and propensity score–matching observational studies demonstrated a higher proportion of aortic valve reintervention in TAVR than in SAVR (RR, 3.16 [95% CI, 1.61–6.19]; heterogeneity $P=0.60$, $I^2=0\%$ at 2 years).[70]
- Among 96256 transfemoral TAVR procedures, adjusted 30-day mortality was higher at institutions with low procedural volume (3.19% [95% CI, 2.78%–3.67%]) than at institutions with high procedural volume (2.66% [95% CI, 2.48%–2.85%]; OR, 1.21; $P=0.02$).[71]

### Mortality

- Calcific aortic valve disease–related death cases increased worldwide from 53298 (95% CI, 47760–59730) in 1990 to 126827 (95% CI, 105600–141390) in 2019.[9]
  - Mortality in patients with calcific aortic valve disease increases exponentially with age, with males having higher mortality than females before 80 years of age.
- Calcific aortic valve disease accounted for 24826 (95% CI, 20354–27718) deaths in the United States in 2019.[8]
- In 145 asymptomatic patients with severe aortic stenosis, the cumulative incidence of a combined outcome of 30-day operative mortality or cardiovascular death was significantly lower in patients undergoing early surgery compared with those using watchful waiting (1% at both 4 and 8 years versus 6% at 4 years and 26% at 8 years; $P=0.003$).[72]
- In the community, morbidity related to bicuspid aortic valve is higher in males than in females, with a total combined risk of aortic regurgitation, surgery, and IE of 52±4% in males versus 35±6% in females ($P=0.01$).[73] Nevertheless, females have a significantly higher RR of death in tertiary and surgical referral cohorts, with an age-adjusted RR of death of 1.63 (95% CI, 1.40–1.89) for females versus 1.34 (95% CI, 1.22–1.47) for males ($P=0.026$).[73] The risk of death is independently associated with aortic regurgitation ($P\leq0.04$).
- In a study of 2429 patients with severe aortic stenosis, of whom 49.5% were females, the 5-year survival was lower especially in females compared with expected survival (62±2% versus 71% for females and 69±1% versus 71% for males) and compared with 5-year survival in males despite females having longer life expectancy than males (66±2% [expected, 75%] versus 68±2% [expected, 70%]; $P<0.001$) after controlling for age.[74] Females also were more symptomatic ($P=0.004$) and used aortic valve replacement therapy less often (64.4% versus 69.1%; $P=0.018$).
- In a single-center study of 5994 adults with and without aortic stenosis between 2015 and 2016, the Vmax on transthoracic echocardiography was linearly related to 5 year all-cause mortality (HR, 1.26 [95% CI, 1.19–1.33] for every 100 cm/s of Vmax).[75]
- A meta-analysis of 25 studies comprising 12143 individuals found that, compared with patients with moderate aortic stenosis, the incidence rate difference of all-cause mortality was −3.9 (95% CI, −6.7 to −1.1) in patients with no or mild aortic stenosis and 2.2 (95% CI, 0.8–3.5) in patients with severe aortic stenosis.[75]
- In an observational echocardiographic multicenter cohort study of 98565 males and 99357 females ≥65 years of age in Australia from 2003 to 2017, 21.0% of males and 18.7% of females had aortic stenosis.[76] The actual 5-year mortality in males and females with normal aortic valves was 32.1% and 26.1%, respectively. In males and females with mild aortic stenosis, this increased to 40.9% and 35.9%, respectively. In males and females with severe aortic stenosis, this increased 52.2% and 55.3%, respectively.

- A multicenter study of 30 865 US and 217 599 Australian patients between 2003 and 2017 found that moderate aortic stenosis conferred an increased risk of mortality after adjustment for age and sex (US patients: HR, 1.66 [95% CI, 1.52–1.80]; Australian patients: HR, 1.37 [95% CI, 1.34–1.41]).[77]
- Echocardiographic data, including Vmax from 631 824 Australian and 66 846 US patients ≥65 years of age, were linked to all-cause deaths in Australia and the United States between 2003 and 2018.[78] Compared with those with Vmax of 1.0 to 1.49 m/s, those with Vmax of 2.50 to 2.99 m/s and 3.0 to 3.49 m/s had HRs of 1.22 (95% CI, 1.12–1.32) and 1.59 (95% CI, 1.36–1.86), respectively, for mortality within 10 years after adjustment for age, sex, left-sided HD, and LVEF.

### Complications

- One study[79] prospectively studied the progression of AS between patients with bicuspid aortic valve and those with transcatheter aortic valve, finding that when adjusted for age and comorbidities, bicuspid aortic valves have faster hemodynamic progression of AS than transcatheter aortic valves. Specifically, using Doppler echocardiography, they found bicuspid aortic valves to have a 2-year progression in peak aortic velocity of 0.16 m/s, an increase in the mean gradient of 1.8 mm Hg, and a valve area reduction of 0.08 $cm^2$.
- Of 852 adults diagnosed with bicuspid aortic valve from 8 tertiary hospitals in Spain between 2012 and 2015, 76% had a dilated ascending aorta, and 34% had a dilated aortic root.[80]
- Sex differences in the complications of bicuspid aortic valve were examined in 992 patients with an echocardiographic diagnosis of bicuspid aortic valve hospitalized at a single center in Beijing between 2008 and 2017.[81] The following complications of bicuspid aortic valve were more common in males than females: aortic regurgitation (≥2+; 39.0% versus 12.8%; $P<0.001$), only aortic root dilation (3.8% versus 0.8%; $P=0.014$), and diffuse aortic dilation (25.3% versus 4.3%; $P<0.001$). The following complications of bicuspid aortic valve were more common in females: moderate to severe aortic stenosis (21.3% versus 45.7%; $P<0.001$) and only ascending aortic dilation (46.2% versus 61.2%; $P<0.001$). Sex did not predict early adverse events after aortic valve replacement (n=90; HR, 1.21 [95% CI, 0.74–1.98]; $P=0.44$).
- There are complications associated with valvular interventions, both percutaneous and surgical. In a meta-analysis of RCTs of TAVR versus SAVR, TAVR was significantly associated with a lower risk of acute kidney injury (RR, 0.27 [95% CI, 0.13–0.54]; $P=0.0002$), new-onset AF (RR, 0.26 [95% CI, 0.18–0.39]; $P<0.00001$), and life-threatening or disabling bleeding (RR, 0.35 [95% CI, 0.22–0.55]; $P<0.00001$) but a higher risk of moderate to severe paravalvular regurgitation (RR, 4.40 [95% CI, 1.22–15.86]; $P=0.02$) and permanent pacemaker insertion (RR, 2.73 [95% CI, 1.41–5.28]; $P=0.003$).[82]
- In an observational cohort analysis of the multicenter UK TAVR registry involving a total of 8652 TAVR procedures performed from 2007 to 2015, there were 205 in-hospital strokes (incidence, 2.4%).[83] Factors associated with increased risk of in-hospital stroke were previous cerebrovascular disease (OR, 1.51, [95% CI, 1.05–2.17]; $P=0.03$), advanced age (OR, 1.02 [95% CI, 0.10–1.04]; $P=0.05$), coronary stenting at the time of TAVR (OR, 5.94 [95% CI, 2.03–17.39]; $P=0.008$), and earlier year of procedure (OR, 0.93 [95% CI, 0.87–1.00]; $P=0.04$); factors associated with lower risk included no prior cardiac surgery (OR, 0.62 [95% CI, 0.41–0.93]; $P=0.01$) and deployment of a first-generation self-expandable transcatheter heart valve (OR, 0.72 [95% CI, 0.53–0.97]; $P=0.03$). Having a stroke during hospitalization for a TAVR procedure significantly increased 30-day mortality (OR, 5.22 [95% CI, 3.49–7.81]; $P<0.001$) and 1-year mortality (OR, 3.21 [95% CI, 2.15–4.78]; $P<0.001$).
- In a study of all hospitalizations in patients ≥18 years of age who underwent TAVR from 2016 to 2017 in the Nationwide Readmission Database, a total of 54 317 unweighted hospitalizations for TAVR were identified, of which 5639 (10.4%) required permanent pacemaker implantation.[84] The risk of pericardial effusion was significantly greater in patients who required permanent pacemaker (2.4% versus 1.6%; aOR, 1.39 [95% CI, 1.15–1.70]; $P<0.001$), and risk of cardiac tamponade nearly doubled (1.6% versus 0.8%; $P<0.001$; aOR, 1.90 [95% CI, 1.48–2.40]; $P<0.001$). Pericardial complications after permanent pacemaker implantation were associated with increased in-hospital mortality, length of stay, hospital costs, and risk of 30-day readmission after TAVI ($P<0.01$ for all comparisons).

### Cost

- In the 3110 intermediate-risk patients with aortic stenosis treated with TAVR or SAVR in the PARTNER 2 trial and the 1078 patients treated with TAVR using the SAPIEN 3 valve in the PARTNER S3i registry, procedural costs were estimated from measured resource use, from linkage of trial data with Medicare claims, or by linear regression models for unlinked patients.[85]
- Index procedure costs were more than $20 000 higher with both XT-TAVR and SAPIEN 3 valves as a result of the higher cost of the TAVR valve

implantation compared with SAVR.[85] However, the higher procedure costs associated with TAVR were offset by significant reductions in other costs, especially by reductions in total length of stay: Initial length of stay was an average of 4.4 days shorter for patients at high surgical risk who were treated with TAVR than for those who underwent SAVR (difference, 4.5 and 6.3 days with XT-TAVR and SAPIEN 3 valve, respectively; $P<0.001$ compared with SAVR).

- TAVR also reduced the need for rehabilitation services at discharge and was associated with improved 1-month quality of life. TAVR had higher index admission and projected lifetime costs than SAVR (difference, $11 260 and $17 849 per patient, respectively).[85] However, TAVR was estimated to provide a lifetime gain of 0.32 QALYs (0.41) with 3% discounting. Lifetime incremental cost-effectiveness ratios were $55 090 per QALY gained and $43 114 per life-year gained. On the basis of sensitivity analyses, a reduction in the initial cost of TAVR by ≈$1650 was expected to lead to an incremental cost-effectiveness ratio of <$50 000 per QALY gained.
- In a European study of patients at intermediate surgical risk with severe aortic stenosis, TAVR was associated with an increase of 0.42 years and 0.41 QALYs and lifetime cost savings of €439 compared with SAVR.[86]
- In patients undergoing TAVR at low surgical risk in the Danish health care system, the incremental cost-effectiveness ratios (range, 334 200–904 100 Danish kroner per QALY gained) were all below the country-specific willingness to pay of 1.13 million Danish kroner.[87]
- In an Australian study, aortic stenosis was associated with 8 more premature deaths in males and 12 more premature deaths in females per 1000 individuals investigated.[76] Per 1000 individuals, this represents 32.5 more QALYs lost in males, representing a societal cost of $1.40 million Australian dollars, and 57.5 more QALYs lost in females, representing a societal cost of $2.48 million Australian dollars. Therefore, the estimated societal cost of premature mortality associated with aortic stenosis was $629 million Australian dollars in males and $735 million Australian dollars in females.

### Global Burden
### (See Table 23-1 and Charts 23-2 and 23-3)

- The global burden of calcific aortic valve disease based on 204 countries in 2021 is shown in Table 23-1.[4] In 2021, the highest age-standardized death rates of nonrheumatic calcific aortic valve disease were in Western Europe, high-income North America, Australasia, and southern Latin America. The lowest rates were in East Asia (Chart 23-2). In 2021, nonrheumatic calcific aortic valve disease prevalence was highest in Western Europe, high-income North America, Central Europe, and Australasia (Chart 23-3).
- Among the causes of HF between 1990 and 2019, calcific aortic valve disease increased by >90% in both males and females.[88]

## Mitral Valve Disorders

### *ICD-9* 424.0; *ICD-10* I34.

2021, United States: Underlying cause mortality—2731. Any-mention mortality—6909.

2020, United States: Hospital discharges—28 295.

Primary MR includes Carpentier functional classification system types I, II, and IIIa with the most common cause being mitral valve prolapse (type II MR). Secondary MR is associated with ischemic cardiomyopathy, LV dysfunction, or DCM (type IIIb MR).

### Prevalence

- See Global Burden section.

### Subclinical Disease

- Milder, nondiagnostic forms of mitral valve prolapse, first described in the familial context, are also present in the community and are associated with a higher likelihood of mitral valve prolapse in offspring (OR, 2.52 [95% CI, 1.25–5.10]; $P=0.01$). Up to 80% of nondiagnostic morphologies can progress to diagnostic mitral valve prolapse.[90,91]

### Genetics and Family History

- A number of genetic variants have been identified for the rare X-linked valvular dystrophy and the most common form of autosomal dominant mitral valve prolapse through pedigree investigations and GWASs. Genes implicated in mitral valve prolapse include *GLIS1*, *FLNA*, *DCHS1*, *DZIP1*, *TNS1*, and *LMCD1*.[92–96] An updated GWAS meta-analysis using dense imputation coverage revealed several risk loci (*SYT2*, *SRR*, *TSR1*, *SGSM2*, *SIX5*, *DMPK*, and *DMWD*) warranting further functional analysis for these loci.[97]
- Mitral valve prolapse may be seen in syndromes associated with connective tissue diseases such as Marfan syndrome (*FBN1* gene), Loeys-Dietz syndrome (*TGFBR1*, *TGFBR2*, *SMAD3*, *TGFB2*, *TGFB3* genes), and Ehler-Danlos syndrome (*COL5A1*, *COL5A1*, *COL1A1*, *TNXB* genes).[98,99]
- Mitral valve prolapse may also be seen in patients with a specific syndrome not associated with connective tissue disease (Edward syndrome, Patau syndrome, and trisomy of chromosome 15).[99,100] Nonsyndromic mitral valve prolapse may be seen in carriers of variants in the *MMVP1*, *MMVP2*, *MMVP3*, and *FLNA* genes.[101–103]

- Familial clustering exists across different MR subtypes, including both primary (ie, related to mitral valve prolapse) and nonprimary MR. Heritability of MR in the FHS was estimated at 15% (95% CI, 7%–23%), 12% (95% CI, 4%–20%) excluding mitral valve prolapse, and 44% (95% CI, 15%–73%) for moderate or greater MR only (all $P<0.05$).[104] In Sweden, sibling MR was associated with an HR of 3.57 (95% CI, 2.21–5.76; $P<0.001$) for the development of MR.[104]
- Among 3679 young to middle-aged Third Generation participants in the FHS with available parental data, 49 (1%) had mitral valve prolapse.[105] Parental mitral valve prolapse was associated with a higher prevalence of mitral valve prolapse in offspring (10/186 [5.4%]) compared with no parental mitral valve prolapse (39/3493 [1.1%]; aOR, 4.51 [95% CI, 2.13–9.54]; $P<0.0001$).
- An exome sequencing study identified potential associations between variants in known cardiomyopathy genes (*DSP*, *HCN4*, *MYH6*, *TMEM67*, *TRPS1*, and *TTN*) and mitral valve prolapse.[106]

### Treatment
### (See Charts 23-4 and 23-5)

- The treatment of ischemic MR is controversial. In the Cardiothoracic Surgical Trials Network study of 251 patients with severe ischemic MR randomized to mitral valve repair or replacement, after 2 years, the mean LV end-systolic volume index among surviving patients was 52.6±27.7 mL/m$^2$ in the repair group and 60.6±39.0 mL/m$^2$ in the replacement group with no significant between-group difference ($Z$ score=−1.32; $P$=0.19).[107] Two-year mortality was 19.0% in the repair group and 23.2% in the replacement group (HR in the repair group, 0.79 [95% CI, 0.46–1.35]; $P$=0.39). The rate of recurrence of moderate or severe MR was significantly higher with mitral valve repair (24.0 per 100 patient-years versus 15.2 per 100 patient-years; $P$=0.05), leading to higher readmissions for cardiovascular causes (48.3 versus 32.2 per 100 patient-years; $P$=0.01).
- In another Cardiothoracic Surgical Trials Network study of 301 patients with moderate ischemic MR and CAD randomized to mitral valve repair with CABG or CABG alone, the rate of death at 2 years was 10.0% in the combined-surgery group and 10.6% in the CABG-alone group (HR with mitral valve repair, 0.90 [95% CI, 0.45–1.83]; $P$=0.78).[108]
- The 2 main percutaneous mitral valve interventions in the United States are TEER and transcatheter mitral valve replacement. Data from the STS/ACC TVT Registry between 2014 and 2020 are reported.[109] A total of 37 475 patients underwent a mitral transcatheter procedure, including 33 878 TEERs and 3597 transcatheter mitral valve replacements. Annual procedure volumes for TEER have increased from 1152 per year in 2014 to 10 460 per year in 2019 at 403 sites and for transcatheter mitral valve replacement from 84 per year to 1120 per year at 301 centers. Mortality rates have decreased for TEER at 30 days (from 5.6% to −4.1%) and 1 year (from 27.4% to 22.0%). The 30-day mortality rate was 3.9%, reflecting overall improvements in outcomes over the past several years.
- In the EVEREST II trial, which included mostly patients with primary MR (73%) and compared MitraClip with surgical mitral valve repair, the respective rates of the components of the primary end point at 12 months were as follows: death, 6% in each group; surgery for mitral valve dysfunction, 20% versus 2%; and grade 3+ or 4+ MR, 21% versus 20%.[110]
- In the United States, the commercial use of the MitraClip started in 2013, with a steadily growing number of procedures performed. In a study looking at the trend of mitral valve interventions from 2000 to 2016 performed in the United States, MitraClip procedures increased from 415 in 2013 to 4195 in 2016, an increase of ≈90%.[111]
- Use of MitraClip procedures has also increased in Asia, although at a slower pace (Chart 23-4), with the highest increase seen in Japan from 18 procedures in 2011 to 439 procedures in 2018.[112]
- The role of MitraClip in secondary MR has been investigated in 2 published randomized clinical trials with divergent results that may be related to differences in sample characteristics, sample size, duration of follow-up, and primary end point (Chart 23-5).[113–115]
  - MITRA-FR included 304 patients with HF, severe secondary MR, and LVEF of 15% to 40% on optimal medical therapy and cardiac resynchronization therapy as indicated. There was no difference in the combined end point of death or rehospitalization for HF at 12 months (83/152 patients [54.6%] versus 78/152 [51.3%] for interventional and conservative management, respectively).
  - The COAPT trial included 614 patients with HF and moderate to severe or severe secondary MR who were symptomatic (New York Heart Association functional class II–IV) despite optimal medical therapy and cardiac resynchronization therapy.[114] With MitraClip, there was a significant reduction in the primary end point of rehospitalization for HF at 2 years (35.8% versus 67.9%; HR, 0.53 [95% CI, 0.40–0.70]; $P<0.001$). There was also a significant reduction of all-cause mortality at 2 years (29% versus 46.1%; HR, 0.62 [95% CI, 0.46–0.82]; $P<0.001$).

### Mortality

- Secondary MR (or Carpentier type IIIb) is associated with 47% mortality over 5 years in patients

with HF and is a predictor of long-term mortality (HR, 1.61 [95% CI, 1.22–2.12]; *P*=0.001 after adjustment for clinical variables; and HR, 1.38 [95% CI, 1.03–1.84]; *P*=0.03 after adjustment for echocardiographic parameters).[116]

- With the use of data from Mayo Clinic electronic health records and the Rochester Epidemiology Project to identify all cases of moderate or severe isolated MR diagnosed during a 10-year period in the community setting in Olmsted County, Minnesota, at 15 years of follow-up, females with no or mild MR had better survival than males (87% versus 77%; aRR, 0.82 [95% CI, 0.76–0.89]). In contrast, in individuals with severe MR, females had worse survival than males (60% versus 68%; aRR, 1.13 [95% CI, 1.01–1.26]). Survival 10 years after surgery was similar in females and males (77% versus 79%; *P*=0.14).[117]
- Females treated with mitral valve surgery for severe MR secondary to ischemic cardiomyopathy have a higher mortality at 2 years (27.1% versus 17.4%; absolute risk increase, 9.7%; aHR, 1.86 [95% CI, 1.05–3.29]; *P*=0.03) and a trend toward higher surgical failure (57.0% versus 43.2%; absolute risk increase, 13.8%; aOR, 1.78 [95% CI, 0.98–3.23]; *P*=0.06) compared with males.[118]

### Complications

- In 2017, there were 35 700 (95% CI, 30 500–42 500) degenerative mitral valve deaths globally.[118a]
- AF is a common occurrence of severe primary regurgitation and is associated with persistence of excess risk after mitral valve repair. In MIDA, 10-year postsurgical survival in sinus rhythm and in paroxysmal and persistent AF was 82±1%, 70±4%, and 57±3%, respectively (*P*<0.0001).[119]
- In a study using the Nationwide Readmission Database to identify adult patients who underwent TEER from 2014 to 2018,[120] of the 21 323 patients identified, 1615 (7.5%) had major bleeding. Coagulopathy, ESRD, nonelective admission, weekend admission, weight loss, cancer, CKD, anemia, and female sex were identified as independent predictors of major bleeding.
  - Patients with major bleeding had significantly higher rates of in-hospital mortality (aOR, 2.70 [95% CI, 1.70–4.10]; *P*<0.001), acute kidney injury (aOR, 3.57 [95% CI, 2.85–4.48]; *P*<0.001), AMI (aOR, 1.80 [95% CI, 1.37–2.36]; *P*<0.001), cardiogenic shock (aOR, 2.55 [95% CI, 1.82–3.57]; *P*<0.001), 30-day all-cause readmissions (OR, 2.12 [95% CI, 1.69–2.65]; *P*<0.001), and 30-day HF readmissions (OR, 1.33 [95% CI, 1.05-1.68]; *P*<0.01) compared with patients without major bleeding. The rates of stroke/TIA did not differ between the 2 groups (OR, 1.28 [95% CI, 0.97–1.69]; *P*<0.001).
- At 1 year after TEER, as many as 30% of patients have moderate to severe mitral valve regurgitation and an additional 25% have mitral stenosis, which affect survival, symptomatic congestive HF, and need for reintervention.[114,121] The STS Adult Cardiac Surgery Database was used to identify 524 adults who underwent first mitral surgery after TEER from 2014 to 2021.[122] Median time from TEER to mitral valve surgery was 3.5 months. Only 4.5% (n=22) of mitral valves could be repaired with >90% (n=438) of cases requiring mitral valve replacement. Concomitant tricuspid repair or replacement was performed in 32.8% (n=152) with moderate or severe tricuspid regurgitation, and CABG was performed in 12.3% (n=57). The 30-day or in-hospital mortality was 10.6% (n=49).

### Cost

- Lifetime costs, life-years, QALYs, and incremental cost per life-year and QALYs gained were estimated for patients receiving MitraClip therapy compared with patients receiving standard of care for primary MR.[123] EVEREST II HRS provided data on treatment-specific overall survival, risk of clinical events, quality of life, and resource use (2013 Canadian dollars). The incremental cost per QALY gained was $23 433. On the basis of sensitivity analysis, MitraClip therapy had a 92% chance of being cost-effective compared with standard of care at a $50 000 per QALY willingness-to-pay threshold.
- In the COAPT trial comparing MitraClip plus optimal medical therapy with optimal medical therapy alone in symptomatic patients with HF with moderate to severe or severe secondary MR, MitraClip increased life expectancy by 1.13 years and QALYs by 0.82 years at a cost of $45 648. This translated into an incremental cost-effectiveness ratio of $40 361 per life-year and $55 600 per QALY gained.[124]

### Global Burden

### (See Table 23-2 and Charts 23-6 and 23-7)

- The global burden of degenerative mitral valve disease is shown in Table 23-2. In 2021, the highest age-standardized mortality rates of nonrheumatic degenerative mitral valve disease were in Central Europe. Oceania and East Asia had the lowest mortality rates (Chart 23-6). In 2021, nonrheumatic degenerative mitral valve disease prevalence was highest in high-income North America and Central Asia. The lowest prevalence rates were in sub-Saharan Africa (Chart 23-7).

## Pulmonary Valve Disorders

### *ICD-9* 424.3; *ICD-10* I37.

2021, United States: Underlying cause mortality—14. Any-mention mortality—69.

2020, United States: Hospital discharges—700.

- Pulmonic valve stenosis is a relatively common congenital defect, occurring in ≈10% of children with congenital HD.[125] Among 44 neonates with critical pulmonic stenosis who underwent balloon pulmonary valvuloplasty from 1990 to 2017, 15 (34.1%) needed reintervention. At a median follow-up of 8.2 years (IQR, 3.4–13.1 years), moderate or severe pulmonary regurgitation was seen in 22 children (half of the sample), 3 of whom required pulmonary valve repair/replacement.[126]
- In an observational registry of 82 adults with either congenital pulmonic stenosis or subpulmonic stenosis associated with TOF, percutaneous pulmonic valve implantation with a SAPIEN valve was demonstrated to be feasible and safe.[127]
- The most common cause of severe pulmonic regurgitation is iatrogenic, resulting from surgical valvotomy/valvectomy or balloon pulmonary valvuloplasty performed for RV outflow tract obstruction as part of TOF repair.[128] Transcatheter pulmonic valve implantation of either a Melody or a SAPIEN valve is effective and relatively safe,[128,129] with serious complications occurring in only 3 patients (1 died and 2 required surgical intervention in a study using the NIS database, which included 57 transcatheter pulmonic valve implantation procedures performed in 2012).[130] Surgical pulmonary valve replacement is preferred for native pulmonic valve regurgitation (caused by endocarditis, carcinoid) and is associated with <1% periprocedural mortality and excellent long-term outcome, with >60% freedom from reoperation at 10 years.[131]
- In a meta-analysis including 4364 patients with either pulmonic stenosis or regurgitation, transcatheter pulmonic valve replacement had lower in-hospital mortality (OR, 0.18 [95% CI, 0.03–0.98]) and long-term mortality (OR,0.43 [95% CI, 0.22–0.87]) compared with surgical pulmonic valve replacement.[132] However, postprocedural IE was higher (OR, 4.56 [95% CI, 0.07–0.42]) compared with surgical replacement. The risk of reoperation was higher in the group treated with transcatheter pulmonic valve replacement, although it was not statistically significant (OR, 2.19 [95% CI, 2.03–10.26]).

## Tricuspid Valve Disorders

### *ICD-9* 424.2; *ICD-10* I36.

2021, United States: Underlying cause mortality—75. Any-mention mortality—283.

2020, United States: Hospital discharges—925.

- From January 2006 to September 2015, tricuspid valve disease was present in 3 235 292 or 1.7% of US hospitalized patients >50 years of age.[133]
  - The prevalence of tricuspid valve disease was higher in women than men and increased with increasing age.
  - From 2006 to 2015, the prevalence of tricuspid valve disease in all hospitalizations increased from 1.7% to 2.0%.
- Patients with rapid (≤1.2 years) development of significant tricuspid regurgitation have worse survival than patients in whom severe tricuspid regurgitation develops more slowly (log-rank *P*=0.001). Fast development of severe tricuspid regurgitation is the most powerful predictor of all-cause mortality (HR per preceding year of development, 0.92 [95% CI, 0.90–0.94]; *P*<0.001).[134]
- An analysis of the NIS demonstrated an increase in the number of isolated tricuspid valve surgeries performed over a 10-year period, from 290 in 2004 to 780 in 2013. In-hospital mortality was consistent over this time period at 8.8%.[135]
- Outcomes of transcatheter tricuspid valve interventions were analyzed in 317 high-risk patients with severe tricuspid regurgitation from the international Trivalve registry.[136] Such patients were treated either with transcatheter repair at the level of the leaflets (MitraClip, PASCAL), annulus (Cardioband, TriCinch, Trialign), or coaptation (FORMA) or with transcatheter replacement (Caval Implants). Procedural success, defined as successful device implantation with moderate or less tricuspid regurgitation, was 72.8%. Thirty-day mortality was significantly lower among patients with procedural success (1.9% versus 6.9%; *P*=0.04). Actuarial survival at 1.5 years was 82.8±4% and was significantly higher among patients who had procedural success (70.3±8% versus 90.8±4%; *P*<0.0002).
- Four hundred one patients from 39 clinical centers in the United States, Canada, and Germany undergoing mitral valve surgery for degenerative MR were randomly assigned to receive mitral valve surgery with or without tricuspid annuloplasty.[137] At 2 years, patients who underwent mitral valve surgery with tricuspid annuloplasty had fewer primary end-point events (death, reoperation for tricuspid regurgitation, progression of tricuspid regurgitation by 2 grades from baseline, or presence of severe tricuspid regurgitation) than those who underwent mitral valve surgery alone (3.9% versus 10.2%; RR, 0.37 [95% CI, 0.16–0.86]; *P*=0.02).

## Rheumatic Fever/Rheumatic HD

### *ICD-9* 390 to 398; *ICD-10* I00 to I09.

2021, United States: Underlying cause mortality—3907. Any-mention mortality—8771.

2020, United States: Hospital discharges—23 435.

### Prevalence

- Rheumatic HD remains endemic in some low- and middle-income countries.[138] It is a leading cause of HF across the world.[88]

### Subclinical Disease

- The prevalence of subclinical or latent rheumatic HD among children is estimated by echocardiography and can be classified as definite or borderline.[139] The prevalence of combined definite and borderline disease ranges between 10 and 45 per 1000 in studies from endemic countries (eg, Nepal, Brazil, and Uganda) compared with <8 per 1000 in low-risk populations.[140–143]
- The natural history of latent rheumatic HD detected by echocardiography is not clear. Emerging data suggest that up to 20% to 30% of children with definite rheumatic HD may have progression of disease, but 30% to 50% of those with borderline rheumatic HD may return to normal over 2 to 8 years of follow-up.[144–147]
- Few echocardiographic screening studies for rheumatic HD have been conducted in adults, for whom the criteria are not well validated. In a study from Uganda, the prevalence of rheumatic HD in adults >20 years of age was 2.34% (95% CI, 1.49%–3.49%).[148]
- Latent rheumatic HD appears to be half as common among youth living with HIV compared with the general Ugandan population (1.5% [95% CI, 0.88%–2.54%] versus 3% [95% CI, 2.7%–3.24%]), possibly related to improved access to preventive care or nearly universal trimethoprim-sulfamethoxazole prophylaxis among youth living with HIV.[149]

### Treatment

- REMEDY is a prospective registry of 3343 patients with rheumatic HD from 25 hospitals in 12 African countries, India, and Yemen.[150] This study highlighted consistently poor access to recommended therapies among people living with rheumatic HD; only 55% were taking penicillin prophylaxis, and only 3.6% of females of childbearing age were using contraception. Although 70% of those with indications (mechanical valve, AF, or severe mitral stenosis) were appropriately prescribed anticoagulant drugs, only one-quarter of them had therapeutic international normalized ratios.
- In Uganda, retention in care over time is poor (56.9% [95% CI, 54.1%–59.7%] seen in clinic in the past 12 months), but among those retained in care, optimal adherence to benzathine penicillin G is high (91.4% [95% CI, 88.7%–93.5%]).[151]
- A meta-analysis of 13 studies including 2410 mitral valve repairs and 3598 mitral replacements for rheumatic valve disease revealed that operative mortality of repair versus replacement was 3.2% versus 4.3% (OR, 0.68 [95% CI, 0.50–0.92]; *P*=0.01).[152] Mitral valve repair also conferred lower long-term mortality (OR, 0.41 [95% CI, 0.30–0.56]; *P*<0.001) and reoperation (OR, 3.02 [95% CI, 1.72–5.31]; *P*<0.001).
- There are limited data on TEER in patients with rheumatic HD. One study compiled all mitral valve TEER procedures[153] from the US Nationwide Readmissions Database for hospitalizations between 2016 and 2018. A total of 18240 procedures were included in the analysis, including 1779 in patients with rheumatic HD. Mitral TEER in patients with rheumatic HD was associated with in-hospital mortality similar to that in patients without rheumatic HD (OR, 1.47 [95% CI, 0.94–2.30]; *P*=0.089). However, rheumatic HD was associated with higher AMI (OR, 1.65 [95% CI, 1.07–2.56]), acute kidney injury (OR, 1.58 [95% CI, 1.30–1.94]), ventricular arrhythmia (OR, 1.50 [95% CI, 1.12–2.01]), high-degree heart block (OR, 1.67 [95% CI, 1.25–2.23]), and conversion to open surgical repair or replacement (OR, 2.53 [95% CI, 1.02–6.30]). Mitral transcatheter edge-to edge repair in rheumatic HD was also associated with higher 90-day all-cause readmission (HR, 1.19 [95% CI, 1.04–1.47]; *P*=0.012).

### Mortality (See Table 23-3)

- In the United States in 2021, mortality attributable to rheumatic fever/rheumatic HD was 3907 for all ages (2525 females and 1382 males; Table 23-3).
- Mortality attributable to rheumatic HD varies widely across the United States with the highest rates clustered in Alaska, Mississippi, Alabama, Kentucky, and Utah, where age-standardized mortality rates were estimated to be 5 to 10 per 100000 population in 2014.[154]
- In 1950, ≈15000 Americans (adjusted for changes in *ICD* codes) died of rheumatic fever/rheumatic HD compared with ≈3900 annually in the present era (Table 23-3). Recent declines in mortality have been slowest in the South compared with other regions.[154]

### Complications

- People living with rheumatic HD experience high rates of morbid complications. In the international REMEDY cohort study, 33% had HF, 22% had AF, 7% had prior stroke, and 4% had prior endocarditis at baseline.[150] After 2 years of follow-up, the incidence of new events was 38 per 1000 patient-years for HF, 8.5 per 1000 patient-years for stroke or TIA, and 3.7 per 1000 patient-years for endocarditis.[155]
- Prognosis after the development of complications is also worse for people living with rheumatic HD.

In Thailand, patients with rheumatic mitral valve disease who had ischemic stroke had a higher risk of cardiac arrest (OR, 2.1), shock (OR, 2.1), arrhythmias (OR, 1.7), respiratory failure (OR, 2.1), pneumonia (OR, 2.0), and sepsis (OR, 1.4) after controlling for age, sex, and other comorbid chronic diseases.[156]

- The PAR of rheumatic HD for maternal mortality may approach 10% in sub-Saharan Africa.[157]
- In a study at 2 Gambian referral hospitals involving 255 registered patients with rheumatic HD, the case fatality rate in 2017 was estimated at 19.6%.[158] The median age at first presentation was 13 years (IQR, 9–18 years); 57% of patients had late-stage HF; and 84.1% had a pathological heart murmur. A history suggestive of acute rheumatic fever was reported by 48.7% of patients; only 15.8% were adequately treated, and 65.5% of those prescribed penicillin were fully adherent. As many as 46.8% of the patients had worsening of their symptoms and repeat hospitalizations. Ninety-four patients were deemed eligible for cardiac surgery. However, only 18.1% (17 of 94) underwent surgery.

### *Global Burden of Rheumatic HD (See Charts 23-8 through 23-10)*

- The age and sex distributions of the subjects in the REMEDY study are shown in Chart 23-8. Rheumatic HD was twice as common among females, a finding consistent with prior studies across various populations.[150]
- Mortality attributable to rheumatic HD remains exceptionally high in endemic settings. In a study from Fiji of 2619 people followed up from 2008 to 2012, the age-standardized death rate was 9.9 (95% CI, 9.8–10.0) per 100 000, or more than twice the GBD estimates.[159] Prognosis is exceptionally poor in sub-Saharan Africa, as highlighted by a follow-up study of REMEDY, which had a mortality rate of 116 per 1000 patient-years in the first year and 65 per 1000 patient-years in the second year.[155]
- Based on 204 countries and territories in 2021[160]:
  - There were 0.38 (95% UI, 0.33–0.44) million deaths estimated for rheumatic HD, a decrease of 8.36% (95% UI, −23.66% to 9.91%) from 1990 to 2021.
  - There was substantial geographic heterogeneity in mortality estimated for rheumatic HD with the highest rates in South Asia and Oceania (Chart 23-9).
  - The number of prevalent cases of rheumatic HD in 2021 was 54.78 (95% UI, 43.32–65.49) million, an increase of 69.44% (95% UI, 65.15%–73.22%) compared with 1990.
  - Rheumatic HD age-standardized prevalence was highest in sub-Saharan Africa, tropical and Andean Latin America, and the Caribbean (Chart 23-10).
- Among 56.2 million people living with HF across 204 countries and territories in the world in 2019, rheumatic HD was the third leading cause of HF.[88] The age-standardized prevalence of HF from rheumatic HD increased between 1990 and 2019; this was driven by increasing rates in males in low (5% increase) and low-middle (9.2% increase) SDI regions, most notably in Andean Latin America (16.7% increase). HF from rheumatic HD decreased in middle-, high-middle–, and high-income regions.

## Infective Endocarditis

### *ICD-9* 421.0; *ICD-10* I33.0

2021, United States: Underlying cause mortality—1706. Any-mention mortality—3925.

2020, United States: Hospital discharges—11 850.

### *Prevalence and Incidence*

- In US commercial and Medicaid health insurance databases, the weighted incidence rate of IE was 13.8 cases per 100 000 among individuals 18 to 64 years of age with commercial insurance and 78.7 per 100 000 among those with Medicaid.[161] Incidence was higher in males versus females (16.9 versus 10.8 per 100 000 among those with commercial insurance; 104.6 versus 63.5 per 100 000 with Medicaid).
- Data from the GBD Study show that the incidence of IE has continued to rise over the past 30 years globally.[162] In North America, age-standardized incidence rates went from 10.11 (95% CI, 8.32–12.27) per 100 000 in 1990 to 12.54 (95% CI, 10.35–15.15) per 100 000 in 2019.

### *Secular Trends*

- A systematic review that included 160 studies and 27 083 patients from 1960 to 2011 demonstrated that in hospital-based studies (142 studies, 23 606 patients), staphylococcal endocarditis has increased over 5 decades (coagulase-negative *Staphylococcus*, 2% to 10%; $P<0.001$), with increases in *S aureus* IE (21% to 30%; $P<0.05$) and enterococcal IE (6.8% to 10.5%; $P<0.001$) over the decade from 2000 to 2011 and a corresponding decrease in streptococcal endocarditis (32% to 17%) over the same time period.[163] Admissions for IE related to injection drug use have risen in parallel with the opioid drug crisis. IE admissions increased from 33 073 in 2008 to 39 805 in 2014. At the same time, the prevalence of documented intravenous drug use among patients admitted for IE in the NIS rose from 4.3%

in 2008 to 10% in 2014. This trend was accentuated among the young (<30 years of age) and among White individuals compared with Black individuals and those of other races (73% versus 63%; *P*<0.01).[164]

- Data from the North Carolina Hospital Discharge Database show similar trends with rates of drug use–associated IE rising from 0.08 per 100 000 residents in 2013 to 2014 to 1.38 per 100 000 residents in 2016 to 2017.[165] In the final year (2016–2017), 42% of IE valve surgeries were for drug use–associated IE.
- Using 2003 to 2010 data from 37 centers in the Pediatric Health Information Systems Database, Pasquali and colleagues[166] did not demonstrate a significant difference in the number of IE hospitalizations after the 2007 AHA guidelines[167] for antibiotic prophylaxis were implemented (1.6% difference after versus before guideline implementation [95% CI, −6.4% to 10.3%]; *P*=0.7).

### Risk Factors

- The 15-year cohort risk (through 2006) of IE after diagnosis of mitral valve prolapse (between 1989 and 1998) among Olmsted County, Minnesota, residents was 1.1±0.4% (incidence, 86.6 cases per 100 000 person-years [95% CI, 43.3–173.2]).
  - There was a higher age- and sex-adjusted risk of IE in patients with mitral valve prolapse (RR, 8.1 [95% CI, 3.6–18.0]) compared with the general population of Olmsted County (*P*<0.001). No IE cases were identified among patients without previously diagnosed MR.
  - There was a higher incidence of IE in patients with mitral valve prolapse and moderate or greater MR (289.5 cases per 100 000 person-years [95% CI, 108.7–771.2]; *P*=0.02 compared with less than moderate MR) and in patients with a flail mitral leaflet (715.5 cases per 100 000 person-years [95% CI, 178.9–2861.0]; *P*=0.02 compared with no flail mitral leaflet).[168]
- Congenital HD is known to predispose to IE. In a nationwide Swedish registry case-control study, the cumulative incidence of IE was 8.5% at 87 years of age among 89 541 patients with congenital HD compared with 0.7% in matched controls, with incidence rates of 65.5 (95% CI, 62.2–68.9) and 1.8 (95% CI, 1.7–2.0) per 100 000 person-years, respectively.[169]
- Data from the IE After TAVI International Registry show stable rates for IE after TAVI when earlier (2005–2013) and later (2014–2020) study periods are compared, with an incidence of 6.52 (95% CI, 5.54–7.67) versus 5.45 (95% CI, 4.65–6.38) per 1000 patient-years (*P*=0.12 for difference).[170] In-hospital mortality (36.4% versus 26.6%; *P*=0.016) and 1-year mortality (53.5% versus 37.8%; *P*<0.001) have decreased over these 2 study periods. In the Swiss TAVI Registry, IE after TAVI occurred most frequently in the early period (<100 days; 2.59 events per 100 person-years) and was most commonly caused by *Enterococcus* species (30.1% of cases).[171]
- In a Spanish registry of 3208 consecutive patients with IE, subjects with bicuspid aortic valve and mitral valve prolapse had a higher incidence of viridans group streptococci IE than did a high-risk (those who met the criteria for IE antibiotic prophylaxis) group with an antibiotic prophylaxis indication and patients in a low- to moderate-risk group without an antibiotic prophylaxis indication (35.2% and 39.3% versus 12.1% and 15.0%, respectively; all *P*<0.01).[172] Subjects with bicuspid aortic valve and mitral valve prolapse had more intracardiac complications than those at low or moderate risk (50% and 47.2% versus 30.6%; both *P*<0.01) and had complications similar to those of patients in the high-risk group.

### Awareness, Treatment, and Control

- Surgery was performed in 47% of cases of definite left-sided, non–cardiac device–related IE in the ICE-PLUS registry of 1296 patients from 16 countries.[173]
- In a randomized, noninferiority multicenter trial of 400 stable cases with left-sided native IE, the combined outcome of all-cause mortality, unplanned surgery, embolic events, or relapse of bacteremia was similar in those treated with continuous intravenous antibiotic drugs compared with those switched from intravenous to oral antibiotic drugs after 10 days (24 cases [12.1%] versus 18 cases [9%]; between-group difference, 3.1 percentage points [95% CI, −3.4 to 9.6]; *P*=0.40).[174] After a median follow-up of 3.5 years, the primary composite end point had occurred in 38.2% of patients in the intravenous group and 26.4% in the oral antibiotic group (HR, 0.64 [95% CI, 0.45–0.91]).[175]
- A single-center retrospective observational study of 413 patients (25.4% female) who received surgery for IE showed that females had a higher 30-day mortality than males (26.7% versus 14.9%; *P*=0.007).[176] Female sex was predictive for 30-day mortality (OR, 2.090 [95% CI, 1.077–4.053]; *P*=0.029).

### Mortality

- According to the GBD Study 2020, the age-standardized death rate of endocarditis in 2020 was 0.93 (95% UI, 0.82–1.05) per 100 000 (data courtesy of the GBD Study 2020). Prosthetic valve IE continues to be associated with high in-hospital and 1-year mortality, although early surgery is

associated with improved outcomes compared with medical therapy alone (1-year mortality, 22% versus 27%; HR, 0.68 [95% CI, 0.53–0.87]), even in propensity-adjusted analyses (HR, 0.57 [95% CI, 0.49–0.67]).[177]

- Between 1999 and 2019, there were a total of 279 154 reported deaths across the United States related to IE.[178]
  - The overall age-adjusted mortality rates from IE in the United States declined from 54.2 per 1 million in 1999 to 51.4 per 1 million in 2019.
  - Age-adjusted mortality rates from IE in the United States increased during this time period among males (2009–2019 annual percentage change, 0.4% [95% CI, 0.1%–0.6%]), NH White individuals (annual percentage change, 0.8% from 2009–2019 [95% CI, 0.5%–1.1%]), American Indian and Alaska Native individuals (annual percentage change, 1.4% from 2009–2019 [95% CI, 0.7%–2.0%]), and those in rural areas (annual percentage change, 1.0% from 2009–2019 [95% CI, 0.5%–1.5%]).
- Data collected between 2004 and 2010 from the Pediatric Health Information System database from 37 centers that included 1033 cases of IE demonstrated a mortality rate of 6.7% (n=45) and 3.5% (n=13) among children (0–19 years of age) with and without congenital HD, respectively.[179]

### *Complications*

- Among 162 cases of left-sided native-valve *S aureus* IE retrospectively identified in 1254 patients hospitalized between 1990 and 2010 for IE, *Staphylococcus* represented 18% of all IE cases and 23% of native-valve IE cases. HF occurred in 45% of IE cases, acute renal failure in 23%, sepsis in 29%, neurological events in 36%, systemic embolic events in 55%, and in-hospital mortality in 25%.[180] The risk of in-hospital mortality was higher in patients with HF (OR, 2.5; *P*=0.04) and sepsis (OR, 5.3; *P*=0.001).
- Long-term 5-year survival was 49.6±4.9%. There was higher long-term risk of death among individuals with HF (OR, 1.7; *P*=0.03), sepsis (OR, 3.0; *P*=0.0001), and delayed surgery (OR, 0.43; *P*=0.003).[180]
- When the authors compared 2 study periods, 1990 to 2000 and 2001 to 2010, there was a significant increase in bivalvular involvement, valvular insufficiency, and acute renal failure from 2001 to 2010. In-hospital mortality rates and long-term 5-year survival were not significantly different between the 2 study periods (28.1% versus 23.5%; *P*=0.58).[180]

## Heart Valve Procedure Costs

- In 2014, for heart valve procedures[181]:
  - The mean inflation-adjusted cost per hospitalization in 2014 dollars was $51 896 compared with $56 426 in 2010 and $44 609 in 2000.
  - The number of discharges for which heart valve surgery was the principal operating room procedure was 110 915, which was an increase from 98 101 in 2010 and 79 719 in 2000.
- Total inflation-adjusted national cost in 2014 dollars (in millions) was $5756, which was an increase from the mean cost (in millions) of $5541 in 2010 and $3550 in 2000.[181]
- Among 190 563 patients with aortic valve disease in the Nationwide Readmissions Database between 2012 and 2016, the average aggregate 6-month inpatient costs starting with index admission over 6 months were as follows: for individuals who underwent SAVR, $59 743; TAVR, $64 395; and medical therapy, $23 460. TAVR costs decreased over time and were similar to SAVR index admission costs by 2016.[182]

**Table 23-1. Global Mortality and Prevalence of Nonrheumatic Calcific Aortic Valve Disease, by Sex, 2021**

| | Both sexes | | Males | | Females | |
|---|---|---|---|---|---|---|
| | Deaths (95% UI) | Prevalence (95% UI) | Deaths (95% UI) | Prevalence (95% UI) | Deaths (95% UI) | Prevalence (95% UI) |
| Total number (millions), 2021 | 0.15 (0.12 to 0.16) | 13.32 (11.52 to 15.22) | 0.06 (0.06 to 0.06) | 7.30 (6.30 to 8.42) | 0.08 (0.07 to 0.09) | 6.02 (5.16 to 6.80) |
| Percent change in total number, 1990–2021 | 150.39 (130.15 to 165.13) | 184.21 (171.90 to 197.05) | 139.96 (123.53 to 154.38) | 192.90 (179.24 to 207.03) | 158.46 (133.67 to 176.33) | 174.35 (161.20 to 188.41) |
| Percent change in total number, 2010–2021 | 38.69 (35.02 to 41.18) | 35.87 (31.88 to 40.17) | 42.02 (37.00 to 45.63) | 37.90 (33.01 to 42.82) | 36.39 (32.51 to 38.89) | 33.49 (29.32 to 38.11) |
| Rate per 100 000, age standardized, 2021 | 1.84 (1.53 to 2.01) | 159.75 (138.10 to 181.81) | 1.84 (1.65 to 1.97) | 194.88 (168.58 to 223.01) | 1.77 (1.41 to 1.96) | 130.13 (111.58 to 146.90) |
| Percent change in rate, age standardized, 1990–2021 | −6.96 (−12.61 to −2.52) | 22.12 (17.32 to 28.19) | −7.87 (−13.00 to −3.45) | 23.72 (18.21 to 29.44) | −5.99 (−12.44 to −0.76) | 19.17 (13.84 to 25.71) |
| Percent change in rate, age standardized, 2010–2021 | −10.04 (−12.10 to −8.50) | −1.57 (−4.21 to 1.58) | −7.29 (−9.94 to −5.31) | −0.25 (−3.36 to 3.44) | −11.55 (−13.50 to −9.97) | −2.97 (−6.08 to 0.35) |

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Disease; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[160]

**Table 23-2. Global Prevalence and Mortality of Nonrheumatic Degenerative Mitral Valve Disease, 2021**

| | Both sexes | | Males | | Females | |
|---|---|---|---|---|---|---|
| | Deaths (95% UI) | Prevalence (95% UI) | Deaths (95% UI) | Prevalence (95% UI) | Deaths (95% UI) | Prevalence (95% UI) |
| Total number (millions), 2021 | 0.04 (0.03 to 0.04) | 15.49 (14.58 to 16.38) | 0.01 (0.01 to 0.02) | 9.83 (9.25 to 10.41) | 0.02 (0.02 to 0.03) | 5.66 (5.33 to 5.96) |
| Percent change in total number, 1990–2021 | 56.74 (40.40 to 69.48) | 117.89 (112.05 to 121.88) | 68.55 (54.73 to 85.04) | 127.29 (121.19 to 131.50) | 50.20 (31.12 to 67.29) | 103.29 (98.22 to 107.65) |
| Percent change in total number, 2010–2021 | 29.57 (24.62 to 33.73) | 31.65 (28.73 to 33.38) | 35.99 (29.93 to 41.94) | 33.79 (30.62 to 35.85) | 25.87 (20.47 to 32.60) | 28.09 (25.62 to 29.76) |
| Rate per 100 000, age standardized, 2021 | 0.46 (0.40 to 0.51) | 183.53 (172.73 to 193.96) | 0.40 (0.36 to 0.45) | 260.00 (244.80 to 275.24) | 0.50 (0.41 to 0.58) | 122.09 (114.95 to 128.38) |
| Percent change in rate, age standardized, 1990–2021 | −36.88 (−41.90 to −32.31) | −5.57 (−7.94 to −4.01) | −32.86 (−37.40 to −26.92) | −5.23 (−7.43 to −3.79) | −38.50 (−44.71 to −31.76) | −9.89 (−11.94 to −8.00) |
| Percent change in rate, age standardized, 2010–2021 | −11.02 (−13.91 to −7.59) | −5.24 (−7.34 to −4.02) | −5.86 (−9.35 to −2.21) | −4.67 (−6.89 to −3.17) | −12.83 (−16.82 to −8.34) | −7.00 (−8.77 to −5.81) |

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Disease; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[160]

**Table 23-3. Rheumatic Fever/Rheumatic HD in the United States**

| Population group | Mortality, 2021: all ages* | Hospital discharges, 2020: all ages |
|---|---|---|
| Both sexes | 3907 | 23 435 |
| Males | 1382 (35.4%)† | |
| Females | 2525 (64.6%)† | |
| NH White males | 1110 | … |
| NH White females | 2009 | … |
| NH Black males | 114 | … |
| NH Black females | 219 | … |
| Hispanic males | 95 | … |
| Hispanic females | 171 | … |
| NH Asian males | 37‡ | … |
| NH Asian females | 80‡ | … |
| NH American Indian or Alaska Native | 25 | … |
| NH Hawaiian or Pacific Islander | 16 | |

Ellipses (…) indicate data not available; HD, heart disease; and NH, non-Hispanic.

*Mortality for American Indian or Alaska Native and Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native, Asian, Pacific Islander, and Hispanic decedents, as well as undercounts of these groups in censuses.

†These percentages represent the portion of total mortality that is for males vs females.

‡Includes Chinese, Filipino, Japanese, and other Asian people.

Sources: Mortality (for underlying cause of rheumatic fever/rheumatic HD): Unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using National Vital Statistics[1]; data represent underlying cause of death only. Hospital discharges (with a principal diagnosis of rheumatic fever/rheumatic HD): Unpublished NHLBI tabulation using Healthcare Cost and Utilization Project[3]; data include those inpatients discharged alive, dead, or status unknown.

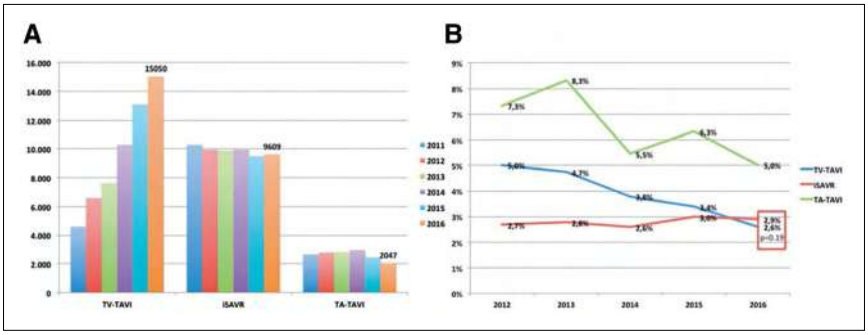



**Chart 23-1. Number of TAVI and SAVR procedures performed and in-hospital mortality according to type of procedure, Germany, 2011 to 2016.**

**A**, Number of TAVI and SAVR procedures. **B**, In-hospital mortality.

iSAVR indicates isolated surgical aortic valve replacement; SAVR, surgical aortic valve replacement; TA, transapical; TAVI, transcatheter aortic valve implantation; and TV, transvascular.

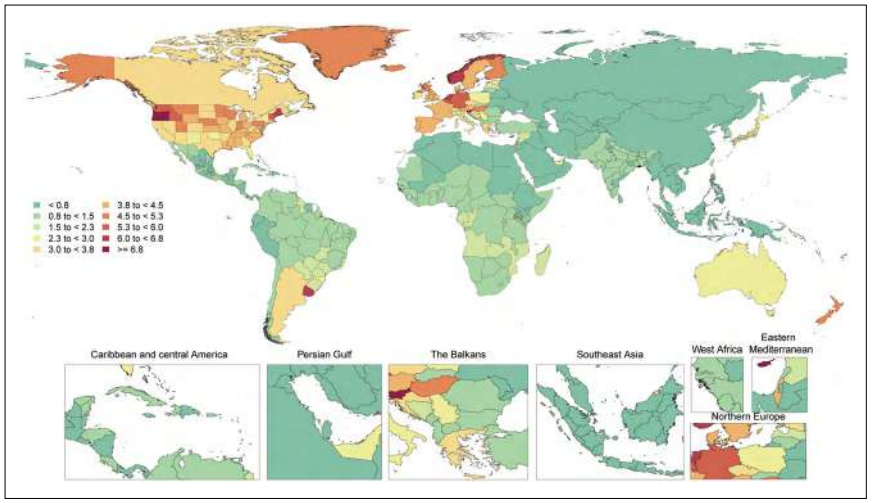



**Chart 23-2. Age-standardized mortality rates of nonrheumatic calcific aortic valve disease per 100 000, both sexes, 2021.**
During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.
GBD indicates Global Burden of Disease.
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[160]

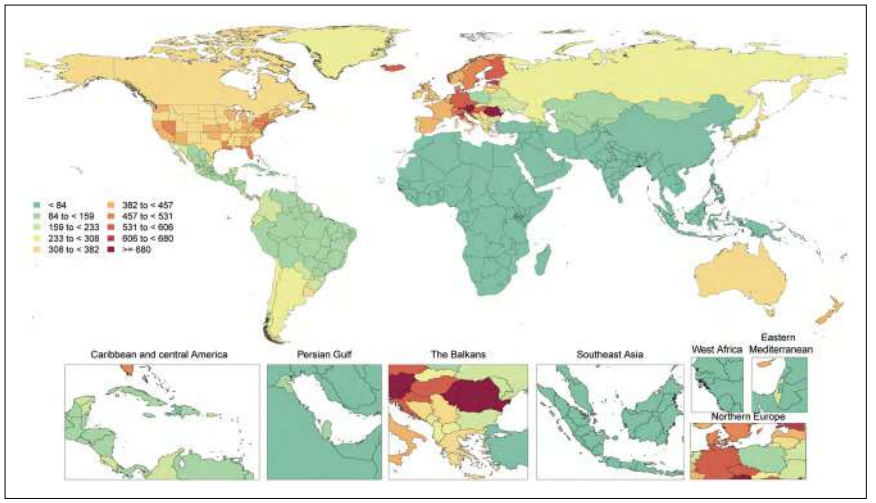



**Chart 23-3. Age-standardized prevalence rates of nonrheumatic calcific aortic valve disease per 100 000, both sexes, 2021.**
During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.
GBD indicates Global Burden of Disease.
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[160]

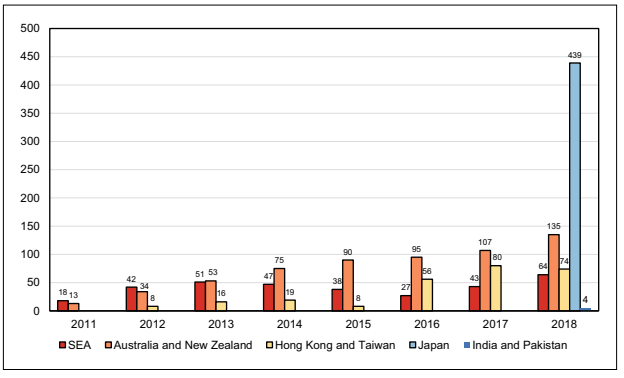



**Chart 23-4. Asia-Pacific MitraClip cases, 2011 to 2018.**
SEA indicates Southeast Asia (Singapore, Malaysia, Indonesia, Brunei, Philippines, Vietnam, Thailand).
Source: Data derived from Wong et al.[112]

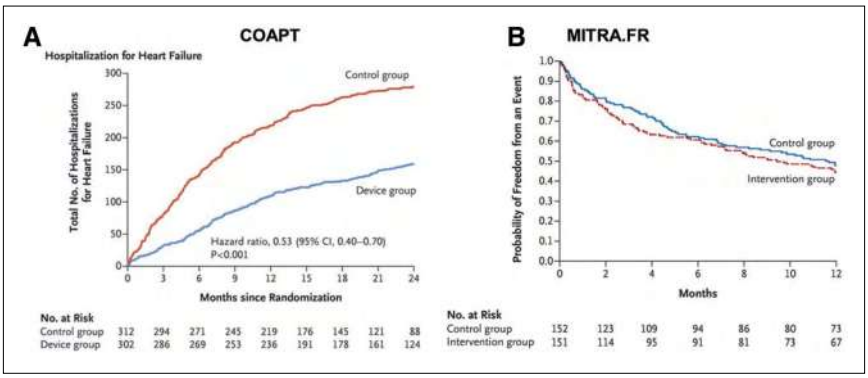



**Chart 23-5. Comparison of primary outcomes after MitraClip implantation for secondary MR in the COAPT and MITRA-FR trials.**
**A**, COAPT trial. **B**, MITRA-FR trial.
COAPT indicates Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional; MITRA-FR, Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation; and MR, mitral regurgitation.
Source: **A**, Reprinted from Stone et al[114] with permission from the Massachusetts Medical Society. Copyright © 2018 Massachusetts Medical Society. **B**, Reprinted from Obadia et al[115] with permission from the Massachusetts Medical Society. Copyright © 2018 Massachusetts Medical Society.

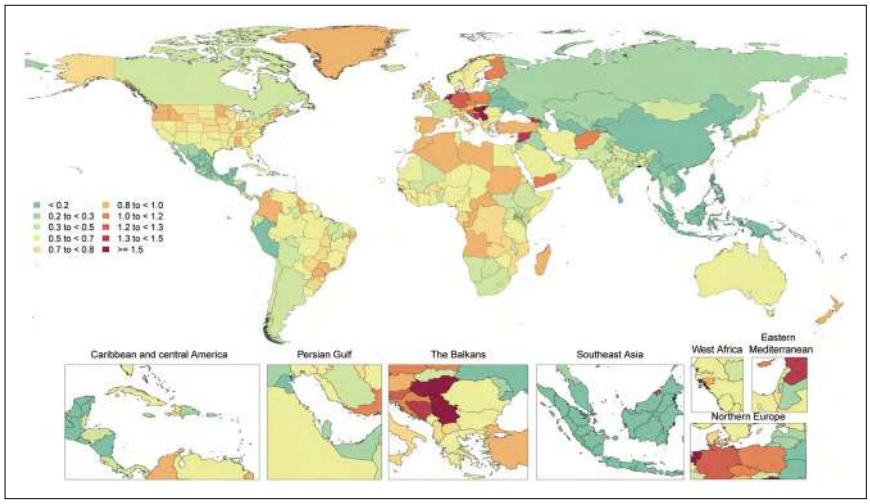



**Chart 23-6. Age-standardized mortality rates of nonrheumatic degenerative mitral valve disease per 100 000, both sexes, 2021.**
During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.
GBD indicates Global Burden of Disease.
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[160]

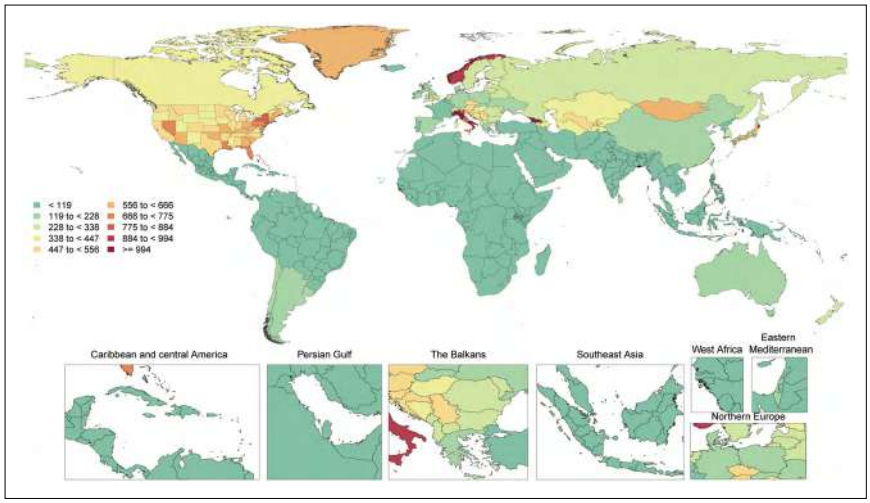



**Chart 23.7. Age-standardized prevalence rates of nonrheumatic degenerative mitral valve disease per 100 000, both sexes, 2021.**
During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.
GBD indicates Global Burden of Disease.
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[160]

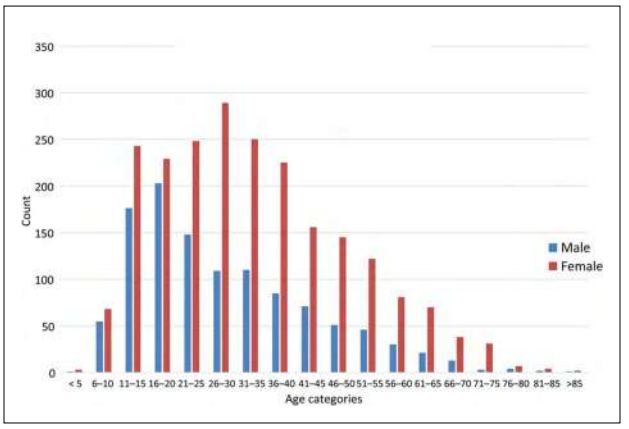



**Chart 23-8. Age and sex distribution of 3343 subjects with rheumatic HD participating in the REMEDY study, 2010 to 2012.**
HD indicates heart disease; and REMEDY, Global Rheumatic Heart Disease Registry.
Source: Reprinted from Zühlke et al[150] with permission of the European Society of Cardiology. Copyright © 2014, The Authors. Published by Oxford University Press on behalf of the European Society of Cardiology.

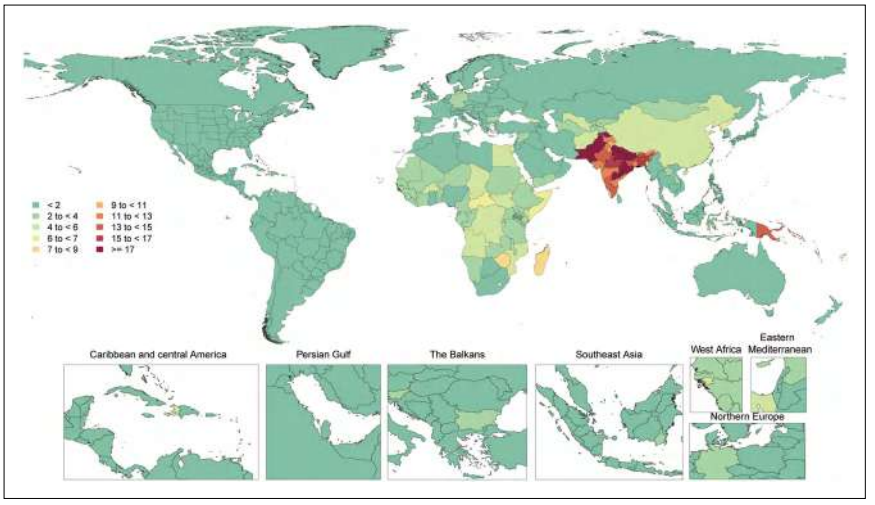



**Chart 23-9. Age-standardized global mortality rates of rheumatic HD per 100 000, both sexes, 2021.**
During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.
GBD indicates Global Burden of Disease; and HD, heart disease.
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[160]

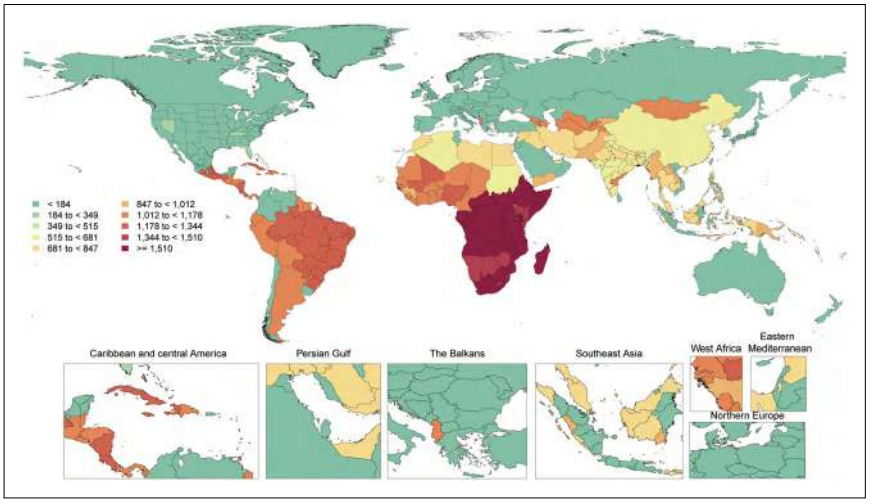



**Chart 23-10. Age-standardized global prevalence rates of rheumatic HD per 100 000, both sexes, 2021.**
During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.
GBD indicates Global Burden of Disease; and HD, heart disease.
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[160]

## REFERENCES


1. Centers for Disease Control and Prevention and National Center for Health Statistics. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death micro-data files. Accessed April 8, 2023. https://cdc.gov/nchs/nvss/mortality_public_use_data.htm
2. Centers for Disease Control and Prevention and National Center for Health Statistics. Multiple cause of death, CDC WONDER online database. Accessed April 1, 2023. https://wonder.cdc.gov/mcd-icd10.html
3. Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project (HCUP). Accessed April 1, 2023. http://hcupnet.ahrq.gov/
4. Global Burden of Disease Study and Institute for Health Metrics and Evaluation. Accessed March 6, 2023. https://vizhub.healthdata.org/gbd-results/
5. Shelbaya K, Claggett B, Dorbala P, Skali H, Solomon SD, Matsushita K, Konety S, Mosley TH, Shah AM. Stages of valvular heart disease among older adults in the community: the Atherosclerosis Risk in Communities study. *Circulation*. 2023;147:638–649. doi: 10.1161/CIRCULATIONAHA.122.061396
6. Rubin J, Aggarwal SR, Swett KR, Kirtane AJ, Kodali SK, Nazif TM, Pu M, Dadhania R, Kaplan RC, Rodriguez CJ. Burden of valvular heart diseases in Hispanic/Latino individuals in the United States: the Echocardiographic Study of Latinos. *Mayo Clin Proc*. 2019;94:1488–1498. doi: 10.1016/j.mayocp.2018.12.035
7. Andell P, Li X, Martinsson A, Andersson C, Stagmo M, Zoller B, Sundquist K, Smith JG. Epidemiology of valvular heart disease in a Swedish nationwide hospital-based register study. *Heart*. 2017;103:1696–1703. doi: 10.1136/heartjnl-2016-310894
8. Shu S, Yang Y, Sun B, Su Z, Fu M, Xiong C, Zhang X, Hu S, Song J. Alerting trends in epidemiology for calcific aortic valve disease, 1990 - 2019: an age-period-cohort analysis for the Global Burden of Disease Study 2019. *Eur Heart J Qual Care Clin Outcomes*. 2023;9:459–473. doi: 10.1093/ehjqcco/qcad018
9. Yu J, Wang Z, Bao Q, Lei S, You Y, Yin Z, Xie X. Global burden of calcific aortic valve disease and attributable risk factors from 1990 to 2019. *Front Cardiovasc Med*. 2022;9:1003233. doi: 10.3389/fcvm.2022.1003233
10. Kontogeorgos S, Thunstrom E, Basic C, Hansson PO, Zhong Y, Ergatoudes C, Morales D, Mandalenakis Z, Rosengren A, Caidahl K, et al. Prevalence and risk factors of aortic stenosis and aortic sclerosis: a 21-year follow-up of middle-aged men. *Scand Cardiovasc J*. 2020;54:115–123. doi: 10.1080/14017431.2019.1685126
11. Sillesen A-S, Vøgg O, Pihl C, Raja AA, Sundberg K, Vedel C, Zingenberg H, Jørgensen FS, Vejlstrup N, Iversen K, et al. Prevalence of bicuspid aortic valve and associated aortopathy in newborns in Copenhagen, Denmark. *JAMA*. 2021;325:561–567. doi: 10.1001/jama.2020.27205
12. Li P, Bačová M, Dalla-Pozza R, Haas NA, Oberhoffer FS. Prevalence of bicuspid aortic valve in Turner syndrome patients receiving cardiac MRI and CT: a meta-analysis. *Congenit Heart Dis*. 2022;17:129–140. doi: 10.32604/chd.2022.018300
13. Czarny MJ, Shah SJ, Whelton SP, Blaha MJ, Tsai MY, Denis R, Bertoni A, Post WS. Race/ethnicity and prevalence of aortic stenosis by echocardiography in the Multi-Ethnic Study of Atherosclerosis. *J Am Coll Cardiol*. 2021;78:195–197. doi: 10.1016/j.jacc.2021.04.078
14. Ahmed Y, van Bakel PAJ, Hou H, Sukul D, Likosky DS, van Herwaarden JA, Watkins DC, Ailawadi G, Patel HJ, Thompson MP; Structural Heart and Aortic Diseases Outcomes Research Workgroup Investigators. Racial and ethnic disparities in diagnosis, management and outcomes of aortic stenosis in the Medicare population. *PLoS One*. 2023;18:e0281811. doi: 10.1371/journal.pone.0281811
15. Martinsson A, Li X, Andersson C, Nilsson J, Smith JG, Sundquist K. Temporal trends in the incidence and prognosis of aortic stenosis: a nationwide study of the Swedish population. *Circulation*. 2015;131:988–994. doi: 10.1161/CIRCULATIONAHA.114.012906
16. Eveborn GW, Schirmer H, Heggelund G, Lunde P, Rasmussen K. The evolving epidemiology of valvular aortic stenosis, the Tromso study. *Heart*. 2013;99:396–400. doi: 10.1136/heartjnl-2012-302265
17. Yan AT, Koh M, Chan KK, Guo H, Alter DA, Austin PC, Tu JV, Wijeysundera HC, Ko DT. Association between cardiovascular risk factors and aortic stenosis: the CANHEART Aortic Stenosis Study. *J Am Coll Cardiol*. 2017;69:1523–1532. doi: 10.1016/j.jacc.2017.01.025
18. Kurasawa S, Okazaki M, Imaizumi T, Kondo T, Hishida M, Nishibori N, Takeda Y, Kasuga H, Maruyama S. Number of calcified aortic valve leaflets: natural history and prognostic value in patients undergoing haemodialysis. *Eur Heart J Cardiovasc Imaging*. 2023;24:909–920. doi: 10.1093/ehjci/jead020
19. Yang Y, Wang Z, Chen Z, Wang X, Zhang L, Li S, Zheng C, Kang Y, Jiang L, Zhu Z, et al. Current status and etiology of valvular heart disease in China: a population-based survey. *BMC Cardiovasc Disord*. 2021;21:339. doi: 10.1186/s12872-021-02154-8
20. Osnabrugge RL, Mylotte D, Head SJ, Van Mieghem NM, Nkomo VT, LeReun CM, Bogers AJ, Piazza N, Kappetein AP. Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study. *J Am Coll Cardiol*. 2013;62:1002–1012. doi: 10.1016/j.jacc.2013.05.015
21. Danielsen R, Aspelund T, Harris TB, Gudnason V. The prevalence of aortic stenosis in the elderly in Iceland and predictions for the coming decades: the AGES-Reykjavik study. *Int J Cardiol*. 2014;176:916–922. doi: 10.1016/j.ijcard.2014.08.053
22. Kontogeorgos S, Thunstrom E, Lappas G, Rosengren A, Fu M. Cumulative incidence and predictors of acquired aortic stenosis in a large population of men followed for up to 43 years. *BMC Cardiovasc Disord*. 2022;22:43. doi: 10.1186/s12872-022-02487-y
23. Kaltoft M, Langsted A, Nordestgaard BG. Obesity as a causal risk factor for aortic valve stenosis. *J Am Coll Cardiol*. 2020;75:163–176. doi: 10.1016/j.jacc.2019.10.050
24. Huang N, Zhuang Z, Liu Z, Huang T. Observational and genetic associations of modifiable risk factors with aortic valve stenosis: a prospective cohort study of 05 million participants. *Nutrients*. 2022;14:2273. doi: 10.3390/nu14112273
25. Kaltoft M, Langsted A, Afzal S, Kamstrup PR, Nordestgaard BG. Lipoprotein(a) and body mass compound the risk of calcific aortic valve disease. *J Am Coll Cardiol*. 2022;79:545–558. doi: 10.1016/j.jacc.2021.11.043
26. Wodaje T, Littmann K, Häbel H, Bottai M, Bäck M, Parini P, Brinck J. Plasma lipoprotein(a) measured in routine clinical care and the association with incident calcified aortic valve stenosis during a 14-year observational period. *Atherosclerosis*. 2022;349:175–182. doi: 10.1016/j.atherosclerosis.2022.02.016
27. Sasakawa Y, Okamoto N, Fujii M, Kato J, Yuzawa Y, Inaguma D. Factors associated with aortic valve stenosis in Japanese patients with end-stage kidney disease. *BMC Nephrol*. 2022;23:129. doi: 10.1186/s12882-022-02758-y
28. Galian-Gay L, Carro Hevia A, Teixido-Tura G, Rodriguez Palomares J, Gutierrez-Moreno L, Maldonado G, Gonzalez-Alujas MT, Sao-Aviles A, Gallego P, Calvo-Iglesias F, et al; BICUSPID Investigators. Familial clustering of bicuspid aortic valve and its relationship with aortic dilation in first-degree relatives. *Heart*. 2019;105:603–608. doi: 10.1136/heartjnl-2018-313802
29. Padang R, Bagnall RD, Richmond DR, Bannon PG, Semsarian C. Rare non-synonymous variations in the transcriptional activation domains of *GATA5* in bicuspid aortic valve disease. *J Mol Cell Cardiol*. 2012;53:277–281. doi: 10.1016/j.yjmcc.2012.05.009
30. Yang B, Zhou W, Jiao J, Nielsen JB, Mathis MR, Heydarpour M, Lettre G, Folkersen L, Prakash S, Schurmann C, et al. Protein-altering and regulatory genetic variants near *GATA4* implicated in bicuspid aortic valve. *Nat Commun*. 2017;8:15481. doi: 10.1038/ncomms15481
31. Xu YJ, Di RM, Qiao Q, Li XM, Huang RT, Xue S, Liu XY, Wang J, Yang YQ. *GATA6* loss-of-function mutation contributes to congenital bicuspid aortic valve. *Gene*. 2018;663:115–120. doi: 10.1016/j.gene.2018.04.018
32. Luyckx I, MacCarrick G, Kempers M, Meester J, Geryl C, Rombouts O, Peeters N, Claes C, Boeckx N, Sakalihasan N, et al. Confirmation of the role of pathogenic *SMAD6* variants in bicuspid aortic valve-related aortopathy. *Eur J Hum Genet*. 2019;27:1044–1053. doi: 10.1038/s41431-019-0363-z
33. Hanchard NA, Swaminathan S, Bucasas K, Furthner D, Fernbach S, Azamian MS, Wang X, Lewin M, Towbin JA, D'Alessandro LC, et al. A genome-wide association study of congenital cardiovascular left-sided lesions shows association with a locus on chromosome 20. *Hum Mol Genet*. 2016;25:2331–2341. doi: 10.1093/hmg/ddw071
34. Fulmer D, Toomer K, Guo L, Moore K, Glover J, Moore R, Stairley R, Lobo G, Zuo X, Dang Y, et al. Defects in the exocyst-cilia machinery cause bicuspid aortic valve disease and aortic stenosis. *Circulation*. 2019;140:1331–1341. doi: 10.1161/CIRCULATIONAHA.119.038376
35. Bjornsson T, Thorolfsdottir RB, Sveinbjornsson G, Sulem P, Norddahl GL, Helgadottir A, Gretarsdottir S, Magnusdottir A, Danielsen R, Sigurdsson EL, et al. A rare missense mutation in *MYH6* associates with non-syndromic coarctation of the aorta. *Eur Heart J*. 2018;39:3243–3249. doi: 10.1093/eurheartj/ehy142

36. Gould RA, Aziz H, Woods CE, Seman-Senderos MA, Sparks E, Preuss C, Wunnemann F, Bedja D, Moats CR, McClymont SA, et al; Baylor-Hopkins Center for Mendelian Genomics. *ROBO4* variants predispose individuals to bicuspid aortic valve and thoracic aortic aneurysm. *Nat Genet*. 2019;51:42–50. doi: 10.1038/s41588-018-0265-y
37. Martinsson A, Li X, Zoller B, Andell P, Andersson C, Sundquist K, Smith JG. Familial aggregation of aortic valvular stenosis: a nationwide study of sibling risk. *Circ Cardiovasc Genet*. 2017;10:e001742. doi: 10.1161/CIRCGENETICS.117.001742
38. Thanassoulis G, Campbell CY, Owens DS, Smith JG, Smith AV, Peloso GM, Kerr KF, Pechlivanis S, Budoff MJ, Harris TB, et al; CHARGE Extracoronary Calcium Working Group. Genetic associations with valvular calcification and aortic stenosis. *N Engl J Med*. 2013;368:503–512. doi: 10.1056/NEJMoa1109034
39. Perrot N, Theriault S, Dina C, Chen HY, Boekholdt SM, Rigade S, Despres AA, Poulin A, Capoulade R, Le Tourneau T, et al. Genetic variation in *LPA*, calcific aortic valve stenosis in patients undergoing cardiac surgery, and familial risk of aortic valve microcalcification. *JAMA Cardiol*. 2019;4:620–627. doi: 10.1001/jamacardio.2019.1581
40. Guertin J, Kaiser Y, Manikpurage H, Perrot N, Bourgeois R, Couture C, Wareham NJ, Bossé Y, Pibarot P, Stroes ESG, et al. Sex-specific associations of genetically predicted circulating Lp(a) (lipoprotein(a)) and hepatic *LPA* gene expression levels with cardiovascular outcomes: mendelian randomization and observational analyses. *Circ Genom Precis Med*. 2021;14:e003271. doi: 10.1161/CIRCGEN.120.003271
41. Theriault S, Dina C, Messika-Zeitoun D, Le Scouarnec S, Capoulade R, Gaudreault N, Rigade S, Li Z, Simonet F, Lamontagne M, et al; DESIR Study Group. Genetic association analyses highlight *IL6*, *ALPL*, and *NAV1* as 3 new susceptibility genes underlying calcific aortic valve stenosis. *Circ Genom Precis Med*. 2019;12:e002617. doi: 10.1161/CIRCGEN.119.002617
42. Helgadottir A, Thorleifsson G, Gretarsdottir S, Stefansson OA, Tragante V, Thorolfsdottir RB, Jonsdottir I, Bjornsson T, Steinthorsdottir V, Verweij N, et al. Genome-wide analysis yields new loci associating with aortic valve stenosis. *Nat Commun*. 2018;9:987. doi: 10.1038/s41467-018-03252-6
43. Theriault S, Gaudreault N, Lamontagne M, Rosa M, Boulanger MC, Messika-Zeitoun D, Clavel MA, Capoulade R, Dagenais F, Pibarot P, et al. A transcriptome-wide association study identifies *PALMD* as a susceptibility gene for calcific aortic valve stenosis. *Nat Commun*. 2018;9:988. doi: 10.1038/s41467-018-03260-6
44. Small AM, Peloso G, Linefsky J, Aragam J, Galloway A, Tanukonda V, Wang LC, Yu Z, Sunitha Selvaraj M, Farber-Eger EH, et al; VA Million Veteran Program. Multiancestry genome-wide association study of aortic stenosis identifies multiple novel loci in the Million Veteran Program. *Circulation*. 2023;147:942–955. doi: 10.1161/CIRCULATIONAHA.122.061451
45. Smith JG, Luk K, Schulz CA, Engert JC, Do R, Hindy G, Rukh G, Dufresne L, Almgren P, Owens DS, et al; Cohorts for Heart and Aging Research in Genetic Epidemiology (CHARGE) Extracoronary Calcium Working Group. Association of low-density lipoprotein cholesterol-related genetic variants with aortic valve calcium and incident aortic stenosis. *JAMA*. 2014;312:1764–1771. doi: 10.1001/jama.2014.13959
46. Perrot N, Valerio V, Moschetta D, Boekholdt SM, Dina C, Chen HY, Abner E, Martinsson A, Manikpurage HD, Rigade S, et al. Genetic and in vitro inhibition of PCSK9 and calcific aortic valve stenosis. *JACC Basic Transl Sci*. 2020;5:649–661. doi: 10.1016/j.jacbts.2020.05.004
47. Nazarzadeh M, Pinho-Gomes AC, Smith Byrne K, Canoy D, Raimondi F, Ayala Solares JR, Otto CM, Rahimi K. Systolic blood pressure and risk of valvular heart disease: a mendelian randomization study. *JAMA Cardiol*. 2019;4:788–795. doi: 10.1001/jamacardio.2019.2202
48. Banovic M, Putnik S, Penicka M, Doros G, Deja MA, Kockova R, Kotrc M, Glaveckaite S, Gasparovic H, Pavlovic N, et al; AVATAR Trial Investigators. Aortic valve replacement versus conservative treatment in asymptomatic severe aortic stenosis: the AVATAR trial. *Circulation*. 2022;145:648–658. doi: 10.1161/CIRCULATIONAHA.121.057639
49. El-Hamamsy I, Toyoda N, Itagaki S, Stelzer P, Varghese R, Williams EE, Erogova N, Adams DH. Propensity-matched comparison of the ross procedure and prosthetic aortic valve replacement in adults. *J Am Coll Cardiol*. 2022;79:805–815. doi: 10.1016/j.jacc.2021.11.057
50. Yokoyama Y, Kuno T, Toyoda N, Fujisaki T, Takagi H, Itagaki S, Ibrahim M, Ouzounian M, El-Hamamsy I, Fukuhara S. Ross procedure versus mechanical versus bioprosthetic aortic valve replacement: a network meta-analysis. *J Am Heart Assoc*. 2023;12:e8066. doi: 10.1161/JAHA.122.027715
51. Lansac E, Di Centa I, Danial P, Bouchot O, Arnaud-Crozat E, Hacini R, Doguet F, Demaria R, Verhoye JP, Jouan J, et al. Aortic valve repair versus mechanical valve replacement for root aneurysm: the CAVIAAR multicentric study. *Eur J Cardiothorac Surg*. 2022;62:ezac283. doi: 10.1093/ejcts/ezac283
52. Russo MJ, Thourani VH, Cohen DJ, Malaisrie SC, Szeto WY, George I, Kodali SK, Makkar R, Lu M, Williams M, et al. Minimally invasive versus full sternotomy for isolated aortic valve replacement in low-risk patients. *Ann Thorac Surg*. 2022;114:2124–2130. doi: 10.1016/j.athoracsur.2021.11.048
53. Telyuk P, Hancock H, Maier R, Batty JA, Goodwin A, Owens WA, Ogundimu E, Akowuah E. Long-term outcomes of mini-sternotomy versus conventional sternotomy for aortic valve replacement: a randomised controlled trial. *Eur J Cardiothorac Surg*. 2022;63:ezac540. doi: 10.1093/ejcts/ezac540
54. Carroll JD, Mack MJ, Vemulapalli S, Herrmann HC, Gleason TG, Hanzel G, Deeb GM, Thourani VH, Cohen DJ, Desai N, et al. STS-ACC TVT Registry of transcatheter aortic valve replacement. *J Am Coll Cardiol*. 2020;76:2492–2516. doi: 10.1016/j.jacc.2020.09.595
55. Toff WD, Hildick-Smith D, Kovac J, Mullen MJ, Wendler O, Mansouri A, Rombach I, Abrams KR, Conroy SP, Flather MD, et al; UK TAVI Trial Investigators. Effect of transcatheter aortic valve implantation vs surgical aortic valve replacement on all-cause mortality in patients with aortic stenosis: a randomized clinical trial. *JAMA*. 2022;327:1875–1887. doi: 10.1001/jama.2022.5776
56. Alkhouli M, Holmes DR Jr, Carroll JD, Li Z, Inohara T, Kosinski AS, Szerlip M, Thourani VH, Mack MJ, Vemulapalli S. Racial disparities in the utilization and outcomes of TAVR: TVT Registry report. *JACC Cardiovasc Interv*. 2019;12:936–948. doi: 10.1016/j.jcin.2019.03.007
57. Gaede L, Blumenstein J, Liebetrau C, Dorr O, Kim WK, Nef H, Husser O, Elsasser A, Hamm CW, Mollmann H. Outcome after transvascular transcatheter aortic valve implantation in 2016. *Eur Heart J*. 2018;39:667–675. doi: 10.1093/eurheartj/ehx688
58. Doshi R, Shlofmitz E, Meraj P. Comparison of outcomes and complications of transcatheter aortic valve implantation in women versus men (from the National Inpatient Sample). *Am J Cardiol*. 2018;121:73–77. doi: 10.1016/j.amjcard.2017.09.015
59. Beyersdorf F, Bauer T, Freemantle N, Walther T, Frerker C, Herrmann E, Bleiziffer S, Möllmann H, Landwehr S, Ensminger S, et al; GARY Executive Board. Five-year outcome in 18 010 patients from the German Aortic Valve Registry. *Eur J Cardiothorac Surg*. 2021;60:1139–1146. doi: 10.1093/ejcts/ezab216
60. Mack MJ, Leon MB, Smith CR, Miller DC, Moses JW, Tuzcu EM, Webb JG, Douglas PS, Anderson WN, Blackstone EH, et al; PARTNER 1 Trial Investigators. 5-Year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet*. 2015;385:2477–2484. doi: 10.1016/S0140-6736(15)60308-7
61. Gleason TG, Reardon MJ, Popma JJ, Deeb GM, Yakubov SJ, Lee JS, Kleiman NS, Chetcuti S, Hermiller JB Jr, Heiser J, et al; CoreValve U.S. Pivotal High Risk Trial Clinical Investigators. 5-Year outcomes of self-expanding transcatheter versus surgical aortic valve replacement in high-risk patients. *J Am Coll Cardiol*. 2018;72:2687–2696. doi: 10.1016/j.jacc.2018.08.2146
62. Reardon MJ, Van Mieghem NM, Popma JJ, Kleiman NS, Søndergaard L, Mumtaz M, Adams DH, Deeb GM, Maini B, Gada H, et al; SURTAVI Investigators. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. *N Engl J Med*. 2017;376:1321–1331. doi: 10.1056/NEJMoa1700456
63. Van Mieghem NM, Deeb GM, Søndergaard L, Grube E, Windecker S, Gada H, Mumtaz M, Olsen PS, Heiser JC, Merhi W, et al; SURTAVI Trial Investigators. Self-expanding transcatheter vs surgical aortic valve replacement in intermediate-risk patients: 5-year outcomes of the SURTAVI randomized clinical trial. *JAMA Cardiol*. 2022;7:1000–1008. doi: 10.1001/jamacardio.2022.2695
64. Makkar RR, Thourani VH, Mack MJ, Kodali SK, Kapadia S, Webb JG, Yoon SH, Trento A, Svensson LG, Herrmann HC, et al; PARTNER 2 Investigators. Five-year outcomes of transcatheter or surgical aortic-valve replacement. *N Engl J Med*. 2020;382:799–809. doi: 10.1056/NEJMoa1910555
65. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, Thourani VH, Tuzcu EM, Miller DC, Herrmann HC, et al; PARTNER 2 Investigators. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med*. 2016;374:1609–1620. doi: 10.1056/NEJMoa1514616
66. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, Kapadia SR, Malaisrie SC, Cohen DJ, Pibarot P, et al; PARTNER 3 Investigators. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med*. 2019;380:1695–1705. doi: 10.1056/NEJMoa1814052

67. Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, Bajwa T, Heiser JC, Merhi W, Kleiman NS, et al; Evolut Low Risk Trial Investigators. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. *N Engl J Med*. 2019;380:1706–1715. doi: 10.1056/NEJMoa1816885
68. Forrest JK, Deeb GM, Yakubov SJ, Rovin JD, Mumtaz M, Gada H, O'Hair D, Bajwa T, Sorajja P, Heiser JC, et al. 2-Year outcomes after transcatheter versus surgical aortic valve replacement in low-risk patients. *J Am Coll Cardiol*. 2022;79:882–896. doi: 10.1016/j.jacc.2021.11.062
69. Thyregod HGH, Ihlemann N, Jorgensen TH, Nissen H, Kjeldsen BJ, Petursson P, Chang Y, Franzen OW, Engstrom T, Clemmensen P, et al. Five-year clinical and echocardiographic outcomes from the Nordic Aortic Valve Intervention (NOTION) randomized clinical trial in lower surgical risk patients. *Circulation*. 2019;139:2714–2723. doi: 10.1161/CIRCULATIONAHA.118.036606
70. Fu J, Popal MS, Li Y, Li G, Qi Y, Fang F, Kwong JSW, You B, Meng X, Du J. Transcatheter versus surgical aortic valve replacement in low and intermediate risk patients with severe aortic stenosis: systematic review and meta-analysis of randomized controlled trials and propensity score matching observational studies. *J Thorac Dis*. 2019;11:1945–1962. doi: 10.21037/jtd.2019.04.97
71. Vemulapalli S, Carroll JD, Mack MJ, Li Z, Dai D, Kosinski AS, Kumbhani DJ, Ruiz CE, Thourani VH, Hanzel G, et al. Procedural volume and outcomes for transcatheter aortic-valve replacement. *N Engl J Med*. 2019;380:2541–2550. doi: 10.1056/NEJMsa1901109
72. Kang DH, Park SJ, Lee SA, Lee S, Kim DH, Kim HK, Yun SC, Hong GR, Song JM, Chung CH, et al. Early surgery or conservative care for asymptomatic aortic stenosis. *N Engl J Med*. 2020;382:111–119. doi: 10.1056/NEJMoa1912846
73. Michelena HI, Suri RM, Katan O, Eleid MF, Clavel MA, Maurer MJ, Pellikka PA, Mahoney D, Enriquez-Sarano M. Sex differences and survival in adults with bicuspid aortic valves: verification in 3 contemporary echocardiographic cohorts. *J Am Heart Assoc*. 2016;5:e004211. doi: 10.1161/JAHA.116.004211
74. Tribouilloy C, Bohbot Y, Rusinaru D, Belkhir K, Diouf M, Altes A, Delpierre Q, Serbout S, Kubala M, Levy F, et al. Excess mortality and undertreatment of women with severe aortic stenosis. *J Am Heart Assoc*. 2021;10:e018816. doi: 10.1161/JAHA.120.018816
75. Alcón B, Martínez-Legazpi P, Stewart S, Gonzalez-Mansilla A, Cuadrado V, Strange G, Yotti R, Cascos E, Delgado-Montero A, Prieto-Arévalo R, et al. Transvalvular jet velocity, aortic valve area, mortality, and cardiovascular outcomes. *Eur Heart J Cardiovasc Imaging*. 2022;23:601–612. doi: 10.1093/ehjci/jeac003
76. Stewart S, Afoakwah C, Chan YK, Strom JB, Playford D, Strange GA. Counting the cost of premature mortality with progressively worse aortic stenosis in Australia: a clinical cohort study. *Lancet Healthy Longev*. 2022;3:e599–e606. doi: 10.1016/S2666-7568(22)00168-4
77. Strom JB, Playford D, Stewart S, Li S, Shen C, Xu J, Strange G. Increasing risk of mortality across the spectrum of aortic stenosis is independent of comorbidity & treatment: an international, parallel cohort study of 248,464 patients. *PLoS One*. 2022;17:e0268580. doi: 10.1371/journal.pone.0268580
78. Strange G, Stewart S, Playford D, Strom JB. Risk for mortality with increasingly severe aortic stenosis: an international cohort study. *J Am Soc Echocardiogr*. 2023;36:60–68.e2. doi: 10.1016/j.echo.2022.09.020
79. Shen M, Tastet L, Capoulade R, Arsenault M, Bedard E, Clavel MA, Pibarot P. Effect of bicuspid aortic valve phenotype on progression of aortic stenosis. *Eur Heart J Cardiovasc Imaging*. 2020;21:727–734. doi: 10.1093/ehjci/jeaa068
80. Evangelista A, Gallego P, Calvo-Iglesias F, Bermejo J, Robledo-Carmona J, Sanchez V, Saura D, Arnold R, Carro A, Maldonado G, et al. Anatomical and clinical predictors of valve dysfunction and aortic dilation in bicuspid aortic valve disease. *Heart*. 2018;104:566–573. doi: 10.1136/heartjnl-2017-311560
81. Li Y, Chen X, Qi Y, Qu Y, Kumar A, Dong S, Yang Y, Zhao Q. Gender differences in bicuspid aortic valve Sievers types, valvulopathy, aortopathy, and outcome of aortic valve replacement. *Echocardiogr*. 2022;39:1064–1073. doi: 10.1111/echo.15405
82. Al-Abdouh A, Upadhrasta S, Fashanu O, Elias H, Zhao D, Hasan RK, Michos ED. Transcatheter aortic valve replacement in low-risk patients: a meta-analysis of randomized controlled trials. *Cardiovasc Revasc Med*. 2020;21:461–466. doi: 10.1016/j.carrev.2019.08.008
83. Myat A, Buckner L, Mouy F, Cockburn J, Baumbach A, Banning AP, Blackman DJ, Curzen N, MacCarthy P, Mullen M, et al. In-hospital stroke after transcatheter aortic valve implantation: a UK observational cohort analysis. *Catheter Cardiovasc Interv*. 2021;97:E552–E559. doi: 10.1002/ccd.29157
84. Bansal A, Kalra A, Puri R, Saliba W, Krishnaswamy A, Kapadia SR, Reed GW. Incidence and outcomes of pericardial effusion and cardiac tamponade following permanent pacemaker implantation after transcatheter aortic valve implantation. *Am J Cardiol*. 2021;157:135–139. doi: 10.1016/j.amjcard.2021.07.027
85. Reynolds MR, Lei Y, Wang K, Chinnakondepalli K, Vilain KA, Magnuson EA, Galper BZ, Meduri CU, Arnold SV, Baron SJ, et al; CoreValve US High Risk Pivotal Trial Investigators. Cost-effectiveness of transcatheter aortic valve replacement with a self-expanding prosthesis versus surgical aortic valve replacement. *J Am Coll Cardiol*. 2016;67:29–38. doi: 10.1016/j.jacc.2015.10.046
86. Goodall G, Lamotte M, Ramos M, Maunoury F, Pejchalova B, de Pouvourville G. Cost-effectiveness analysis of the SAPIEN 3 TAVI valve compared with surgery in intermediate-risk patients. *J Med Econ*. 2019;22:289–296. doi: 10.1080/13696998.2018.1559600
87. Geisler BP, Jorgensen TH, Thyregod HGH, Pietzsch JB, Sondergaard L. Cost-effectiveness of transcatheter versus surgical aortic valve replacement in patients at lower surgical risk: results from the NOTION trial. *EuroIntervention*. 2019;15:e959–e967. doi: 10.4244/EIJ-D-18-00847
88. Wei S, Miranda JJ, Mamas MA, Zuhlke LJ, Kontopantelis E, Thabane L, Van Spall HGC. Sex differences in the etiology and burden of heart failure across country income level: analysis of 204 countries and territories 1990-2019 [published online December 28, 2022]. *Eur Heart J Qual Care Clin Outcomes*. doi: 10.1093/ehjqcco/qcac088. https://academic.oup.com/ehjqcco/advance-article/doi/10.1093/ehjqcco/qcac088/6964647?login=false
89. Deleted in proof
90. Delling FN, Gona P, Larson MG, Lehman B, Manning WJ, Levine RA, Benjamin EJ, Vasan RS. Mild expression of mitral valve prolapse in the Framingham offspring: expanding the phenotypic spectrum. *J Am Soc Echocardiogr*. 2014;27:17–23. doi: 10.1016/j.echo.2013.09.015
91. Delling FN, Rong J, Larson MG, Lehman B, Fuller D, Osypiuk E, Stantchev P, Hackman B, Manning WJ, Benjamin EJ, et al. Evolution of mitral valve prolapse: insights from the Framingham Heart Study. *Circulation*. 2016;133:1688–1695. doi: 10.1161/CIRCULATIONAHA.115.020621
92. Durst R, Sauls K, Peal DS, deVlaming A, Toomer K, Leyne M, Salani M, Talkowski ME, Brand H, Perrocheau M, et al. Mutations in *DCHS1* cause mitral valve prolapse. *Nature*. 2015;525:109–113. doi: 10.1038/nature14670
93. Toomer KA, Yu M, Fulmer D, Guo L, Moore KS, Moore R, Drayton KD, Glover J, Peterson N, Ramos-Ortiz S, et al. Primary cilia defects causing mitral valve prolapse. *Sci Transl Med*. 2019;11:eaax0290. doi: 10.1126/scitranslmed.aax0290
94. Yu M, Georges A, Tucker NR, Kyryachenko S, Toomer K, Schott JJ, Delling FN, Fernandez-Friera L, Solis J, Ellinor PT, et al. Genome-wide association study-driven gene-set analyses, genetic, and functional follow-up suggest *GLIS1* as a susceptibility gene for mitral valve prolapse. *Circ Genom Precis Med*. 2019;12:e002497. doi: 10.1161/CIRCGEN.119.002497
95. Le Tourneau T, Merot J, Rimbert A, Le Scouarnec S, Probst V, Le Marec H, Levine RA, Schott JJ. Genetics of syndromic and non-syndromic mitral valve prolapse. *Heart*. 2018;104:978–984. doi: 10.1136/heartjnl-2017-312420
96. Trenkwalder T, Krane M. Mitral valve prolapse: will genetics finally solve the puzzle? *Eur Heart J*. 2022;43:1681–1683. doi: 10.1093/eurheartj/ehac048
97. Yu M, Kyryachenko S, Debette S, Amouyel P, Schott JJ, Le Tourneau T, Dina C, Norris RA, Hagege AA, Jeunemaitre X, et al. Genome-wide association meta-analysis supports genes involved in valve and cardiac development to associate with mitral valve prolapse. *Circ Genom Precis Med*. 2021;14:e003148. doi: 10.1161/CIRCGEN.120.003148
98. Brady AF, Demirdas S, Fournel-Gigleux S, Ghali N, Giunta C, Kapferer-Seebacher I, Kosho T, Mendoza-Londono R, Pope MF, Rohrbach M, et al. The Ehlers-Danlos syndromes, rare types. *Am J Med Genet C Semin Med Genet*. 2017;175:70–115. doi: 10.1002/ajmg.c.31550
99. Morningstar JE, Nieman A, Wang C, Beck T, Harvey A, Norris RA. Mitral valve prolapse and its motley crew: syndromic prevalence, pathophysiology, and progression of a common heart condition. *J Am Heart Assoc*. 2021;10:e020919. doi: 10.1161/JAHA.121.020919
100. Chahal A, Bouatia-Naji N. Genetics of mitral valve prolapse and its clinical impact. *eJ Cardiol Pract*. 2019. Accessed December 3, 2023. https://www.escardio.org/Journals/E-Journal-of-Cardiology-Practice/Volume-16/Genetics-of-mitral-valve-prolapse-and-its-clinical-impact

101. Nesta F, Leyne M, Yosefy C, Simpson C, Dai D, Marshall JE, Hung J, Slaugenhaupt SA, Levine RA. New locus for autosomal dominant mitral valve prolapse on chromosome 13: clinical insights from genetic studies. *Circulation*. 2005;112:2022–2030. doi: 10.1161/CIRCULATIONAHA.104.516930
102. Disse S, Abergel E, Berrebi A, Houot AM, Le Heuzey JY, Diebold B, Guize L, Carpentier A, Corvol P, Jeunemaitre X. Mapping of a first locus for autosomal dominant myxomatous mitral-valve prolapse to chromosome 16p112-p121. *Am J Hum Genet*. 1999;65:1242–1251. doi: 10.1086/302624
103. Le Tourneau T, Le Scouarnec S, Cueff C, Bernstein D, Aalberts JJJ, Lecointe S, Merot J, Bernstein JA, Oomen T, Dina C, et al. New insights into mitral valve dystrophy: a Filamin-A genotype-phenotype and outcome study. *Eur Heart J*. 2018;39:1269–1277. doi: 10.1093/eurheartj/ehx505
104. Delling FN, Li X, Li S, Yang Q, Xanthakis V, Martinsson A, Andell P, Lehman BT, Osypiuk EW, Stantchev P, et al. Heritability of mitral regurgitation: observations from the Framingham Heart Study and Swedish population. *Circ Cardiovasc Genet*. 2017;10:e001736. doi: 10.1161/CIRCGENETICS.117.001736
105. Delling FN, Rong J, Larson MG, Lehman B, Osypiuk E, Stantchev P, Slaugenhaupt SA, Benjamin EJ, Levine RA, Vasan RS. Familial clustering of mitral valve prolapse in the community. *Circulation*. 2015;131:263–268. doi: 10.1161/CIRCULATIONAHA.114.012594
106. van Wijngaarden AL, Hiemstra YL, Koopmann TT, Ruivenkamp CAL, Aten E, Schalij MJ, Bax JJ, Delgado V, Barge-Schaapveld D, Ajmone Marsan N. Identification of known and unknown genes associated with mitral valve prolapse using an exome slice methodology. *J Med Genet*. 2020;57:843–850. doi: 10.1136/jmedgenet-2019-106715
107. Goldstein D, Moskowitz AJ, Gelijns AC, Ailawadi G, Parides MK, Perrault LP, Hung JW, Voisine P, Dagenais F, Gillinov AM, et al; CTSN. Two-year outcomes of surgical treatment of severe ischemic mitral regurgitation. *N Engl J Med*. 2016;374:344–353. doi: 10.1056/NEJMoa1512913
108. Michler RE, Smith PK, Parides MK, Ailawadi G, Thourani V, Moskowitz AJ, Acker MA, Hung JW, Chang HL, Perrault LP, et al; CTSN. Two-year outcomes of surgical treatment of moderate ischemic mitral regurgitation. *N Engl J Med*. 2016;374:1932–1941. doi: 10.1056/NEJMoa1602003
109. Mack M, Carroll JD, Thourani V, Vemulapalli S, Squiers J, Manandhar P, Deeb GM, Batchelor W, Herrmann HC, Cohen DJ, et al. Transcatheter mitral valve therapy in the United States: a report from the STS-ACC TVT Registry. *J Am Coll Cardiol*. 2021;78:2326–2353. doi: 10.1016/j.jacc.2021.07.058
110. Feldman T, Foster E, Glower D, Kar S, Rinaldi M, Fail P, Smalling R, Siegel R, Rose G, Engeron E, et al; EVEREST II Investigators. Percutaneous repair or surgery for mitral regurgitation. *N Engl J Med*. 2011;364:1395–1406. doi: 10.1056/NEJMoa1009355
111. Zhou S, Egorova N, Moskowitz G, Giustino G, Ailawadi G, Acker MA, Gillinov M, Moskowitz A, Gelijns A. Trends in MitraClip, mitral valve repair, and mitral valve replacement from 2000 to 2016. *J Thorac Cardiovasc Surg*. 2021;162:551–562.e4. doi: 10.1016/j.jtcvs.2019.12.097
112. Wong N, Yeo KK. MitraClip in Asia: current adoption and regional data. *Circ Rep*. 2019;1:397–400. doi: 10.1253/circrep.CR-19-0074
113. Wojakowski W, Baumgartner H. The year in cardiology 2018: valvular heart disease. *Eur Heart J*. 2019;40:414–421. doi: 10.1093/eurheartj/ehy893
114. Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, Whisenant B, Grayburn PA, Rinaldi M, Kapadia SR, et al; COAPT Investigators. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med*. 2018;379:2307–2318. doi: 10.1056/NEJMoa1806640
115. Obadia JF, Messika-Zeitoun D, Leurent G, Iung B, Bonnet G, Piriou N, Lefevre T, Piot C, Rouleau F, Carrie D, et al; MITRA-FR Investigators. Percutaneous repair or medical treatment for secondary mitral regurgitation. *N Engl J Med*. 2018;379:2297–2306. doi: 10.1056/NEJMoa1805374
116. Goliasch G, Bartko PE, Pavo N, Neuhold S, Wurm R, Mascherbauer J, Lang IM, Strunk G, Hulsmann M. Refining the prognostic impact of functional mitral regurgitation in chronic heart failure. *Eur Heart J*. 2018;39:39–46. doi: 10.1093/eurheartj/ehx402
117. Dziadzko V, Clavel MA, Dziadzko M, Medina-Inojosa JR, Michelena H, Maalouf J, Nkomo V, Thapa P, Enriquez-Sarano M. Outcome and undertreatment of mitral regurgitation: a community cohort study. *Lancet*. 2018;391:960–969. doi: 10.1016/S0140-6736(18)30473-2
118. Giustino G, Overbey J, Taylor D, Ailawadi G, Kirkwood K, DeRose J, Gillinov MA, Dagenais F, Mayer ML, Moskowitz A, et al. Sex-based differences in outcomes after mitral valve surgery for severe ischemic mitral regurgitation: from the Cardiothoracic Surgical Trials Network. *JACC Heart Fail*. 2019;7:481–490. doi: 10.1016/j.jchf.2019.03.001
118a. Yadgir S, Johnson CO, Aboyans V, Adebayo OM, Adedoyin RA, Afarideh M, Alahdab F, Alashi A, Alipour V, Arabloo J, et al; Global Burden of Disease Study 2017 Nonrheumatic Valve Disease Collaborators. Global, regional, and national burden of calcific aortic valve and degenerative mitral valve diseases, 1990-2017. *Circulation*. 2020;141:1670–1680. doi: 10.1161/CIRCULATIONAHA.119.043391
119. Grigioni F, Benfari G, Vanoverschelde JL, Tribouilloy C, Avierinos JF, Bursi F, Suri RM, Guerra F, Pasquet A, Rusinaru D, et al; MIDA Investigators. Long-term implications of atrial fibrillation in patients with degenerative mitral regurgitation. *J Am Coll Cardiol*. 2019;73:264–274. doi: 10.1016/j.jacc.2018.10.067
120. Nazir S, Gupta T, Ahuja KR, Minhas AMK, Ariss RW, Gupta R, Goel SS, Kleiman NS. Association of peri-procedural major bleeding with outcomes in patients undergoing transcatheter mitral edge-to-edge repair. *Am J Cardiol*. 2021;152:172–174. doi: 10.1016/j.amjcard.2021.04.025
121. Ailawadi G, Lim DS, Mack MJ, Trento A, Kar S, Grayburn PA, Glower DD, Wang A, Foster E, Qasim A, et al; EVEREST II Investigators. One-year outcomes after MitraClip for functional mitral regurgitation. *Circulation*. 2019;139:37–47. doi: 10.1161/CIRCULATIONAHA.117.031733
122. Chikwe J, O'Gara P, Fremes S, Sundt TM 3rd, Habib RH, Gammie J, Gaudino M, Badhwar V, Gillinov M, Acker M, et al. Mitral surgery after transcatheter edge-to-edge repair: Society of Thoracic Surgeons database analysis. *J Am Coll Cardiol*. 2021;78:1–9. doi: 10.1016/j.jacc.2021.04.062
123. Cameron HL, Bernard LM, Garmo VS, Hernandez JB, Asgar AW. A Canadian cost-effectiveness analysis of transcatheter mitral valve repair with the MitraClip system in high surgical risk patients with significant mitral regurgitation. *J Med Econ*. 2014;17:599–615. doi: 10.3111/13696998.2014.923892
124. Baron SJ, Wang K, Arnold SV, Magnuson EA, Whisenant B, Brieke A, Rinaldi M, Asgar AW, Lindenfeld J, Abraham WT, et al; COAPT Investigators. Cost-effectiveness of transcatheter mitral valve repair versus medical therapy in patients with heart failure and secondary mitral regurgitation: results from the COAPT trial. *Circulation*. 2019;140:1881–1891. doi: 10.1161/CIRCULATIONAHA.119.043275
125. Allen H, Shaddy R, Penny D, Feltes T, Cetta F. *Heart Disease In Infants, Children, and Adolescents*. 9th ed. Wolters Klewer; 2016.
126. Aggarwal V, Mulukutla V, Maskatia S, Justino H, Mullins CE, Qureshi AM. Outcomes after balloon pulmonary valvuloplasty for critical pulmonary stenosis and incidence of coronary artery fistulas. *Am J Cardiol*. 2018;121:1617–1623. doi: 10.1016/j.amjcard.2018.02.049
127. Hascoet S, Dalla Pozza R, Bentham J, Carere RG, Kanaan M, Ewert P, Biernacka EK, Kretschmar O, Deutsch C, Lecerf F, et al. Early outcomes of percutaneous pulmonary valve implantation using the Edwards SAPIEN 3 transcatheter heart valve system. *EuroIntervention*. 2019;14:1378–1385. doi: 10.4244/EIJ-D-18-01035
128. Chatterjee A, Bajaj NS, McMahon WS, Cribbs MG, White JS, Mukherjee A, Law MA. Transcatheter pulmonary valve implantation: a comprehensive systematic review and meta-analyses of observational studies. *J Am Heart Assoc*. 2017;6:e006432. doi: 10.1161/JAHA.117.006432
129. Haas NA, Carere RG, Kretschmar O, Horlick E, Rodes-Cabau J, de Wolf D, Gewillig M, Mullen M, Lehner A, Deutsch C, et al. Early outcomes of percutaneous pulmonary valve implantation using the Edwards SAPIEN XT transcatheter heart valve system. *Int J Cardiol*. 2018;250:86–91. doi: 10.1016/j.ijcard.2017.10.015
130. Patel A, Patel A, Bhatt P, Savani C, Thakkar B, Sonani R, Patel NJ, Arora S, Panaich S, Singh V, et al. Transcatheter pulmonary valve implantation: a cross-sectional US experience. *Int J Cardiol*. 2015;199:186–188. doi: 10.1016/j.ijcard.2015.07.021
131. Lee C, Kim YM, Lee CH, Kwak JG, Park CS, Song JY, Shim WS, Choi EY, Lee SY, Baek JS. Outcomes of pulmonary valve replacement in 170 patients with chronic pulmonary regurgitation after relief of right ventricular outflow tract obstruction: implications for optimal timing of pulmonary valve replacement. *J Am Coll Cardiol*. 2012;60:1005–1014. doi: 10.1016/j.jacc.2012.03.077
132. Zhou Y, Xiong T, Bai P, Chu C, Dong N. Clinical outcomes of transcatheter versus surgical pulmonary valve replacement: a meta-analysis. *J Thorac Dis*. 2019;11:5343–5351. doi: 10.21037/jtd.2019.11.64
133. Kolte D, Kennedy KF, Passeri JJ, Inglessis I, Elmariah S. Temporal trends in prevalence of tricuspid valve disease in hospitalized patients in the United States. *Am J Cardiol*. 2020;125:1879–1883. doi: 10.1016/j.amjcard.2020.03.033
134. Prihadi EA, van der Bijl P, Gursoy E, Abou R, Mara Vollema E, Hahn RT, Stone GW, Leon MB, Ajmone Marsan N, Delgado V, et al. Development of significant tricuspid regurgitation over time and prognostic implications: new insights into natural history. *Eur Heart J*. 2018;39:3574–3581. doi: 10.1093/eurheartj/ehy352

135. Zack CJ, Fender EA, Chandrashekar P, Reddy YNV, Bennett CE, Stulak JM, Miller VM, Nishimura RA. National trends and outcomes in isolated tricuspid valve surgery. *J Am Coll Cardiol*. 2017;70:2953–2960. doi: 10.1016/j.jacc.2017.10.039
136. Taramasso M, Alessandrini H, Latib A, Asami M, Attinger-Toller A, Biasco L, Braun D, Brochet E, Connelly KA, Denti P, et al. Outcomes after current transcatheter tricuspid valve intervention: mid-term results from the international TriValve registry. *JACC Cardiovasc Interv*. 2019;12:155–165. doi: 10.1016/j.jcin.2018.10.022
137. Gammie JS, Chu MWA, Falk V, Overbey JR, Moskowitz AJ, Gillinov M, Mack MJ, Voisine P, Krane M, Yerokun B, et al; CTSN Investigators. Concomitant tricuspid repair in patients with degenerative mitral regurgitation. *N Engl J Med*. 2022;386:327–339. doi: 10.1056/NEJMoa2115961
138. Watkins DA, Johnson CO, Colquhoun SM, Karthikeyan G, Beaton A, Bukhman G, Forouzanfar MH, Longenecker CT, Mayosi BM, Mensah GA, et al. Global, regional, and national burden of rheumatic heart disease, 1990-2015. *N Engl J Med*. 2017;377:713–722. doi: 10.1056/NEJMoa1603693
139. Nunes MCP, Sable C, Nascimento BR, Lima EM, da Silva JLP, Diamantino AC, Oliveira KKB, Okello E, Aliku T, Lwabi P, et al. Simplified echocardiography screening criteria for diagnosing and predicting progression of latent rheumatic heart disease. *Circ Cardiovasc Imaging*. 2019;12:e007928. doi: 10.1161/CIRCIMAGING.118.007928
140. Nascimento BR, Beaton AZ, Nunes MC, Diamantino AC, Carmo GA, Oliveira KK, Oliveira CM, Meira ZM, Castilho SR, Lopes EL, et al; PROVAR (Programa de RastreamentO da VAlvopatia Reumática) Investigators. Echocardiographic prevalence of rheumatic heart disease in Brazilian schoolchildren: data from the PROVAR study. *Int J Cardiol*. 2016;219:439–445. doi: 10.1016/j.ijcard.2016.06.088
141. Ploutz M, Lu JC, Scheel J, Webb C, Ensing GJ, Aliku T, Lwabi P, Sable C, Beaton A. Handheld echocardiographic screening for rheumatic heart disease by non-experts. *Heart*. 2016;102:35–39. doi: 10.1136/heartjnl-2015-308236
142. Shrestha NR, Karki P, Mahto R, Gurung K, Pandey N, Agrawal K, Rothenbuhler M, Urban P, Juni P, Pilgrim T. Prevalence of subclinical rheumatic heart disease in eastern Nepal: a school-based cross-sectional study. *JAMA Cardiol*. 2016;1:89–96. doi: 10.1001/jamacardio.2015.0292
143. Clark BC, Krishnan A, McCarter R, Scheel J, Sable C, Beaton A. Using a low-risk population to estimate the specificity of the World Heart Federation criteria for the diagnosis of rheumatic heart disease. *J Am Soc Echocardiogr*. 2016;29:253–258. doi: 10.1016/j.echo.2015.11.013
144. Engelman D, Wheaton GR, Mataika RL, Kado JH, Colquhoun SM, Remenyi B, Steer AC. Screening-detected rheumatic heart disease can progress to severe disease. *Heart Asia*. 2016;8:67–73. doi: 10.1136/heartasia-2016-010847
145. Bertaina G, Rouchon B, Huon B, Guillot N, Robillard C, Noel B, Nadra M, Tribouilloy C, Marijon E, Jouven X, et al. Outcomes of borderline rheumatic heart disease: a prospective cohort study. *Int J Cardiol*. 2017;228:661–665. doi: 10.1016/j.ijcard.2016.11.234
146. Zuhlke L, Engel ME, Lemmer CE, van de Wall M, Nkepu S, Meiring A, Bestawros M, Mayosi BM. The natural history of latent rheumatic heart disease in a 5 year follow-up study: a prospective observational study. *BMC Cardiovasc Disord*. 2016;16:46. doi: 10.1186/s12872-016-0225-3
147. Beaton A, Aliku T, Dewyer A, Jacobs M, Jiang J, Longenecker CT, Lubega S, McCarter R, Mirabel M, Mirembe G, et al. Latent rheumatic heart disease: identifying the children at highest risk of unfavorable outcome. *Circulation*. 2017;136:2233–2244. doi: 10.1161/CIRCULATIONAHA.117.029936
148. Scheel A, Ssinabulya I, Aliku T, Bradley-Hewitt T, Clauss A, Clauss S, Crawford L, DeWyer A, Donofrio MT, Jacobs M, et al. Community study to uncover the full spectrum of rheumatic heart disease in Uganda. *Heart*. 2019;105:60–66. doi: 10.1136/heartjnl-2018-313171
149. Hovis IW, Namuyonga J, Kisitu GP, Ndagire E, Okello E, Longenecker CT, Sanyahumbi A, Sable CA, Penny DJ, Lwabi P, et al. Decreased prevalence of rheumatic heart disease confirmed among HIV-positive youth. *Pediatr Infect Dis J*. 2019;38:406–409. doi: 10.1097/INF.0000000000002161
150. Zühlke L, Engel ME, Karthikeyan G, Rangarajan S, Mackie P, Cupido B, Mauff K, Islam S, Joachim A, Daniels R, et al. Characteristics, complications, and gaps in evidence-based interventions in rheumatic heart disease: the Global Rheumatic Heart Disease Registry (the REMEDY study). *Eur Heart J*. 2015;36:1115–1122a. doi: 10.1093/eurheartj/ehu449
151. Longenecker CT, Morris SR, Aliku TO, Beaton A, Costa MA, Kamya MR, Kityo C, Lwabi P, Mirembe G, Nampijja D, et al. Rheumatic heart disease treatment cascade in Uganda. *Circ Cardiovasc Qual Outcomes*. 2017;10:e004037. doi: 10.1161/CIRCOUTCOMES.117.004037
152. Liao YB, Wang TKM, Wang MTM, Ramanathan T, Wheeler M. Meta-analysis of mitral valve repair versus replacement for rheumatic mitral valve disease. *Heart Lung Circ*. 2022;31:705–710. doi: 10.1016/j.hlc.2021.11.011
153. Elzeneini M, Ashraf H, Mahmoud A, Elgendy IY, Elbadawi A, Assaf Y, Anderson RD, Jneid H. Outcomes of mitral transcatheter edge-to-edge repair in patients with rheumatic heart disease. *Am J Cardiol*. 2023;192:166–173. doi: 10.1016/j.amjcard.2023.01.034
154. Roth GA, Dwyer-Lindgren L, Bertozzi-Villa A, Stubbs RW, Morozoff C, Naghavi M, Mokdad AH, Murray CJL. Trends and patterns of geographic variation in cardiovascular mortality among US counties, 1980-2014. *JAMA*. 2017;317:1976–1992. doi: 10.1001/jama.2017.4150
155. Zuhlke L, Karthikeyan G, Engel ME, Rangarajan S, Mackie P, Cupido-Katya Mauff B, Islam S, Daniels R, Francis V, Ogendo S, et al. Clinical outcomes in 3343 children and adults with rheumatic heart disease from 14 low- and middle-income countries: two-year follow-up of the Global Rheumatic Heart Disease Registry (the REMEDY study). *Circulation*. 2016;134:1456–1466. doi: 10.1161/CIRCULATIONAHA.116.024769
156. Wood AD, Mannu GS, Clark AB, Tiamkao S, Kongbunkiat K, Bettencourt-Silva JH, Sawanyawisuth K, Kasemsap N, Barlas RS, Mamas M, et al. Rheumatic mitral valve disease is associated with worse outcomes in stroke: a Thailand national database study. *Stroke*. 2016;47:2695–2701. doi: 10.1161/STROKEAHA.116.014512
157. Beaton A, Okello E, Scheel A, DeWyer A, Ssembatya R, Baaka O, Namisanvu H, Njeri A, Matovu A, Namagembe I, et al. Impact of heart disease on maternal, fetal and neonatal outcomes in a low-resource setting. *Heart*. 2018;105:755–760. doi: 10.1136/heartjnl-2018-313810
158. Jaiteh LES, Drammeh L, Anderson ST, Mendy J, Ceesay S, D'Alessandro U, Carapetis J, Mirabel M, Erhart A. Rheumatic heart disease in The Gambia: clinical and valvular aspects at presentation and evolution under penicillin prophylaxis. *BMC Cardiovasc Disord*. 2021;21:503. doi: 10.1186/s12872-021-02308-8
159. Parks T, Kado J, Miller AE, Ward B, Heenan R, Colquhoun SM, Barnighausen TW, Mirabel M, Bloom DE, Bailey RL, et al. Rheumatic heart disease-attributable mortality at ages 5-69 years in Fiji: a five-year, national, population-based record-linkage cohort study. *PLoS Negl Trop Dis*. 2015;9:e0004033. doi: 10.1371/journal.pntd.0004033
160. Global Burden of Disease Study and Institute for Health Metrics and Evaluation. University of Washington. Accessed August 2, 2023. http://ghdx.healthdata.org/
161. Wong CY, Zhu W, Aurigemma GP, Furukawa N, Teshale EH, Huang YA, Peters PJ, Hoover KW. Infective endocarditis among persons aged 18-64 years living with human immunodeficiency virus, hepatitis C infection, or opioid use disorder, United States, 2007-2017. *Clin Infect Dis*. 2021;72:1767–1781. doi: 10.1093/cid/ciaa372
162. Yang X, Chen H, Zhang D, Shen L, An G, Zhao S. Global magnitude and temporal trend of infective endocarditis, 1990-2019: results from the Global Burden of Disease Study. *Eur J Prev Cardiol*. 2022;29:1277–1286. doi: 10.1093/eurjpc/zwab184
163. Slipczuk L, Codolosa JN, Davila CD, Romero-Corral A, Yun J, Pressman GS, Figueredo VM. Infective endocarditis epidemiology over five decades: a systematic review. *PLoS One*. 2013;8:e82665. doi: 10.1371/journal.pone.0082665
164. Deo SV, Raza S, Kalra A, Deo VS, Altarabsheh SE, Zia A, Khan MS, Markowitz AH, Sabik JF 3rd, Park SJ. Admissions for infective endocarditis in intravenous drug users. *J Am Coll Cardiol*. 2018;71:1596–1597. doi: 10.1016/j.jacc.2018.02.011
165. Schranz AJ, Fleischauer A, Chu VH, Wu LT, Rosen DL. Trends in drug use-associated infective endocarditis and heart valve surgery, 2007 to 2017: a study of statewide discharge data. *Ann Intern Med*. 2019;170:31–40. doi: 10.7326/M18-2124
166. Pasquali SK, He X, Mohamad Z, McCrindle BW, Newburger JW, Li JS, Shah SS. Trends in endocarditis hospitalizations at US children's hospitals: impact of the 2007 American Heart Association antibiotic prophylaxis guidelines. *Am Heart J*. 2012;163:894–899. doi: 10.1016/j.ahj.2012.03.002
167. Wilson W, Taubert KA, Gewitz M, Lockhart PB, Baddour LM, Levison M, Bolger A, Cabell CH, Takahashi M, Baltimore RS, et al. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group [published correction appears in Circulation. 2007;116:e7376–e377]. *Circulation*. 2007;116:1736–1754. doi: 10.1161/CIRCULATIONAHA.106.183095

168. Katan O, Michelena HI, Avierinos JF, Mahoney DW, DeSimone DC, Baddour LM, Suri RM, Enriquez-Sarano M. Incidence and predictors of infective endocarditis in mitral valve prolapse: a population-based study. *Mayo Clin Proc*. 2016;91:336–342. doi: 10.1016/j.mayocp.2015.12.006
169. Snygg-Martin U, Giang KW, Dellborg M, Robertson J, Mandalenakis Z. Cumulative incidence of infective endocarditis in patients with congenital heart disease: a nationwide, case-control study over nine decades. *Clin Infect Dis*. 2021;73:1469–1475. doi: 10.1093/cid/ciab478
170. Del Val D, Abdel-Wahab M, Linke A, Durand E, Ihlemann N, Urena M, Pellegrini C, Giannini F, Landt M, Auffret V, et al. Temporal trends, characteristics, and outcomes of infective endocarditis after transcatheter aortic valve replacement. *Clin Infect Dis*. 2021;73:e3750–e3758. doi: 10.1093/cid/ciaa1941
171. Stortecky S, Heg D, Tueller D, Pilgrim T, Muller O, Noble S, Jeger R, Toggweiler S, Ferrari E, Taramasso M, et al. Infective endocarditis after transcatheter aortic valve replacement. *J Am Coll Cardiol*. 2020;75:3020–3030. doi: 10.1016/j.jacc.2020.04.044
172. Zegri-Reiriz I, de Alarcón A, Muñoz P, Martínez Sellés M, González-Ramallo V, Miro JM, Falces C, Gonzalez Rico C, Kortajarena Urkola X, Lepe JA, et al. Infective endocarditis in patients with bicuspid aortic valve or mitral valve prolapse. *J Am Coll Cardiol*. 2018;71:2731–2740. doi: 10.1016/j.jacc.2018.03.534
173. Chu VH, Park LP, Athan E, Delahaye F, Freiberger T, Lamas C, Miro JM, Mudrick DW, Strahilevitz J, Tribouilloy C, et al; International Collaboration on Endocarditis (ICE) Investigators. Association between surgical indications, operative risk, and clinical outcome in infective endocarditis: a prospective study from the International Collaboration on Endocarditis. *Circulation*. 2015;131:131–140. doi: 10.1161/CIRCULATIONAHA.114.012461
174. Iversen K, Ihlemann N, Gill SU, Madsen T, Elming H, Jensen KT, Bruun NE, Hofsten DE, Fursted K, Christensen JJ, et al. Partial oral versus intravenous antibiotic treatment of endocarditis. *N Engl J Med*. 2019;380:415–424. doi: 10.1056/NEJMoa1808312
175. Bundgaard H, Ihlemann N, Gill SU, Bruun NE, Elming H, Madsen T, Jensen KT, Fursted K, Christensen JJ, Schultz M, et al. Long-term outcomes of partial oral treatment of endocarditis. *N Engl J Med*. 2019;380:1373–1374. doi: 10.1056/NEJMc1902096
176. Friedrich C, Salem M, Puehler T, Panholzer B, Herbers L, Reimers J, Hummitzsch L, Cremer J, Haneya A. Sex-specific risk factors for short-and long-term outcomes after surgery in patients with infective endocarditis. *J Clin Med*. 2022;11:1875. doi: 10.3390/jcm11071875
177. Lalani T, Chu VH, Park LP, Cecchi E, Corey GR, Durante-Mangoni E, Fowler VG Jr, Gordon D, Grossi P, Hannan M, et al; International Collaboration on Endocarditis–Prospective Cohort Study Investigators. In-hospital and 1-year mortality in patients undergoing early surgery for prosthetic valve endocarditis. *JAMA Intern Med*. 2013;173:1495–1504. doi: 10.1001/jamainternmed.2013.8203
178. Agha A, Nazir S, Minhas AMK, Kayani W, Issa R, Moukarbel GV, DeAnda A, Cram P, Jneid H. Demographic and regional trends of infective endocarditis-related mortality in the United States, 1999 to 2019. *Curr Probl Cardiol*. 2023;48:101397. doi: 10.1016/j.cpcardiol.2022.101397
179. Ware AL, Tani LY, Weng HY, Wilkes J, Menon SC. Resource utilization and outcomes of infective endocarditis in children. *J Pediatr*. 2014;165:807–812.e1. doi: 10.1016/j.jpeds.2014.06.026
180. Abdallah L, Remadi JP, Habib G, Salaun E, Casalta JP, Tribouilloy C. Long-term prognosis of left-sided native-valve *Staphylococcus aureus* endocarditis. *Arch Cardiovasc Dis*. 2016;109:260–267. doi: 10.1016/j.acvd.2015.11.012
181. *Health, United States, 2017: With Special Feature on Mortality*. National Center for Health Statistics. 2018:Table 96.
182. Goldsweig AM, Tak HJ, Chen LW, Aronow HD, Shah B, Kolte D, Desai NR, Szerlip M, Velagapudi P, Abbott JD. Relative costs of surgical and transcatheter aortic valve replacement and medical therapy. *Circ Cardiovasc Interv*. 2020;13:e008681. doi: 10.1161/CIRCINTERVENTIONS.119.008681

# 24. VENOUS THROMBOEMBOLISM (DEEP VEIN THROMBOSIS AND PULMONARY EMBOLISM), CHRONIC VENOUS INSUFFICIENCY, PULMONARY HYPERTENSION

*See Charts 24-1 and 24-2*

Click here to return to the Table of Contents

Click here to return to the Abbreviations

In this chapter, 2021 mortality data come from unpublished NHLBI tabulations using NVSS [1] and CDC WONDER.[2] Hospital discharge data, from 2020, come from unpublished NHLBI tabulations using HCUP.[3]

## Pulmonary Embolism

### *ICD-9* 415.1; *ICD-10* I26.

2021, United States: Underlying cause mortality—9452. Any-mention mortality—56 038.

2020, United States: Hospital discharges—181 550 (principal diagnosis), 432 580 (all-listed diagnoses).

## Deep Vein Thrombosis

### *ICD-9* 451.1, 451.2, 451.81, 451.9, 453.0, 453.1, 453.2, 453.3, 453.4, 453.5, 453.9; *ICD-10* I80.1, I80.2, I80.3, I80.9, I82.0, I82.1, I82.2, I82.3, I82.4, I82.5, I82.9.

2021, United States: Underlying cause mortality—3664. Any-mention mortality—24 722.

2020, United States: Hospital discharges—70 915 (principal diagnosis), 666 535 (all-listed diagnoses).

## Venous Thromboembolism

### *Incidence*

*(See Charts 24-1 and 24-2)*

- VTE includes both PE and DVT. In 2020, there were an estimated ≈432 580 cases of PE[3] (Chart 24-1), ≈666 535 cases of DVT[3] (Chart 24-2), and ≈1 199 115 total VTE cases in the United States in inpatient settings. However, it is likely that these numbers are even higher. An analysis of health care claims data between 2011 and 2018 that included ≈200 000 individuals with VTE diagnosis observed that 37.6% of all patients were treated as outpatients. Furthermore, 17.9% of those with PE were treated outside of the hospital setting.[4]
- A study in individuals in Oklahoma (whose ethnic profile is similar to that of the US population) observed an age-standardized incidence of 2.47 (95% CI, 2.39–2.55), 1.47 (95% CI, 1.41–1.54), and 0.99 (95% CI, 0.93–1.04) per 1000 person-years for VTE, DVT, and PE, respectively.[5]
  - In this analysis, the incidence in the Black population for VTE, DVT, and PE was 3.25 (95% CI, 3.02–3.49), 1.97 (95% CI, 1.80–2.16), and 1.27 (95% CI, 1.13–1.43) per 1000 person-years, respectively, much higher than in NH White individuals (2.71 [95% CI, 2.61–2.63], 1.59 [95% CI, 1.50–1.67], and 1.12 [95% CI, 1.06–1.20] per 1000 person-years), Hispanic individuals (0.67 [95% CI, 0.54–0.82], 0.39 [95% CI, 0.30–0.51], and 0.27 [95% CI, 0.19–0.37] per 1000 person-years), and Asian/Pacific Islander individuals (0.63 [95% CI, 0.43–0.91], 0.41 [95% CI, 0.26–0.65], and 0.22 [95% CI, 0.11–0.41] per 1000 person-years).
  - The MESA cohort yielded similar findings, with Black participants having an incidence rate of VTE at 4.02 per 1000 person-years, which was higher compared with White (2.98 per 1000 person-years), Hispanic (2.08 per 1000 person-years), and Chinese (0.79 per 1000 person-years) participants.[6]
- Data from >1.8 million outpatient surgeries in the United States between 2005 and 2016 showed an incidence of 0.19% postoperative VTE.[7]
  - A study using data from 73 million childbirths in the United States found a VTE incidence of 6.6 per 10 000 deliveries.[8]
- VTE is a prevalent disease in the hospitalized patients setting:
  - In an analysis of administrative data from 204 hospitals in Illinois involving 22 244 hospitalizations with a principal diagnosis of PE, ≈50% of patients hospitalized were <65 years of age.[9] In all age groups, NH Black males and females had higher rates of PE hospitalization (14.5 [95% CI, 2.0–103.2] and 16.5 [95% CI, 2.3–117.5] per 10 000 population, respectively) compared with NH White males and females (8.8 [95% CI, 1.2–62.8] and 9.3 [95% CI, 1.3–66.0] per 10 000 population, respectively). Overall, NH Black individuals were almost twice as likely to be

The 2024 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2024. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

hospitalized for PE as NH White individuals (rate ratio, 1.9 [95% CI, 1.5–2.3]) after adjustment for age and sex.
  - In a meta-analysis comprising 3170 patients admitted for acute exacerbation of chronic obstructive pulmonary disease, there was a high prevalence of PE and DVT in this clinical profile (pooled prevalence, 17.2% [95% CI, 13.4%–21.3%] and 7.1% [95% CI, 3.7%–11.4%], respectively).[10]
  - A study with ≈5000 patients in a Level 1 trauma center found that those who underwent screening duplex ultrasonography of the legs had an early DVT incidence of 3.3%. Furthermore, during hospitalization, 3.9% of the total sample were diagnosed with VTE.[11]
  - An analysis of the National Surgical Quality Improvement Program observed a high rate of VTE in 5003 patients undergoing colorectal surgery for inflammatory bowel disease (VTE incidence, 2.49%).[12]
- Several studies since 2020 with data from the COVID-19 pandemic have addressed the incidence and prevalence of VTE in different settings:
  - Data from ≈85 000 US patients hospitalized with COVID-19 revealed a 90-day absolute VTE risk of 9.5% (95% CI, 9.2%–9.7%) before vaccine availability. In the first 6 months of vaccine release, the absolute risk of VTE was 10.9% (95% CI, 10.6%–11.1%). Furthermore, it should be emphasized that the patients were not tracked according to their vaccination status, and no comparisons between periods or adjustments were made according to risk factors.[13]
  - A study with 10 871 patients with COVID-19 admitted in New York observed an incidence of 1.09% in the initial presentation at the hospital.[14]
  - Patients admitted to the ICU had 2- to 3-fold higher incidence of VTE than those who did not need intensive care (PE: pooled incidence, 24.7% [95% CI, 18.6%–32.1%] versus 10.5% [95% CI, 5.1%–20.2%], respectively; DVT: pooled incidence, 21.2% [95% CI, 11.1%–36.8%] versus 7.4% [95% CI, 3.2%–16.2%]).[15]
  - It is important to note that most COVID-19 studies have issues related to selection bias attributable to the severity of the condition of the population admitted in most high-volume tertiary care centers and to the VTE diagnostic protocol; a routine screening showed a much higher VTE incidence compared with centers without a routine screening approach (pooled incidence, 47.5% [95% CI, 25.3%–69.7%] versus 15.1% [95% CI, 8.35%–21.9%]; $P<0.001$).[16]

### Lifetime Risk

- The lifetime risk of VTE at 45 years of age was 8.1% (95% CI, 7.1%–8.7%) overall, 11.5% in Black individuals, 10.9% in those with obesity, 17.1% in individuals with the FVL genetic variant, and 18.2% in people with sickle cell trait or disease, according to data derived from nearly 20 000 participants of 2 US cohorts who were 45 to 99 years of age.[17]

### Secular Trends

#### (See Charts 24-1 and 24-2)

- The HCUP NIS (Chart 24-1) shows increasing numbers of hospitalized cases for all-listed diagnoses of PE from 1996 to 2020, accompanied by a progressive increase in the in-hospital death rate. Although the all-listed diagnoses (Chart 24-2) show that the number of hospitalized DVT cases also increased from 2005 to 2020, discharges with DVT as a principal diagnosis have fallen in the past 5 years.[3]
- From 1999 to 2017, NIS data showed a consistent trend of reduced mortality rates among patients with high-risk PE, whether treated with anticoagulants alone or with thrombolytic therapy. The mortality rate decreased from 72.7% in 1999 to 49.8% in 2017 ($P<0.001$), despite a clear increase in both the absolute number (104 procedures in 1999 versus 955 in 2017; $P<0.001$) and relative rate of high-risk patients treated (6.3% in 1999 versus 19.3% in 2017; $P<0.001$) with thrombolytic therapy.[18]
- Another NIS analysis from 2000 to 2018 showed a progressive increase in incidence of DVT in vaginal deliveries (average annual percent change, 2.5% [95% CI, 1.5%–3.5%]) and in incidence of PE in both vaginal and cesarean deliveries (average annual percent change, 8.7% [95% CI, 6.0%–11.5%] and 4.9% [95% CI, 3.6%–6.2%], respectively).[8]
- There is also a rising incidence of cancer-associated VTE over time, as seen in cases of pancreatic (cumulative incidence, 8.92% [95% CI, 8.31%–9.56%] in 2005–2007 versus 11.9% [95% CI, 11.3%–12.5%] in 2014–2017), lung (cumulative incidence, 5.44% [95% CI, 5.21%–5.69%] in 2005–2007 versus 7.66% [95% CI, 7.39%–7.94%] in 2014–2017), and breast (cumulative incidence, 0.99% [95% CI, 0.90%–1.08%] in 2005–2007 versus 1.12% [95% CI, 1.04%–1.21%] in 2014–2017; all $P<0.0001$) cancer.[19]
- Despite increasing trends in VTE diagnosis, an 18-year study of >6 million cardiac surgeries in the United States showed a consistent reduction in inpatient deaths after VTE complications (percentage change per year, −6.4%; $P<0.001$).[20]
- In the orthopedic leg surgery setting, a study using Medicare data between 2010 and 2017 found a

decrease in VTE incidence after total knee arthroplasty (in-hospital incidence rate, 0.3% in 2010 and 0.1% in 2017, $P_{trend}$=0.035).[21]

### Risk Factors

- In the GARFIELD-VTE study, 40.8% of 10 868 patients with a VTE diagnosis were considered provoked because VTE occurred subsequent to strong triggering factors or persistent risk factors such as immobilization, trauma, surgery, cancer, or hospitalization in the preceding 3 months.[22] However, in the RIETE registry, ≈55% of the >104 000 patients had at least 1 provoking risk factor. The remainder are classified as unprovoked.[23]
- Hospitalized patients are at particularly high risk of VTE:
  - One study demonstrated that asymptomatic DVT was associated with a greater risk of death among acutely ill hospitalized patients (HR, 2.31 [95% CI, 1.52–3.51]).[24]
  - A retrospective cohort with ≈1 110 000 admissions found the following risk factors for hospital-associated VTE, even after adjustment: active cancer (OR, 1.96 [95% CI, 1.85–2.08]), previous VTE (OR, 1.71 [95% CI, 1.63–1.79]), central line (OR, 1.63 [95% CI, 1.53–1.73]), recent surgery or trauma (OR, 1.50 [95% CI, 1.39–1.61]), known thrombophilia (OR, 1.22 [95% CI, 1.06–1.40]), obesity (OR, 1.12 [95% CI, 1.07–1.16] for BMI >30 kg/m$^2$), infection as cause of admission (OR, 1.07 [95% CI, 1.04–1.11]), and male sex (OR, 1.07 [95% CI, 1.03–1.10]).[25]
- In a cancer-associated VTE scenario, a large study conducted in California with ≈940 000 patients and ≈62 000 VTE cases showed that Black individuals had the highest 1-year cumulative VTE incidence compared with White, Hispanic, and Asian individuals across 12 of 13 most common cancers for both all VTE and PE only. This risk of all VTE remained even after multivariate adjustment, including for SES.[26]
- Independent VTE risk factors beyond the provoking factors noted previously:
  - An individual-level study by the Emerging Risk Factors Collaboration found an association between VTE incidence and age (HR per decade, 2.67 [95% CI, 2.45–2.91]), diabetes (HR, 1.69 [95% CI, 1.33–2.16]), WC (HR, 1.54 [95% CI, 1.37–1.73]), and smoking (HR, 1.38 [95% CI, 1.20–1.58]).[27]
  - Presence of HF was associated with a 3-fold greater VTE risk (HR, 3.13 [95% CI, 2.58–3.80]) in a 2019 publication from the ARIC study. The association was present for both HFpEF and HFrEF.[28]
  - Autoimmune diseases such as giant cell arthritis and polymyalgia rheumatica are risk factors for DVT (IRR, 4.12 [95% CI, 3.13–5.35] and 1.44 [95% CI, 1.20–1.72], respectively) and PE (IRR, 3.99 [95% CI, 2.63–5.81] and 1.79 [95% CI, 1.39–2.28], respectively).[29]
  - Use of testosterone therapy was also associated with doubling of VTE risk in males with and without evidence of hypogonadism.[30] These 2019 findings applied a case-crossover design to a large administrative database.
  - An updated 2020 US Preventive Services Task Force systematic review found, among other benefits and harms, an increased risk of both DVT and PE in postmenopausal females using hormone therapy during the estrogen plus progestin strategy (HR for DVT, 1.87 [95% CI, 1.37–2.54] and HR for PE, 1.98 [95% CI, 1.36–2.87] in a follow-up of 5.6 years) in addition to an increased risk in the postintervention period (HR for DVT, 1.24 [95% CI, 1.01–1.53]) and HR for PE, 1.26 [95% CI, 1.00–1.59] in a cumulative follow-up of 13.2 years).[31] However, in females using an estrogen-only strategy, there was no difference in incidence rates of DVT or PE during the postintervention period (total cumulative follow-up of 13 years).
- In the COVID-19 setting, several studies have shown a higher incidence of VTE in hospitalized COVID-19 patients (admission unit or ICU) compared with those with no SARS-CoV-2 infection:
  - Patients admitted with COVID-19 had a significantly higher risk of VTE compared with those hospitalized with a diagnosis of influenza before 2020 (HR, 1.89 [95% CI, 1.68–2.12]), regardless of whether they had a history of VTE (HR, 1.42 [95% CI, 1.16–1.74]) or not (HR, 2.09 [95% CI, 1.82–2.40]).[13] Among these patients admitted with COVID-19, the risk factors for increased risk of VTE were age, male sex, prior VTE, obesity, cancer history, thrombocytosis, and primary thrombophilia.
  - A study involving ≈800 000 US individuals did not find any evidence of increased risk for VTE after COVID-19 vaccination, regardless of the vaccine brand administered (Janssen, Pfizer, or Moderna).[32]
- A database analysis with ≈5000 US transgender participants observed in the transfeminine population (assigned male at birth) a higher incidence of VTE compared with both cisgender men (risk difference, 4.1 [95% CI, 1.6–6.7] and 16.7 [95% CI, 6.4–27.5] for 2 and 8 years, respectively) and cisgender women (risk difference, 3.4 [95% CI, 1.1–5.6] and 13.7 [95% CI, 4.1–22.7] for 2 and 8 years, respectively).[33] In addition, a 2021 meta-analysis with 9180 transgender patients showed a higher risk of VTE in transfeminine compared with transmasculine

(assigned female at birth) people (OR, 5.29 [95% CI, 2.03–13.79]), with a high heterogeneity probably driven by duration of hormone replacement therapy.[34] To date, there are limited data on the risk of VTE in the transmasculine population compared with cisgender men.
- An analysis in the GARFIELD-VTE study population showed that in pregnant females with VTE, the classic risk factors present were obesity, hospitalization, prior surgery, family history of VTE, and diagnosis of thrombophilia. In addition, there was a lower likelihood of PE.[35]

### Social Determinants of Health/Health Equity

- In 2020, patients from rural areas accounted for 16.4% of all PE (95% CI, 15.7%–17.1%) and 13.7% of all DVT (95% CI, 13.0%–14.4%) hospital discharges.[3]
  - Although the rate of admissions for PE was higher in rural areas than in urban areas (discharges for 100 000 population, 65.6 [95% CI, 62.3–68.9]) versus 47.0 [95% CI, 43.9–50.1] for patients living in large metro areas), the individual spendings were lower for rural inhabitants than for urban inhabitants who were admitted (average hospital charges per stay, $43 153 [95% CI, $41 152–$45 154] versus $68 782 [95% CI, $65 521–$72 043] for those living in large metro areas).
  - There is a similar scenario in those with DVT diagnosis (average hospital charges per stay, $49 085 [95% CI, $46 410–$51 760] for patients living in rural areas versus $68 175 [95% CI, $64 692–$71 658] for patients living in large metro areas).
- In a US cohort of 14 140 patients with diagnosed VTE, Black individuals were less likely to be prescribed DOACs than White individuals (OR, 0.86 [95% CI, 0.77–0.97]). However, Hispanic and Asian individuals had no difference in DOAC prescription compared with White individuals ($P$=0.66 and $P$=0.74, respectively).[36]
- In a 2021 analysis of 65 000 elderly Medicare patients, Black individuals who used both apixaban and warfarin had a higher risk of adverse events after experiencing a VTE compared with White individuals (incidence rates per 100 person-years versus White individuals: recurrent VTE, 2.0 versus 1.4 [apixaban] and 3.3 versus 2.2 [warfarin]; major bleeding, 7.4 versus 3.5 [apixaban] and 10.1 versus 5.3 [warfarin]).[37] Patients with lower SES also had worse outcomes (incidence rates per 100 person-years versus high SES: recurrent VTE, 3.6 versus 2.6 [apixaban] and 3.3 versus 2.7 [warfarin]; major bleeding, 5.7 versus 3.2 [apixaban] and 7.0 versus 5.1 [warfarin]).

### Family History and Genetics

- VTE is highly heritable, estimated to be 47% for males and 40% for females from an analysis of 881 206 full-sibling pairs and 95 198 half-sibling pairs in the Swedish Multi-Generation Register.[38]
- FVL is the most common inherited thrombophilia in populations of European descent (prevalence, 5.2%) but is rare in African (1.2%) and Asian (0.45%) populations.[39] In ARIC, ≈5% of White and <1% of Black people were heterozygous carriers of FVL, and lifetime risk of VTE was 17.1% in individuals with the FVL genetic variant.[17] Pooling data from 36 epidemiological studies showed that risk of VTE was increased 4-fold in people with heterozygous FVL (OR, 4.2 [95% CI, 3.4–5.3]) and 11-fold in those with homozygous FVL (OR, 11.4 [95% CI, 6.8–19.3]) compared with noncarriers.[40]
- Antithrombin deficiency is a rare disease (prevalence, 0.02%–0.2%) that is associated with greatly increased risk of incident VTE (OR, 14.0 [95% CI, 5.5–29.0]).[41] A Bayesian meta-analysis found that for childbearing females with this variant, VTE risk was 7% in the antepartum period and 11% postpartum.[42]
- Whole-exome sequencing of a panel of 55 thrombophilia genes in 64 patients with VTE identified a probable disease-causing genetic variant or variant of unknown significance in 39 of 64 individuals (60.9%).[43]
- GWASs have identified additional common genetic variants associated with VTE risk, including variants in *F5*, *F2*, *F11*, *FGG*, and *ZFPM2*.[44] These common variants individually increase the risk of VTE to a small extent, but a GRS composed of a combination of 5 common variants yielded an OR for VTE risk of 7.5.[45]
- Exome-wide analysis of rare variants in >24 000 individuals of European ancestry and 1858 individuals of African ancestry confirmed previously implicated loci but did not uncover rare novel variants associated with VTE. Similarly, targeted sequencing efforts did not uncover rare novel variants for DVT. However, multiancestry genome-wide GWAS meta-analyses have established >30 novel VTE risk loci.[46,47]
- A GRS including 1 092 045 SNPs was associated with higher odds of incident VTE event (OR, 51% per 1-SD increase in GRS).[47] The risk of VTE in the higher tail end of this GRS was similar to that attributed to monogenic VTE variants. This GRS may guide decision-making on which individuals may benefit from anticoagulant therapy.

### Prevention

- Pharmacological prophylaxis has shown benefit with the use of low-molecular-weight heparin in

critically ill patients (OR for DVT, 0.59 [95% CI, 0.33–0.90]).[48]
  - In an analysis involving ≈5000 high-risk patients for VTE who underwent general surgery, the correct prescription of chemoprophylaxis was associated with lower rates of VTE (OR, 0.58 [95% CI, 0.34–0.95]) and lower mortality (OR, 0.57, [95% CI, 0.34–0.93]).[49]
  - Furthermore, 2 meta-analyses showed benefit of low-molecular-weight heparin over unfractionated heparin in preventing DVT in patients in critical care (OR, 0.72 [95% CI, 0.46–0.98])[48] and patients with trauma (OR for DVT, 0.67 [95% CI, 0.50–0.88]).[50]
  - In patients with cancer, thromboprophylaxis reduces both VTE and DVT by half (RR, 0.51 [95% CI, 0.32–0.81] and 0.53 [95% CI, 0.33–0.87], respectively) with no increase in major bleeding incidence (*P*=0.15).[51]
  - In pregnant females with a history of VTE, there was no superiority of weight-adjusted over fixed-low-dose low-molecular-weight heparin (rate of VTE events up to 6 weeks postpartum, 2% versus 3%; *P*=0.33).[52] For those with VTE risk in the prepartum, peripartum, or postpartum period, it is unclear whether pharmacological prophylaxis brings benefit to this population.[53]
  - DOACs are noninferior to low-molecular-weight heparin in hip fracture scenarios (pooled OR for VTE, 0.52 [95% CI, 0.25–1.11])[54] and are effective in outpatients with cancer (pooled RR for VTE incidence, 0.53 [95% CI, 0.36–0.78]; pooled RR for PE incidence, 0.50 [95% CI, 0.28–0.89]).[55]
  - In patients admitted with COVID-19, a 2022 Cochrane meta-analysis found that a higher dose of anticoagulants resulted in lower risk of PE (pooled RR, 0.46 [95% CI, 0.31–0.70], 4 studies) at the cost of increased risk of major bleeding (pooled RR, 1.78 [95% CI, 1.13–2.80], 4 studies).[56]
- Furthermore, beyond the pharmacological prophylaxis:
  - Elastic stockings play an important role in VTE prevention in individuals on long (>4 hours) airplane flights (OR for DVT, 0.10 [95% CI, 0.04–0.25]),[57] all hospitalized patients (OR for DVT, 0.35 [95% CI, 0.28–0.43]), and surgical patients (OR for DVT, 0.35 [95% CI, 0.28–0.44]; OR for PE, 0.38 [95% CI, 0.15–0.96]).[58]
  - A 2022 Cochrane meta-analysis found that incorporating intermittent pneumatic leg compression into standard VTE drug prevention resulted in a reduction in the incidence of both PE (pooled OR, 0.46 [95% CI, 0.30–0.71]; 15 studies) and DVT (pooled OR, 0.38 [95% CI, 0.21–0.70]; 17 studies). There was no increased risk for orthopedic patients for PE and DVT incidence (*P*=0.82 and *P*=0.69, respectively).[59]
- An early strategy of prophylactic placement of a vena cava filter after major trauma did not result in lower incidence of symptomatic PE or death at 90 days after filter placement (*P*=0.98).[49,60] Even in patients at high risk for VTE, there is no net benefit in extended thromboprophylaxis compared with an inpatient-only strategy (*P*=0.18 for VTE and *P*=0.43 for bleeding).[61,62]

### *Awareness, Treatment, and Control*

- Anticoagulation with oral or parenteral drugs is the mainstay of VTE treatment.
  - After DVT diagnosis, anticoagulants consistently reduced both VTE and DVT recurrence by 66% and 75%, respectively.[63]
  - A study on anticoagulant strategy in ≈64 000 discharges showed an incidence of VTE recurrence with apixaban, rivaroxaban, and warfarin of 9.8 (95% CI, 6.8–13.6), 11.6 (95% CI, 8.5–15.4), and 13.6 (95% CI, 10.2–17.6) per 100 000 person-years.[64] The only statistically significant difference in VTE recurrence was observed in the analysis that compared patients using apixaban with those who were prescribed warfarin (HR, 0.69 [95% CI, 0.49–0.99]).
  - An on-treatment analysis with GARFIELD-VTE data showed a lower all-cause mortality in the DOAC group (eg, rivaroxaban, apixaban, edoxaban, and dabigatran) versus the vitamin K antagonists group (eg, warfarin; HR, 0.57 [95% CI, 0.42–0.79] in a mean follow-up of 12 months).[65]
  - A retrospective analysis with Medicare patients who presented cancer-related VTE observed that the use of DOACs was associated with lower mortality (HR, 0.85 [95% CI, 0.78–0.91]).[66]
  - Retrospective analyses of 5 US claims databases in a specific group of patients observed that the use of apixaban compared with warfarin was associated with the following:
    - Lower recurrent VTE (HR, 0.78 [95% CI, 0.70–0.87]), major bleeding (HR, 0.75 [95% CI, 0.67–0.83]), and intracranial bleeding (HR, 0.56 [95% CI, 0.42–0.76]) in those with high risk of bleeding[67];
    - Lower VTE recurrence (HR, 0.78 [95% CI, 0.66–0.92]) and major bleeding (HR, 0.76 [95% CI, 0.65–0.88]) in patients with VTE diagnosis and prior CKD[68]; and
    - Lower VTE recurrence (HR, 0.58 [95% CI, 0.43–0.77]) and major bleeding (HR, 0.78 [95% CI, 0.62–0.98]) in patients on dialysis.[69]
- A 2021 meta-analysis observed that inferior vena cava filters reduced early (within 3 months) new PE occurrence (pooled RR, 0.17 [95% CI, 0.04–0.65])

but not recurrent PE (*P*=0.33). Furthermore, inferior vena cava filter did not provide a reduction in mortality either at 3 months or at the entire follow-up (*P*=0.13 and 0.61, respectively).[70]
  - In patients who had cancer-related DVT, a US cohort analysis found a significant improvement in PE-free survival in those who underwent vena cava filter placement (HR, 0.69 [95% CI, 0.64–0.75]) regardless of the underlying neoplasm.[71]
- Systemic thrombolysis did not result in a reduction in all-cause mortality (*P*=0.56), lowering the risk of PTS after 6 months (pooled RR, 0.78 [95% CI, 0.66–0.93]) and 5 years (pooled RR, 0.56 [95% CI, 0.43–0.73]) at the cost of a higher bleeding rate (RR, 2.45 [95% CI, 1.58–3.78]).[72] Furthermore, percutaneous pharmacomechanical catheter-directed thrombolysis also showed no benefit for mortality (*P*=0.83).[73]
- Although malignancy is a relevant risk factor with an incidence of 2.4% in 6 months after VTE diagnosis,[74] a Cochrane meta-analysis found no evidence for additional positron emission tomography/CT testing after a first unprovoked VTE because there was no benefit in any outcomes: cancer and all-cause mortality (*P*=0.25 and *P*=0.66, respectively), VTE-related morbidity (*P*=0.96), time to cancer diagnosis (*P*=0.88), and malignancy diagnosis in the early or advanced stage (*P*=0.36 and *P*=1.00, respectively).[75]

### Mortality

- A study based on the analysis of data from CDC WONDER found a significant increase in mortality related to PE during the COVID-19 pandemic compared with the preceding years.[76] The AAMR per 100 000 people was 12.2 (95% CI, 12.1–12.3) in 2020 compared with 9.6 (95% CI, 9.5–9.7) in 2019 and 9.4 (95% CI, 9.3–9.5) in 2018.
- The GARFIELD-VTE study observed a 3-year mortality of 10.9% after a VTE. The incidence of death decreases gradually from the first month (incidence per 100 person-years, 10.69 [95% CI, 8.72–13.11]) compared with months 2 to 12 (6.54 [95% CI, 6.05–7.07]), the second year (3.1 [95% CI, 2.75–3.50]), and the third year (2.0 [95% CI, 1.72–2.34]).[77]
- In the hospitalized population with VTE diagnosis, patients with COVID-19 had at least a 3-fold risk of death compared with those admitted for influenza infection (HR for 30-day all-cause mortality, 2.96 [95% CI, 1.84–4.76] in the prevaccination period and 3.80 [95% CI, 2.41–6.00] at the beginning of vaccine availability).[13] When stratified by disease severity, the OR for mortality in the ICU was 2.63 (95% CI, 1.49–4.67) and for patients on mechanical ventilation was 3.14 (95% CI, 1.97–5.02).[78]
- Asymptomatic DVTs diagnosed with compression ultrasound were associated with a 3-fold increased risk (HR, 2.87 [95% CI, 1.48–5.57]) of short-term all-cause mortality in patients with acute medical illness relative to those with no evidence of DVT.[79]

### Complications

- VTE is a chronic disease with episodic recurrence.
  - An analysis of a US health claims database between January 2010 and December 2019 (with ≈14 000 patients with a prior diagnosed VTE) observed a 6-month VTE recurrence rate of 6.1%, with higher recurrence in patients with arrhythmia (HR, 1.46 [95% CI, 1.07–1.99]), congestive HF (HR, 1.33 [95% CI, 1.07–1.66]), and CKD (HR, 1.24 [95% CI, 1.02–1.50]).[80]
  - Data from GARFIELD-VTE showed a 3-year incidence of recurrent VTE of 3.47 (incidence per 100 person-years [95% CI, 3.24–3.70]) and in the first year of follow-up (incidence per 100 person-years, 5.34 [95% CI, 4.89–5.82]).[77]
  - Although studies have shown an increased risk of VTE in females using estrogen-containing contraceptives, a 2022 Cochrane meta-analysis found no association with recurrent events, whether in a follow-up of ≤1, 1 to 5, or >5 years. The meta-analysis reported a low VTE recurrence (incidence per 100 patient-years, 1.57 [95% CI, 1.10–2.23]).[81]
- Major bleeding is a potentially life-threatening adverse event that can occur during VTE treatment:
  - According to the GARFIELD-VTE data, the main site of major bleeding is the gastrointestinal tract (31.6% of all events) followed by the uterus (13%). Hemorrhagic stroke accounted for 5.5% of the total major bleeding episodes.[77]
  - Data from NIS with >138 000 Americans with proximal DVT indicated an intracranial bleeding rate of 0.2% in patients using anticoagulants and 0.7% in those receiving catheter-directed thrombolysis.[82] In this population, the main predictors of bleeding risk were a history of stroke (OR, 19.4 [95% CI, 8.76–42.77]), age >74 years (OR, 2.20 [95% CI, 1.17–4.28]), and CKD (OR, 2.20 [95% CI, 1.06–4.68]). Centers with expertise were predictors for fewer complications (OR, 0.42 [95% CI, 0.21–0.84]).
  - A study with ≈64 000 US patients followed up for 90 days after a VTE hospitalization showed no difference in major bleeding among apixaban, rivaroxaban, and warfarin prescriptions.[64]
- Superior vena cava syndrome is a complication of thoracic vein thrombosis. Data from ≈1 000 000 visits to 950 US EDs between 2010 and 2018 showed a superior vena cava syndrome incidence of 3.5 per 100 000 emergency admissions.[83] The

most common causes were cancer (10.6%), cardiac implantable electronic devices (7.5%), and intravascular catheters (4.5%).
- PTS/venous stasis syndrome and venous stasis ulcers are important complications of proximal lower-extremity DVT, which are discussed in greater depth in the Chronic Venous Insufficiency section of this chapter. Even under anticoagulation, 2 pooled analyses found incidences for PTS of 45% in the short term[84] and up to 70% in the long term (follow-up >5 years).[72] In this context, DOAC drugs appear to prevent PTS (OR, 0.46 [95% CI, 0.33–0.63]).[84]

### *Health Care Use: Hospital Discharges/Ambulatory Care Visits*

- In 2019, the NAMCS data, which tracks medical care provided by office-based physicians in the United States, indicated that there were ≈1 593 000 physician office visits for DVT (unpublished NHLBI tabulation using NAMCS[85]).
- A study that examined 133 414 US patients with a DVT diagnosis in the ED found that the more proximal the DVT site was, the higher the hospitalization rate was (28% distal, 54% proximal, 64% pelvic, and 78% inferior vena cava; $P<0.0001$).[86]

### *Costs*

- In 2020, the aggregate charges in hospitalized patients amounted to ≈$15.5 billion compared with ≈$10 billion in 2018. Medicare and Medicaid covered two-thirds of the total charge, whereas private insurance accounted for more than one-quarter of all payments.[3]
- The incidence of VTE causes a 2-fold increase in annual costs in rheumatoid arthritis (adjusted annual total health care cost ratio for DVT and PE in the disease-modifying antirheumatic drug–naive population, 2.04 [95% CI, 1.77–2.35] and 2.58 [95% CI, 2.06–3.24], respectively).[87] In those with inflammatory bowel disease, VTE increases 1-year costs 3-fold (cost after VTE, $67 054 versus $22 424; $P<0.01$).[88]
- In a registry of 3 million patients who underwent cardiac surgery, an additional mean cost of $13 000 was observed among those with postoperative VTE diagnosis.[89]

### *Global Burden*

- The Computerized Registry of Patients With Venous Thromboembolism registry, a database from 26 countries (including 6 US centers) that includes ≈113 000 patients, found a 30-day mortality of 2.58% for DVT and 5.11% for PE.[90] The risk of death was lower for distal DVT compared with proximal DVT at a 1-year follow-up (HR, 0.72 [95% CI, 0.64–0.82]).[88]
- In hospitalized patients with COVID-19, the incidence of DVT was higher in Asia (unadjusted pooled incidence, 40.8% [IQR, 24.6%–54.5%]) compared with the Middle East (15.6% [IQR, 8.6%–16.4%]), North America (12.8% [IQR, 3.8%–24.2%]), and Europe (8.0% [IQR, 3.9%–14.9%]).[91]
  - However, the incidence of PE was higher in the Middle East (unadjusted pooled incidence, 16.2% [IQR, 8.1%–24.4%]) and Europe (14.6% [IQR, 6.4%–26.3%]) than in North America (5.0% [IQR, 3.0%–11.8%]) and Asia (3.2% [IQR, 1.9%–3.5%]).

## Chronic Venous Insufficiency

### *ICD-10* I87.2.

2021, United States: Underlying cause mortality—60. Any-mention mortality—896.

### *Prevalence*

- A study including 636 US health care workers (median age, 42 years; 93% females) found a high prevalence of CVI with presence of varicose veins in 20% of the participants.[92]
- Pain is the most common symptom (29%) followed by swelling, heaviness, fatigue, and cramping. Spider veins are seen in 7%, and varicosities and skin changes are seen in 4% each. Stasis ulcer is present in 1% of all patients with CVI.[93]

### *Incidence*

- Data from the Mass General Brigham health care system, with >156 000 females after pregnancy, showed an incidence of 3% in 10 years of follow-up (incidence of varicose veins, 3.0% [95% CI, 2.9%–3.2%]) and 7% in 20 years of follow-up (incidence of varicose veins, 7.3% [95% CI, 7.0%–7.6%]).[94]

### *Risk Factors*

- This study identified risk factors for varicose veins, including age (HR: 35–40 years of age, 1.61, [95% CI, 1.48–1.77]; 40–50 years of age, 1.66 [95% CI, 1.51–1.84]; and >50 years of age, 1.91 [95% CI, 1.63–2.23], all compared with individuals <35 years of age), number of births (HR: 1 delivery, 1.78 [95% CI, 1.55–1.99]; ≥6 deliveries, 4.83 [95% CI, 2.15–10.90]), excessive weight gain during pregnancy (HR, 1.44 [95% CI, 1.09–1.91]), and post-term pregnancy (HR, 1.12 [95% CI, 1.02–1.21]).[94]
- The ARIC researchers found an association between low physical function (evaluated by a score that analyzes components such as chair stands, standing balance, and gait speed) and incidence of varicose veins (HR, 1.77 [95% CI, 1.04–3.00] between those with scores ≤6 and >6).[95]

- PTS, a subset of CVI, has specific risk factors that can be identified at the time of or after DVT: recurrent ipsilateral DVT (OR, 6.30 [95% CI, 1.5–26.9]), obesity (OR, 2.63 [95% CI, 1.47–4.70]), CKD (OR, 2.21 [95% CI, 1.45–3.39]), active cancer (OR, 3.66 [95% CI, 2.30–5.84]), more extensive DVT, poor quality of anticoagulation, and ongoing symptoms or signs of DVT 1 month after diagnosis.[96,97]
  - Using data from 762 patients with DVT, Rabinovich et al[98] developed a clinical prediction model for PTS. High-risk predictors were index DVT in the iliac vein, BMI of ≥35 kg/m$^2$, and moderate to severe Villalta score (PTS severity) at DVT diagnosis (OR, 5.9 [95% CI, 2.1–16.6] for PTS if Villalta score ≥4).
  - In a meta-analysis of patients with DVT who underwent ultrasonography at least 6 weeks after their DVT, 2 ultrasound parameters were predictive of PTS: residual vein thrombosis (pooled OR, 2.17 [95% CI,1.79–2.63]) and venous reflux at the popliteal level (pooled OR, 1.34 [95% CI, 1.03–1.75]).[99]

### Social Determinants of Health/Health Equity

- A prospective study involving 449 US patients observed a linear association between CVI severity, measured by clinical-etiology-anatomy-pathophysiology classes and lower SES ($P<0.003$).[100] Patients classified with the 2 most severe categories based on clinical-etiology-anatomy-pathophysiology classification system for chronic venous disorders had a median annual household income of <$40 000.

### Family History and Genetics

- Varicose veins are more likely to occur in the setting of a positive family history, consistent with a heritable component. Heritability of varicose veins and CVI has been estimated at 17%.[101]
- Although a number of genes have been implicated,[102] to date, no causal association has been proven.[103]
- GWASs in >400 000 individuals established 12 candidate loci for varicose veins in individuals with European ancestry, highlighting the SNPs in the *CASZ1*, *PIEZO1*, *PPP3R1*, *EBF1*, *STIM2*, *HFE*, *GATA2*, *NFATC2*, and *SOX9* gene regions.[104]

### Prevention

- In a meta-analysis of ≈60 000 patients with VTE on anticoagulant therapy, the use of rivaroxaban reduced the risk of PTS by half compared with warfarin (OR, 0.52 [95% CI, 0.43–0.63]).[105]
- For patients with DVT, use of compression stockings for 24 months is standard therapy for the prevention of PTS. In a 2018 RCT, a total of 865 patients were randomized to either standard duration of or individualized therapy length.[106] Individualized therapy was noninferior to standard duration of therapy of 24 months (OR, 1.06 [95% CI, 0.78–1.44]). Multilayer bandaging was slightly more effective than compression hosiery but had higher costs without a gain in health-related quality of life ($P=1.00$).[107]

### Awareness, Treatment, and Control

- Several treatment options are available for patients with severe varicose veins, but evidence for the best approach is scarce. A 2021 Cochrane meta-analysis found a borderline benefit in technical success up to 5 years after endoscopic laser ablation over ultrasound-guided foam sclerotherapy (pooled OR, 6.47 [95% CI, 2.60–16.10], 3 studies) and surgery (pooled OR, 2.31 [95% CI, 1.27–4.23], 6 studies), in addition to the benefit of the surgery over ultrasound-guided foam sclerotherapy (pooled OR, 0.09 [95% CI, 0.03–0.30], 3 studies). None of the procedures showed a solid benefit over the others when the recurrence rate was analyzed.[108] The success of these procedures is critically compromised according to the progressive increase in weight, especially in those with a BMI ≥35 kg/m$^2$.[109] Compiled data from the Vascular Quality Initiative Varicose Vein Registry and the American Vein & Lymphatic Society PRO Venous Registry showed that patients undergoing these procedures in accredited centers experience greater benefit than those in nonaccredited centers. There was an absolute reduction in Venous Clinical Severity Score of 5.61±3.6 compared with 4.98±4.0 ($P<0.001$), in addition to a lower incidence of complications (absolute incidence, 0.1% versus 0.4%; $P<0.001$).[110]
- Among those treated with endovenous ablation, data for ≈10 000 patients from the Vascular Quality Initiative's Varicose Vein Registry found sex-related differences in outcomes: Females have fewer local complications (incidence rate compared with males, 6.1% versus 8.6%; $P=0.001$), site infections (incidence rate, 0.4% versus 0.7%; $P=0.001$), and procedure-induced venous thromboses (incidence rate, 1.1% versus 2.2%; $P=0.002$).[111]
- Oral phlebotonics (eg, benzopyrones, saponins, synthetic products, and other plant extracts) may contribute to reducing edema (pooled RR, 0.70 [95% CI, 0.60–0.78]), pain (pooled RR, 0.63 [95% CI, 0.48–0.83]), swelling (pooled RR, 0.63 [95% CI, 0.50–0.80]), and paresthesia (pooled RR, 0.67 [95% CI, 0.50–0.88]). In addition, there is likely to be a slight improvement in trophic changes (pooled RR, 0.87 [95% CI, 0.81–0.95]).[112]

### Complications

- The presence of varicose veins was associated a higher risk of VTE in patients undergoing lower-limb arthroplasty (OR, 2.37 [95% CI, 1.54–3.63]).[113]

- Leg wound is one of the most critical complications of CVI:
  - A study of the American Vein & Lymphatic Society Patient Reported Outcome involving ≈270 000 patients with CVI diagnosis found a leg wound prevalence of 1.1%.[114]
  - Compression bandages or stockings are associated with reduced wound healing time (pooled HR, 2.17 [95% CI, 1.52–3.10]), a higher rate of fully healed wounds (pooled RR, 1.77 [95% CI, 1.41–2.21]), and reduced pain (pooled median difference in 10-point pain scale, −1.39 [95% CI, −1.79 to −0.98]) with no adverse effects (*P*=0.97).[115]

### *Costs*

- Annual US spending on venous leg ulcers, a common complication of CVI, is estimated at ≈$5 billion, most of which is for practitioner and hospital expenses.[116]
  - A cost-effectiveness analysis found a dominance of compression therapy with early endovenous ablation over deferred ablation (per-patient cost, $12 527 versus $15 208 and QALY, 2.011 versus 1.985 in a 3-year scenario).[117]

### *Health Care Use: Hospital Discharges/Ambulatory Care Visits*

- In 2020, varicose veins and CVI/PTS were the main diagnosis in >66 000 ED visits. Furthermore, ≈11 600 discharges were attributed to CVI/PTS and varicose veins.[3]

### *Global Burden*

- In a Spanish registry covering 5.8 million people, CVI incidence was 3.37 per 1000 person-years (95% CI, 3.31–3.43), increasing with age: 0.61 per 1000 person-years in those <30 years of age and up to 10.95 per 1000 person-years in those ≥80 years of age. Females presented ≈2.5-fold more CVI incidence than males (4.77 and 1.95 per 1000 person-years, respectively). Venous stasis ulcer incidence was 0.23 per 1000 person-years (95% CI, 0.21–0.24).[118]
- A Brazilian study with ≈870 000 public health care surgeries between 2009 and 2018 observed a rate of 4.52 CVI procedures per 10 000 person-years at a cost of US $230 million.[119] The in-hospital mortality rate was 0.0056%.
- An online-based survey of 16 015 individuals from different nations showed a 22% prevalence of CVI, from 14% in French respondents to 37% in Russian respondents, and fewer than half of those with CVI sought medical attention.[120] Among 19 104 workers in Germany in a population-based study, the prevalence of CVI was similar (22.3%).[121]

## Pulmonary Hypertension

### *ICD-10* I27.0, I27.2.

2021, United States: Underlying cause mortality—9296. Any-mention mortality—33 025.

### *Incidence*

- A 2023 analysis of the OPTUM claims database with ≈61 000 000 US patients found a PH diagnosis in 5.2% of ≈855 000 of those who had chronic unexplained dyspnea. Furthermore, 0.1% had a diagnosis of PAH.[122]
- In the United States, PH accounted for 0.8% of all ED visits from 2011 to 2015 with a high hospitalization rate (87% of all patients with PH in the ED).[123]
- PH incidence is somewhat higher in females than males,[122,124] and females have at least a 3-fold higher prevalence of PAH in the inpatient setting.[125]
- Data from the US kidney transplantation registry observed a PH prevalence of 8.2% before the transplantation.[126] The cumulative incidence after 3 years after transplantation was 10.6% (95% CI, 10.3%–11.0%).
- Among ≈600 000 Medicare patients admitted with acute exacerbated chronic obstructive pulmonary disease, secondary PH diagnosis was present in 10.9%.[127]

## Lifetime Risk and Cumulative Incidence

- In in a US health care claim database study involving ≈170 000 patients after a VTE between 2011 and 2018[124]:
  - The 1-, 2-, and 5-year cumulative incidence of CTEPH was 2.09% (95% CI, 2.01%–2.17%), 3.54% (95% CI, 3.43%–3.65%), and 7.24% (95% CI, 7.01%–7.48%), respectively.
  - In individuals with a PE diagnosis, the 1-, 2-, and 5- year cumulative incidence of CTEPH was 3.82% (95% CI, 3.68%–3.97%), 6.24% (95% CI, 6.03%–6.45%), and 12.12% (95% CI, 11.69%–12.56%), respectively.

### *Secular Trends*

- In the United States, data from HCUP NIS show an upward trend in hospitalizations for PH between 1993 and 2020 in both principal and all-listed diagnoses.[3]

### *Risk Factors*

- PH incidence is somewhat higher in females than males (PH incidence rate per 1000 person-years after a VTE, 20.1 [95% CI, 19.4–20.8] in females versus 15.9 [95% CI, 15.3–16.6] in males),[122,124] and females have at least 3-fold higher prevalence of PAH in a study of US hospitalized patients.[125]

- Risk factors are implicit in the WHO disease classification of the 5 mechanistic subtypes of PH. The most common risk factors are left-sided HD and lung disease.
  - In WHO group I PH patients, a 10-year analysis from HCUP data found a high prevalence of CHF (32.0%), hypertension (19.7%), chronic pulmonary disease (17.7%), valvular HD (12.5%), congenital HD (13.5%), and hypothyroidism (12%).[125] A study of the REVEAL registry showed that males with newly diagnosed PAH with a smoking history had worse outcomes (HR for mortality, 1.80 [95% CI, 1.10–3.00]; HR for composite of transplantation or death, 2.23 [95% CI, 1.39–3.56]; and HR for time to first hospitalization, 1.77 [95% CI, 1.18–2.68]).[128]
  - The Pulmonary Hypertension Association Registry researchers found that 21.8% of the 541 patients in the registry had methamphetamine use as the underlying cause of PAH in the United States in 2015 to 2020.[129]
  - A US health care data analysis found higher risk of CTEPH after a VTE in initial presentation as a PE (HR, 5.04 [95% CI, 4.72–5.38]), HF (HR, 2.17 [95% CI, 2.04–2.31]), chronic pulmonary disease (HR, 2.01 [95% CI, 1.90–2.14]), alcohol abuse (HR, 1.66 [95% CI, 1.29–2.13]), AF (HR, 1.55 [95% CI, 1.43–1.68]), MI (HR, 1.53 [95% CI, 1.40–1.67]), hypertension (HR, 1.52 [95% CI, 1.43–1.61]), CKD (HR, 1.46 [95% CI, 1.36–1.58]), diabetes (HR, 1.42 [95% CI, 1.34–1.50]), liver disease (HR, 1.33 [95% CI, 1.23–1.45]), hematological disorders (HR, 1.32 [95% CI, 1.24–1.41]), older age (HR per decade, 1.26 [95% CI, 1.24–1.28]), female sex (HR, 1.24 [95% CI, 1.17–1.31]), autoimmune disease (HR, 1.23 [95% CI, 1.15–1.31]), and metastatic cancer (HR, 1.17 [95% CI, 1.06–1.30]).[124]
  - In patients undergoing kidney transplantation, newly diagnosed PH was associated with older age (HR: >60 years of age, 2.88 [95% CI, 2.15–3.86]; 45–59 years of age, 2.18 [95% CI, 1.63–2.91]; and 31–44 years of age, 1.55 [95% CI, 1.15–2.10], all compared with individuals between 18 and 30 years of age), valvular HD (HR, 1.51 [95% CI, 1.37–1.67]), chronic obstructive pulmonary disease (HR, 1.44 [95% CI, 1.28–1.61]), smoking history (HR, 1.32 [95% CI, 1.03–1.70]), female sex (HR, 1.29 [95% CI, 1.15–2.10]), OSA (HR, 1.28 [95% CI, 1.11–1.49]), >5 years of hemodialysis (HR, 1.26 [95% CI, 1.07–1.47]), diabetes (HR, 1.23 [95% CI, 1.07–1.42]), obesity (HR, 1.18 [95% CI, 1.05–1.33]), and CAD (HR, 1.15 [95% CI, 1.02–1.30]).[126]

### Social Determinants of Health/Health Equity

- An analysis of patients in the Pulmonary Hypertension Association Registry showed an important impact of annual income, education level, and health insurance on death/lung transplantation in the Hispanic population with PAH. After adjustment for these social factors, the difference in transplantation-free survival between the Hispanic and NH population was attenuated, and there was no significant difference (HR for transplantation-free survival, 0.70 [95% CI, 0.35–1.62] after social determinants of health adjustment; $P$=0.474).[130]
- Among the WHO group I PH patients:
  - Those with methamphetamine-related PAH had a clearly lower SES compared with the other patients in this group (prevalence of patients with college education, 17% versus 34%; prevalence of patients with a taxable income per year <$50 000, 84% versus 50%, respectively; $P$<0.001).[129]
  - Veterans in the highest annual income strata (>$100 000) had shorter time to diagnosis than those with household income <$20 000 (HR, 0.74 [95% CI, 0.60–0.91]).[131]
- The risk of CTEPH in the United States is lower among those with a high-deductible health plan compared with those with other health insurance plans (HR, 0.83 [95% CI, 0.72–0.96]).[124,129,131]

### Family History and Genetics

- A 2018 study reported clustering of CTEPH in families, providing novel evidence that heritable genetic factors influence an individual's risk of developing CTEPH.[132]
- A Japanese family study identified *BMPR2* (bone morphogenetic protein receptor type 2) as a risk factor for PAH.[133] In whole-exome sequencing, a Japanese cohort of patients with CTEPH were noted to carry nonsynonymous variants associated with acute PE, indicating a partial genetic overlap of CTEPH with acute PE.[134]
- GWASs in >11 000 individuals have identified risk loci for PAH, including *SOX17* and *HLA-DPA1/DPB1*.[135]
- Exome sequencing in 2572 individuals and case-control gene-based association analyses in 1832 cases and 12 771 controls identified candidate risk genes for idiopathic PAH, including *KLK1*, *GGCX*, and *GDF2*.[136]

### Awareness, Treatment, and Control

- There is a meaningful delay between the beginning of the symptoms and PAH diagnosis (median interval time, 2.26 years [IQR, 0.73–4.22 years]), requiring a median of 3 (IQR, 2–4) echocardiograms, 6 (IQR, 3–12) specialist visits, and 2 (IQR, 1–4) hospitalizations until a definitive diagnosis is made.[122]

- As nonpharmacological therapy, exercise-based rehabilitation programs have shown improvements in cardiovascular fitness including 6-minute walk distance (+47.7 m [95% CI, 33.9–61.7]) and $Vo_2$peak (+2.96 mL·kg$^{-1}$·min$^{-1}$ [95% CI, 2.49–3.43]).[137]
- In the WHO group 1 PH:
  - An analysis between 2010 and 2015 using both Truven Commercial and Medicare databases of 13 633 adults with PAH observed that 74.5% received a phosphodiesterase 5 inhibitor, 41.6% received an endothelin receptor antagonist, and 22% received a prostacyclin drug. There was no linear trend in drug prescription.[138]
  - Phosphodiesterase 5 inhibitors showed a clear benefit in 6-minute walk distance (+48 m [95% CI, 40–56]), WHO functional class (OR, 8.59 [95% CI, 3.95–18.72]), and mortality (OR, 0.22 [95% CI, 0.07–0.68]).[139] Endothelin receptor antagonists improve 6-minute walk distance (+25 m [95% CI, 17–33]) and WHO functional class (OR, 1.41 [95% CI, 1.16–1.70]) without a statistically significant reduction in mortality (OR, 0.78 [95% CI, 0.58–1.07]).[140]
  - In symptomatic patients with intermediate risk of 1-year mortality, the REPLACE investigators found benefit of switching from other phosphodiesterase 5 inhibitors to riociguat for improvement of 2- of 6-minute walk distance, WHO functional class, and NT-proBNP (OR, 2.78 [95% CI, 1.53–5.06]) with no clinical worsening (OR, 0.10 [95% CI, 0.01–0.73]).[141]
  - Intravenous prostacyclin exhibited improvements in WHO functional class (OR, 14.96 [95% CI, 4.76–47.04]), 6-minute walk distance (+91 m [95% CI, 59–124]), and mortality (OR, 0.29 [95% CI, 0.12–0.69]).[142] However, serious adverse events may occur in 12% to 25% of cases, including sepsis, hemorrhage, pneumothorax, and PE.
  - Anticoagulation therapy showed no benefit in mortality regardless of the underlying cause of PH ($P$=0.11), in addition to worsening of quality of life (adjusted mean difference of emPHasis-10 score, 1.74 [95% CI, 0.40–3.09]), more ED visits (aIRR, 1.41 [95% CI, 1.28–1.56]), hospitalization (aIRR, 1.33 [95% CI, 1.14–1.55]), and days in the hospital (aIRR, 1.30 [95% CI, 1.23–1.37]).[143]
- In the CTEPH scenario, pulmonary thromboendoarterectomy surgery resulted in better WHO functional class (rate in WHO functional class I/II, 82.9% versus 56% versus 48.2% in operated, operable but not operated, and inoperable, respectively; $P$<0.001) and less use of oxygen ($P$<0.001 versus inoperable cohort), diuretics ($P$<0.001 versus inoperable cohort), and specific medications for PH ($P$<0.001 versus operable but not operated and inoperable).[144]
- A comprehensive study of data from 132 552 veterans with PH diagnosed in groups 2 and 3 found a 39% increased mortality or organ failure in those exposed to pulmonary vasodilators (HR, 1.31 [95% CI, 1.25–1.37]).[145]

### *Mortality*

- Data from HCUP show that the in-hospital PH mortality rate jumped from 3.9% in 2016 to 5.9% in 2020.[3]
- In a 2019 study of US veterans with PH, 5-year survival was 66.1% for group 1 (PAH), 42.4% for group 2 (left-sided HD), 52.3% for group 3 (lung disease), 72.7% for group 4 (CTEPH), 67.8% for group 5 (miscellaneous), and 34.9% for PH with multiple causes.[146]
  - The Pulmonary Hypertension Association Registry, a US multicenter cohort of ≈1000 patients with group I PH, observed a 1-, 2-, and 3-year composite of death/lung transplantation of 8.6% (95% CI, 6.8%–10.7%), 16.9% (95% CI, 14.1%–20.2%), and 23.1% (95% CI, 19.4%–27.7%), respectively.[147] In high-risk strata, the 3-year mortality rate was from 28% to 56% according to risk tool used.
  - In the United States, patients with PH admitted to the hospital have high in-hospital mortality (4.2% versus 2.6% for all other patients). Furthermore, the mortality risk increases according to the age group, reaching a 10-fold risk in those ≥80 years of age.[123]
  - In PH group 3, patients with PH and lung disease had an increased in-hospital mortality compared with those with no PH (OR, 1.89 [95% CI, 1.73–2.07]).[127]
- Data from the US CTEPH Registry showed a 1-year mortality, stratified by pulmonary thromboendarterectomy status, of 5.6% in operated patients, 9.9% in those in whom surgery was feasible but who decided not to have the procedure, and 12.4% in inoperable patients ($P$=0.028).[144]
- Mortality rates also vary according to WHO functional class. A meta-analysis including 10 studies found a 1-, 2-, and 3-year survival rate for patients with PAH in WHO functional class I/II of 93.3%, 85.5%, and 78.4%, respectively. However, in patients with worse functional class (WHO functional class III/IV), the survival rates were 81.2% at year 1, 66.7% at year 2, and 54.8% at year 3.[148]
- Among group 1 PH in WHO functional class I/II, a post hoc analysis including PHIRST and TRIUMPH participants found that those who achieved 6-minute walk distance ≥440 m had a better prognosis (HR, 0.225 [95% CI, 0.098–0.519]).[149] For patients with groups 2 through 4 PH, 2019 findings from the ASPIRE registry demonstrated that greater incremental shuttle walking test distance

was associated with better survival (AUC, 0.693 [95% CI, 0.646–0.739]).[150]
- In terms of pregnancy, a systematic review of 13 studies (4 in the United States) observed a 12% overall maternal mortality rate. Of all deaths, 61% occurred within the first 4 days of labor.[151] In addition, 58% of births were PTBs.
- Despite the mortality rate noted previously, only 5.8% of patients enrolled in the Pulmonary Hypertension Association Registry were referred for palliative care. Among them, 43% were referred in the last appointment before death.[152]
- A retrospective analysis of 6169 US patients with PH observed a higher mortality in those living in small urban counties (HR, 1.48 [95% CI, 1.14–1.92]) and rural areas (HR, 2.01 [95% CI, 1.13–3.57]) compared with individuals in metropolitan counties.[153]

### Health Care Use: Hospital Discharges/Ambulatory Care Visits

- In 2020, there were 10 900 hospital discharges with PH as the principal diagnosis (HCUP,[3] unpublished NHLBI tabulation).
- In 2019, PH was the principal diagnosis for 278 000 physician office visits (NAMCS,[85] unpublished NHLBI tabulation).

### Costs

- Health care costs associated with PH are substantial. In inpatient scenarios, the mean charge increased progressively from $82 000 in 2016 to $125 000 in 2020.[3]
  - In patients with acute exacerbated chronic obstructive pulmonary disease, an additional diagnosis of WHO group 3 PH results in an increase in hospitalization costs of $2785 (mean difference [95% CI, $2602–$2967]).[127]
- In an analysis of administrative data, the per-patient per-month total all-cause health care costs for patients with PH who were commercially insured were $9503 for those on monotherapy and $16 240 for those on combination therapy. Among patients with PH with Medicare Advantage and Part D, the monthly costs for patients on monotherapy and combination therapy were $6271 and $14 340, respectively.[154]
- Among patients diagnosed with PH referred to the Mayo Clinic specialty center, half had their previously prescribed medications discontinued (eg, sildenafil, tadalafil, riociguat, ambrisentan, treprostinil, macitentan, and selexipag), resulting in a monthly savings of ≈$7000 per patient with an inappropriate diagnosis.[155]

### Global Burden

- A systematic review from the GBD Study 2020 showed a wide range of prevalence of PAH (WHO group I PH) worldwide, ranging from 0.7 to 15 per 100 000 inhabitants in France and Australia, respectively.[156] When stratified by diagnosis through right-sided heart catheterization, the mean PAH prevalence across 37 low-, middle-, and high-income countries was 3.7 per 100 000 people.
- In a study by Wijeratne et al[157] conducted in Ontario, Canada, among adults with PH, the overall prevalence per 100 000 population was 29.1 for group 1 (PAH), 67.4 for group 2 (left-sided HD), 36.4 for group 3 (lung disease), and 12.1 for group 4 (CTEPH and other pulmonary obstructions). Groups 2 through 4 were not mutually exclusive, and group 5 (multifactorial mechanisms) was not reported.
- Of patients with PH, 80% live in developing countries, and the cause of their PH is primarily HD and lung disease (25 million worldwide), but schistosomiasis (≈13 000 in Latin America), rheumatic HD (3.75 million worldwide), HIV (150 000 worldwide), and sickle cell disease (2 million worldwide) remain prominent in developing countries compared with developed countries. In developing countries, younger people are more often affected (average age at onset, <40 years).[158]
- In an English cohort of 23 329 patients with first VTE (mean follow-up, 3.5 years), 283 patients were diagnosed with CTEPH. Cumulative incidence was 1.3% and 3.3% at 2 and 10 years after PE and 0.3% and 1.3% after DVT, respectively.[159]
- A meta-analysis with 5834 patients observed an overall CTEPH incidence after acute PE of 2.82% (95% CI, 2.11%–3.53%).[160] In this scenario, Asian individuals showed a higher risk of CTEPH compared with European individuals (polled incidence, 5.08% [95% CI, 2.67%–7.49%] versus 1.96% [95% CI, 1.29%-2.63%], respectively). However, in high-income countries, the annual incidence of CTEPH is believed to be lower in Japan (1.9 cases/100 000 people) than in the United States and Europe (3–5 cases/100 000 people).[161]

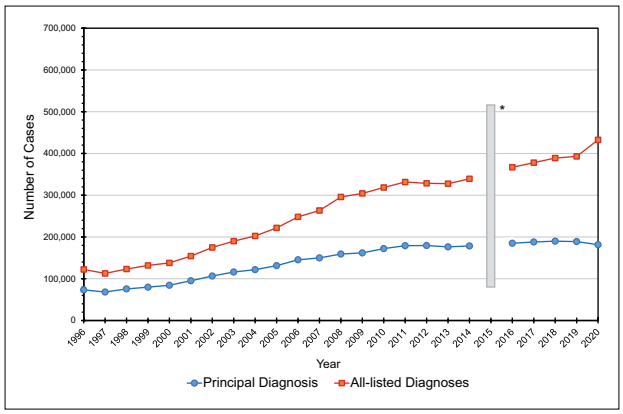



**Chart 24-1. Trends in hospitalized PE, United States, 1996 to 2020.**
PE indicates pulmonary embolism.
*Data not available for 2015. Readers comparing data across years should note that beginning October 1, 2015, a transition was made from the 9th revision to the 10th revision of the *International Classification of Diseases*. This should be kept in consideration because coding changes could affect some statistics, especially when comparisons are made across these years.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Healthcare Cost and Utilization Project.[3]

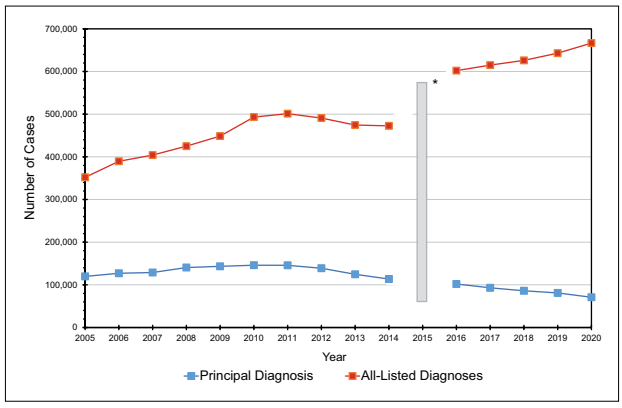



**Chart 24-2. Trends in hospitalized DVT, United States, 2005 to 2020.**
DVT indicates deep vein thrombosis.
*Data not available for 2015. Readers comparing data across years should note that beginning October 1, 2015, a transition was made from the 9th revision to the 10th revision of the *International Classification of Diseases*. This should be kept in consideration because coding changes could affect some statistics, especially when comparisons are made across these years.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Healthcare Cost and Utilization Project.[3]

## REFERENCES


1. Centers for Disease Control and Prevention and National Center for Health Statistics. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death micro-data files. Accessed April 8, 2023. https://cdc.gov/nchs/nvss/mortality_public_use_data.htm
2. Centers for Disease Control and Prevention and National Center for Health Statistics. Multiple cause of death, CDC WONDER online database. Accessed April 1, 2023. https://wonder.cdc.gov/mcd-icd10.html.
3. Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project (HCUP). Accessed April 1, 2023. http://hcupnet.ahrq.gov/
4. Lutsey PL, Walker RF, MacLehose RF, Norby FL, Evensen LH, Alonso A, Zakai NA. Inpatient versus outpatient acute venous thromboembolism management: trends and postacute healthcare utilization from 2011 to 2018. *J Am Heart Assoc*. 2021;10:e020428. doi: 10.1161/JAHA.120.020428
5. Wendelboe AM, Campbell J, Ding K, Bratzler DW, Beckman MG, Reyes NL, Raskob GE. Incidence of venous thromboembolism in a racially diverse population of Oklahoma County, Oklahoma. *Thromb Haemost*. 2021;121:816–825. doi: 10.1055/s-0040-1722189
6. Weze KO, Obisesan OH, Dardari ZA, Cainzos-Achirica M, Dzaye O, Graham G, Miedema MD, Yeboah J, DeFilippis AP, Nasir K, et al. The interplay of race/ethnicity and obesity on the incidence of venous thromboembolism. *Am J Prev Med*. 2022;63:e11–e20. doi: 10.1016/j.amepre.2021.12.023
7. Pence K, Fullin D, Kendall MC, Apruzzese P, De Oliveira G. The association between surgical duration and venous thromboembolism in outpatient surgery: a propensity score adjusted prospective cohort study. *Ann Med Surg (Lond)*. 2020;60:498–503. doi: 10.1016/j.amsu.2020.11.003
8. Krenitsky N, Friedman AM, Yu K, Gyamfi-Bannerman C, Williams-Kane J, O'Shaugnessy F, Huang Y, Wright JD, D'Alton ME, Wen T. Trends in venous thromboembolism and associated risk factors during delivery hospitalizations from 2000 to 2018. *Obstet Gynecol*. 2022;139:223–234. doi: 10.1097/AOG.0000000000004648
9. Martin KA, McCabe ME, Feinglass J, Khan SS. Racial disparities exist across age groups in Illinois for pulmonary embolism hospitalizations. *Arterioscler Thromb Vasc Biol*. 2020;40:2338–2340. doi: 10.1161/ATVBAHA.120.314573
10. Fu X, Zhong Y, Xu W, Ju J, Yu M, Ge M, Gu X, Chen Q, Sun Y, Huang H, et al. The prevalence and clinical features of pulmonary embolism in patients with AE-COPD: a meta-analysis and systematic review. *PLoS One*. 2021;16:e0256480. doi: 10.1371/journal.pone.0256480
11. Teichman AL, Walls D, Choron RL, Butts CA, Krumrei N, Amro C, Swaminathan S, Arcomano N, Parekh A, Romeo P. The utility of lower extremity screening duplex for the detection of deep vein thrombosis in trauma. *J Surg Res*. 2022;269:151–157. doi: 10.1016/j.jss.2021.08.010
12. Cheong JY, Connelly TM, Russell T, Valente M, Bhama A, Lightner A, Hull T, Steele SR, Holubar SD. Venous thromboembolism risk stratification for patients undergoing surgery for IBD using a novel six factor scoring system using NSQIP-IBD registry. *ANZ J Surg*. 2023;93:1620–1625. doi: 10.1111/ans.18242
13. Lo Re V 3rd, Dutcher SK, Connolly JG, Perez-Vilar S, Carbonari DM, DeFor TA, Djibo DA, Harrington LB, Hou L, Hennessy S, et al. Association of COVID-19 vs influenza with risk of arterial and venous thrombotic events among hospitalized patients. *JAMA*. 2022;328:637–651. doi: 10.1001/jama.2022.13072
14. Giannis D, Barish MA, Goldin M, Cohen SL, Kohn N, Gianos E, Chatterjee S, Lesser M, Coppa K, Hirsch JS, et al; COVID-19 Consortium Group. Incidence of venous thromboembolism and mortality in patients with initial presentation of COVID-19. *J Thromb Thrombolysis*. 2021;51:897–901. doi: 10.1007/s11239-021-02413-7
15. Suh YJ, Hong H, Ohana M, Bompard F, Revel MP, Valle C, Gervaise A, Poissy J, Susen S, Hekimian G, et al. Pulmonary embolism and deep vein thrombosis in Covid-19: a systematic review and meta-analysis. *Radiology*. 2021;298:E70–E80. doi: 10.1148/radiol.2020203557
16. Wu C, Liu Y, Cai X, Zhang W, Li Y, Fu C. Prevalence of venous thromboembolism in critically ill patients with coronavirus disease 2019: a meta-analysis. *Front Med (Lausanne)*. 2021;8:603558. doi: 10.3389/fmed.2021.603558
17. Bell EJ, Lutsey PL, Basu S, Cushman M, Heckbert SR, Lloyd-Jones DM, Folsom AR. Lifetime risk of venous thromboembolism in two cohort studies. *Am J Med*. 2016;129:339.e19–339.e26. doi: 10.1016/j.amjmed.2015.10.014
18. Stein PD, Matta F, Hughes PG, Hughes MJ. Nineteen-year trends in mortality of patients hospitalized in the United States with high-risk pulmonary embolism. *Am J Med*. 2021;134:1260–1264. doi: 10.1016/j.amjmed.2021.01.026
19. Mahajan A, Brunson A, Adesina O, Keegan THM, Wun T. The incidence of cancer-associated thrombosis is increasing over time. *Blood Adv*. 2022;6:307–320. doi: 10.1182/bloodadvances.2021005590
20. Alabbadi S, Roach A, Chikwe J, Egorova NN. National trend in failure to rescue after cardiac surgeries. *J Thorac Cardiovasc Surg*. 2022;166:1157–1165.e6. doi: 10.1016/j.jtcvs.2022.02.037
21. Halawi MJ, Gronbeck C, Metersky ML, Wang Y, Eckenrode S, Mathew J, Suter LG, Eldridge N. Time trends in patient characteristics and in-hospital adverse events for primary total knee arthroplasty in the United States: 2010-2017. *Arthroplasty Today*. 2021;11:157–162. doi: 10.1016/j.artd.2021.08.010
22. Ageno W, Farjat A, Haas S, Weitz JI, Goldhaber SZ, Turpie AGG, Goto S, Angchaisuksiri P, Dalsgaard Nielsen J, Kayani G, et al. Provoked versus unprovoked venous thromboembolism: findings from GARFIELD-VTE. *Res Pract Thromb Haemost*. 2021;5:326–341. doi: 10.1002/rth2.12482

23. RIETE Registry. Risk factors from the RIETE registry. Accessed February 28, 2023. https://riete.org/info/charts/risk-factors.php
24. Raskob GE, Spyropoulos AC, Cohen AT, Weitz JI, Ageno W, De Sanctis Y, Lu W, Xu J, Albanese J, Sugarmann C, et al. Association between asymptomatic proximal deep vein thrombosis and mortality in acutely ill medical patients. *J Am Heart Assoc*. 2021;10:e019459. doi: 10.1161/JAHA.120.019459
25. Neeman E, Liu V, Mishra P, Thai KK, Xu J, Clancy HA, Schlessinger D, Liu R. Trends and risk factors for venous thromboembolism among hospitalized medical patients. *JAMA Netw Open*. 2022;5:e2240373. doi: 10.1001/jamanetworkopen.2022.40373
26. Datta T, Brunson A, Mahajan A, Keegan T, Wun T. Racial disparities in cancer-associated thrombosis. *Blood Adv*. 2022;6:3167–3177. doi: 10.1182/bloodadvances.2021006209
27. Gregson J, Kaptoge S, Bolton T, Pennells L, Willeit P, Burgess S, Bell S, Sweeting M, Rimm EB, Kabrhel C, et al; Emerging Risk Factors Collaboration. Cardiovascular risk factors associated with venous thromboembolism. *JAMA Cardiol*. 2019;4:163–173. doi: 10.1001/jamacardio.2018.4537
28. Fanola CL, Norby FL, Shah AM, Chang PP, Lutsey PL, Rosamond WD, Cushman M, Folsom AR. Incident heart failure and long-term risk for venous thromboembolism. *J Am Coll Cardiol*. 2020;75:148–158. doi: 10.1016/j.jacc.2019.10.058
29. Michailidou D, Zhang T, Stamatis P, Ng B. Risk of venous and arterial thromboembolism in patients with giant cell arteritis and/or polymyalgia rheumatica: a Veterans Health Administration population-based study in the United States. *J Intern Med*. 2022;291:665–675. doi: 10.1111/joim.13446
30. Walker RF, Zakai NA, MacLehose RF, Cowan LT, Adam TJ, Alonso A, Lutsey PL. Association of testosterone therapy with risk of venous thromboembolism among men with and without hypogonadism. *JAMA Intern Med*. 2019;180:190–197. doi: 10.1001/jamainternmed.2019.5135
31. Gartlehner G, Patel SV, Reddy S, Rains C, Schwimmer M, Kahwati L. Hormone therapy for the primary prevention of chronic conditions in postmenopausal persons: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2022;328:1747–1765. doi: 10.1001/jama.2022.18324
32. Houghton DE, Wysokinski W, Casanegra AI, Padrnos LJ, Shah S, Wysokinska E, Pruthi R, Ashrani A, Sridharan M, Baumann-Kreuziger L, et al. Risk of venous thromboembolism after COVID-19 vaccination. *J Thromb Haemost*. 2022;20:1638–1644. doi: 10.1111/jth.15725
33. Getahun D, Nash R, Flanders WD, Baird TC, Becerra-Culqui TA, Cromwell L, Hunkeler E, Lash TL, Millman A, Quinn VP, et al. Cross-sex hormones and acute cardiovascular events in transgender persons: a cohort study. *Ann Intern Med*. 2018;169:205–213. doi: 10.7326/M17-2785
34. Kotamarti VS, Greige N, Heiman AJ, Patel A, Ricci JA. Risk for venous thromboembolism in transgender patients undergoing cross-sex hormone treatment: a systematic review. *J Sex Med*. 2021;18:1280–1291. doi: 10.1016/j.jsxm.2021.04.006
35. Jerjes-Sanchez C, Rodriguez D, Farjat AE, Kayani G, MacCallum P, Lopes RD, Turpie AGG, Weitz JI, Haas S, Ageno W, et al; GARFIELD-VTE Investigators. Pregnancy-associated venous thromboembolism: insights from GARFIELD-VTE. *TH Open*. 2021;5:e24–e34. doi: 10.1055/s-0040-1722611
36. Nathan AS, Geng Z, Dayoub EJ, Khatana SAM, Eberly LA, Kobayashi T, Pugliese SC, Adusumalli S, Giri J, Groeneveld PW. Racial, ethnic, and socioeconomic inequities in the prescription of direct oral anticoagulants in patients with venous thromboembolism in the United States. *Circ Cardiovasc Qual Outcomes*. 2019;12:e005600. doi: 10.1161/CIRCOUTCOMES.119.005600
37. Cohen AT, Sah J, Dhamane AD, Lee T, Rosenblatt L, Hlavacek P, Emir B, Keshishian A, Yuce H, Luo X. Effectiveness and safety of apixaban versus warfarin among older patients with venous thromboembolism with different demographics and socioeconomic status. *Adv Ther*. 2021;38:5519–5533. doi: 10.1007/s12325-021-01918-0
38. Zoller B, Ohlsson H, Sundquist J, Sundquist K. A sibling based design to quantify genetic and shared environmental effects of venous thromboembolism in Sweden. *Thromb Res*. 2017;149:82–87. doi: 10.1016/j.thromres.2016.10.014
39. Kujovich JL. Factor V Leiden thrombophilia. 1999 May 14 [Updated 2018 Jan 4]. In: Adam MP, Feldman J, Mirzaa GM, et al., eds. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Accessed December 4, 2023. https://www.ncbi.nlm.nih.gov/books/NBK1368/
40. Simone B, De Stefano V, Leoncini E, Zacho J, Martinelli I, Emmerich J, Rossi E, Folsom AR, Almawi WY, Scarabin PY, et al. Risk of venous thromboembolism associated with single and combined effects of factor V Leiden, prothrombin 20210A and methylenetethraydrofolate reductase C677T: a meta-analysis involving over 11,000 cases and 21,000 controls. *Eur J Epidemiol*. 2013;28:621–647. doi: 10.1007/s10654-013-9825-8
41. Croles FN, Borjas-Howard J, Nasserinejad K, Leebeek FWG, Meijer K. Risk of venous thrombosis in antithrombin deficiency: a systematic review and bayesian meta-analysis. *Semin Thromb Hemost*. 2018;44:315–326. doi: 10.1055/s-0038-1625983
42. Croles FN, Nasserinejad K, Duvekot JJ, Kruip MJ, Meijer K, Leebeek FW. Pregnancy, thrombophilia, and the risk of a first venous thrombosis: systematic review and bayesian meta-analysis. *BMJ*. 2017;359:j4452. doi: 10.1136/bmj.j4452
43. Lee EJ, Dykas DJ, Leavitt AD, Camire RM, Ebberink E, Garcia de Frutos P, Gnanasambandan K, Gu SX, Huntington JA, Lentz SR, et al. Whole-exome sequencing in evaluation of patients with venous thromboembolism. *Blood Adv*. 2017;1:1224–1237. doi: 10.1182/bloodadvances.2017005249
44. Klarin D, Emdin CA, Natarajan P, Conrad MF, INVENT Consortium, Kathiresan S. Genetic analysis of venous thromboembolism in UK Biobank identifies the *ZFPM2* locus and implicates obesity as a causal risk factor. *Circ Cardiovasc Genet*. 2017;10:e001643. doi: 10.1161/CIRCULATIONAHA.122.059675
45. de Haan HG, Bezemer ID, Doggen CJ, Le Cessie S, Reitsma PH, Arellano AR, Tong CH, Devlin JJ, Bare LA, Rosendaal FR, et al. Multiple SNP testing improves risk prediction of first venous thrombosis. *Blood*. 2012;120:656–663. doi: 10.1182/blood-2011-12-397752
46. Thibord F, Klarin D, Brody JA, Chen MH, Levin MG, Chasman DI, Goode EL, Hveem K, Teder-Laving M, Martinez-Perez A, et al. Cross-ancestry investigation of venous thromboembolism genomic predictors. *Circulation*. 2022;146:1225–1242. doi: 10.1161/CIRCULATIONAHA.122.059675
47. Ghouse J, Tragante V, Ahlberg G, Rand SA, Jespersen JB, Leinoe EB, Vissing CR, Trudso L, Jonsdottir I, Banasik K, et al. Genome-wide meta-analysis identifies 93 risk loci and enables risk prediction equivalent to monogenic forms of venous thromboembolism. *Nat Genet*. 2023;55:399–409. doi: 10.1038/s41588-022-01286-7
48. Fernando SM, Tran A, Cheng W, Sadeghirad B, Arabi YM, Cook DJ, Moller MH, Mehta S, Fowler RA, Burns KEA, et al. VTE prophylaxis in critically ill adults: a systematic review and network meta-analysis. *Chest*. 2022;161:418–428. doi: 10.1016/j.chest.2021.08.050
49. Baimas-George MR, Ross SW, Yang H, Matthews BD, Nimeri A, Reinke CE. Just what the doctor ordered: missed ordering of venous thromboembolism chemoprophylaxis is associated with increased VTE events in high-risk general surgery patients. *Ann Surg*. 2022;278:e614–e619. doi: 10.1097/SLA.0000000000005779
50. Tran A, Fernando SM, Carrier M, Siegal DM, Inaba K, Vogt K, Engels PT, English SW, Kanji S, Kyeremanteng K, et al. Efficacy and safety of low molecular weight heparin versus unfractionated heparin for prevention of venous thromboembolism in trauma patients: a systematic review and meta-analysis. *Ann Surg*. 2022;275:19–28. doi: 10.1097/SLA.0000000000005157
51. Liu M, Wang G, Li Y, Wang H, Liu H, Guo N, Han C, Peng Y, Yang M, Liu Y, et al. Efficacy and safety of thromboprophylaxis in cancer patients: a systematic review and meta-analysis. *Ther Adv Med Oncol*. 2020;12:1758835920907540. doi: 10.1177/1758835920907540
52. Bistervels IM, Buchmüller A, Wiegers HMG, Ní Áinle F, Tardy B, Donnelly J, Verhamme P, Jacobsen AF, Hansen AT, Rodger MA, et al; Highlow Block Writing Committee; Highlow Investigators. Intermediate-dose versus low-dose low-molecular-weight heparin in pregnant and post-partum women with a history of venous thromboembolism (Highlow Study): an open-label, multicentre, randomised, controlled trial. *Lancet*. 2022;400:1777–1787. doi: 10.1016/S0140-6736(22)02128-6
53. Middleton P, Shepherd E, Gomersall JC. Venous thromboembolism prophylaxis for women at risk during pregnancy and the early postnatal period. *Cochrane Database Systemat Rev*. 2021;3:CD001689. doi: 10.1002/14651858.CD001689.pub4
54. Nederpelt CJ, Bijman Q, Krijnen P, Schipper IB. Equivalence of DOACS and LMWH for thromboprophylaxis after hip fracture surgery: systematic review and meta-analysis. *Injury*. 2022;53:1169–1176. doi: 10.1016/j.injury.2021.11.052
55. Wang Y, Wang M, Ni Y, Liang Z. Direct oral anticoagulants for thromboprophylaxis in ambulatory patients with cancer. *Hematology*. 2020;25:63–70. doi: 10.1080/16078454.2020.1719726
56. Flumignan RL, Civile VT, Tinôco JDS, Pascoal PI, Areias LL, Matar CF, Tendal B, Trevisani VF, Atallah AN, Nakano LC. Anticoagulants for people hospitalised with COVID-19. *Cochrane Database Systemat Rev*. 2022;3:CD013739. doi: 10.1002/14651858.CD013739.pub2
57. Clarke MJ, Broderick C, Hopewell S, Juszczak E, Eisinga A. Compression stockings for preventing deep vein thrombosis in airline passengers. *Cochrane Database Syst Rev*. 2021;4:CD004002. doi: 10.1002/14651858.CD004002.pub4
58. Sachdeva A, Dalton M, Lees T. Graduated compression stockings for prevention of deep vein thrombosis. *Cochrane Database Syst Rev*. 2018;11:CD001484. doi: 10.1002/14651858.CD001484.pub4

59. Kakkos S, Kirkilesis G, Caprini JA, Geroulakos G, Nicolaides A, Stansby G, Reddy DJ. Combined intermittent pneumatic leg compression and pharmacological prophylaxis for prevention of venous thromboembolism. *Cochrane Database Syst Rev*. 2022;1:CD005258. doi: 10.1002/14651858.CD005258.pub4
60. Ho KM, Rao S, Honeybul S, Zellweger R, Wibrow B, Lipman J, Holley A, Kop A, Geelhoed E, Corcoran T, et al. A multicenter trial of vena cava filters in severely injured patients. *N Engl J Med*. 2019;381:328–337. doi: 10.1056/NEJMoa1806515
61. Heijkoop B, Nadi S, Spernat D, Kiroff G. Extended versus inpatient thromboprophylaxis with heparins following major open abdominopelvic surgery for malignancy: a systematic review of efficacy and safety. *Perioper Med (Lond)*. 2020;9:7. doi: 10.1186/s13741-020-0137-8
62. Zayed Y, Kheiri B, Barbarawi M, Banifadel M, Abdalla A, Chahine A, Obeid M, Haykal T, Yelangi A, Malapati S, et al. Extended duration of thromboprophylaxis for medically ill patients: a systematic review and meta-analysis of randomised controlled trials. *Intern Med J*. 2020;50:192–199. doi: 10.1111/imj.14417
63. Kirkilesis G, Kakkos SK, Bicknell C, Salim S, Kakavia K. Treatment of distal deep vein thrombosis. *Cochrane Database Syst Rev*. 2020;4:CD013422. doi: 10.1002/14651858.CD013422.pub2
64. Pawar A, Gagne JJ, Gopalakrishnan C, Iyer G, Tesfaye H, Brill G, Chin K, Bykov K. Association of type of oral anticoagulant dispensed with adverse clinical outcomes in patients extending anticoagulation therapy beyond 90 days after hospitalization for venous thromboembolism. *JAMA*. 2022;327:1051–1060. doi: 10.1001/jama.2022.1920
65. Haas S, Farjat AE, Pieper K, Ageno W, Angchaisuksiri P, Bounameaux H, Goldhaber SZ, Goto S, Mantovani L, Prandoni P, et al; GARFIELD-VTE Investigators. On-treatment comparative effectiveness of vitamin K antagonists and direct oral anticoagulants in GARFIELD-VTE, and focus on cancer and renal disease. *TH Open*. 2022;6:e354–e364. doi: 10.1055/s-0042-1757744
66. Khan AM, Chiasakul T, Redd R, Patell R, McCarthy EP, Neuberg D, Zwicker JI. Survival outcomes with warfarin compared with direct oral anticoagulants in cancer-associated venous thromboembolism in the United States: a population-based cohort study. *PLoS Med*. 2022;19:e1004012. doi: 10.1371/journal.pmed.1004012
67. Cohen AT, Sah J, Dhamane AD, Lee T, Rosenblatt L, Hlavacek P, Emir B, Keshishian A, Yuce H, Luo X. Effectiveness and safety of apixaban vs warfarin among venous thromboembolism patients at high-risk of bleeding. *PLoS One*. 2022;17:e0274969. doi: 10.1371/journal.pone.0274969
68. Cohen AT, Sah J, Dhamane AD, Lee T, Rosenblatt L, Hlavacek P, Emir B, Delinger R, Yuce H, Luo X. Effectiveness and safety of apixaban versus warfarin in venous thromboembolism patients with chronic kidney disease. *Thromb Haemost*. 2022;122:926–938. doi: 10.1055/s-0041-1740254
69. Wetmore JB, Herzog CA, Yan H, Reyes JL, Weinhandl ED, Roetker NS. Apixaban versus warfarin for treatment of venous thromboembolism in patients receiving long-term dialysis. *Clin J Am Soc Nephrol*. 2022;17:693–702. doi: 10.2215/CJN.14021021
70. Liu Y, Lu H, Bai H, Liu Q, Chen R. Effect of inferior vena cava filters on pulmonary embolism-related mortality and major complications: a systematic review and meta-analysis of randomized controlled trials. *J Vasc Surg Venous Lymphat Disord*. 2021;9:792–800.e2. doi: 10.1016/j.jvsv.2021.02.008
71. Balabhadra S, Kuban JD, Lee S, Yevich S, Metwalli Z, McCarthy CJ, Huang SY, Tam A, Gupta S, Sheth SA, et al. Association of inferior vena cava filter placement with rates of pulmonary embolism in patients with cancer and acute lower extremity deep venous thrombosis. *JAMA Netw Open*. 2020;3:e2011079. doi: 10.1001/jamanetworkopen.2020.11079
72. Broderick C, Watson L, Armon MP. Thrombolytic strategies versus standard anticoagulation for acute deep vein thrombosis of the lower limb. *Cochrane Database Syst Rev*. 2021;1:CD002783. doi: 10.1002/14651858.CD002783.pub5
73. Lichtenberg MKW, Stahlhoff S, Mlynczak K, Golicki D, Gagne P, Razavi MK, de Graaf R, Kolluri R, Kolasa K. Endovascular mechanical thrombectomy versus thrombolysis in patients with iliofemoral deep vein thrombosis: a systematic review and meta-analysis. *Vasa*. 2021;50:59–67. doi: 10.1024/0301-1526/a000875
74. Pandit V, Kempe K, Hanna K, Baab K, Jennings W, Khorgami Z, Zamor K, Shakir Z, Kim H, Nelson P. Venous thromboembolism as the first sign of malignancy. *J Vasc Surg Venous Lymphat Disord*. 2022;10:1260–1266. doi: 10.1016/j.jvsv.2022.05.014
75. Robertson L, Broderick C, Yeoh SE, Stansby G. Effect of testing for cancer on cancer- or venous thromboembolism (VTE)-related mortality and morbidity in people with unprovoked VTE. *Cochrane Database Syst Rev*. 2021;10:CD010837. doi: 10.1002/14651858.CD010837.pub5
76. Martin KA, Harrington K, Huang X, Khan SS. Pulmonary embolism-related mortality during the COVID-19 pandemic: data from the United States. *Res Pract Thromb Haemost*. 2022;6:e12845. doi: 10.1002/rth2.12845
77. Turpie AGG, Farjat AE, Haas S, Ageno W, Weitz JI, Goldhaber SZ, Goto S, Angchaisuksiri P, Kayani G, Lopes RD, et al; GARFIELD-VTE Investigators. 36-Month clinical outcomes of patients with venous thromboembolism: GARFIELD-VTE. *Thromb Res*. 2023;222:31–39. doi: 10.1016/j.thromres.2022.11.016
78. Wang C, Zhang H, Zhou M, Cheng Y, Ye L, Chen J, Wang M, Feng Z. Prognosis of COVID-19 in patients with vein thrombosis: a systematic review and meta-analysis. *Eur Rev Med Pharmacol Sci*. 2020;24:10279–10285. doi: 10.26355/eurrev_202010_23252
79. Kalayci A, Gibson CM, Chi G, Yee MK, Korjian S, Datta S, Nafee T, Gurin M, Haroian N, Qamar I, et al. Asymptomatic deep vein thrombosis is associated with an increased risk of death: insights from the APEX trial. *Thromb Haemost*. 2018;118:2046–2052. doi: 10.1055/s-0038-1675606
80. Fu AZ, Feng X, Ashton V, Kharat A. Risk factors for recurrent venous thromboembolism: a real-world analysis. *Blood Coagul Fibrinolysis*. 2022;33:301–309. doi: 10.1097/MBC.0000000000001140
81. Wiegers HMG, Knijp J, van Es N, Coppens M, Moll S, Klok FA, Middeldorp S. Risk of recurrence in women with venous thromboembolism related to estrogen-containing contraceptives: systematic review and meta-analysis. *J Thromb Haemost*. 2022;20:1158–1165. doi: 10.1111/jth.15661
82. Lakhter V, Zack CJ, Brailovsky Y, Azizi AH, Weinberg I, Rosenfield K, Schainfeld R, Kolluri R, Katz P, Zhao H, et al. Predictors of intracranial hemorrhage in patients treated with catheter-directed thrombolysis for deep vein thrombosis. *J Vasc Surg Venous Lymphat Disord*. 2021;9:627–634.e2. doi: 10.1016/j.jvsv.2020.08.029
83. Mir T, Uddin M, Shafi O, Qureshi W, Kaur J, Zghouzi M, Lohia P, Soubani A, Burket M, Sheikh M, et al. Thrombotic superior vena cava syndrome: a national emergency department database study. *J Thromb Thrombolysis*. 2022;53:372–379. doi: 10.1007/s11239-021-02548-7
84. Prandoni P, Ageno W, Ciammaichella M, Mumoli N, Zanatta N, Imberti D, Visona A, Bucherini E, Di Nisio M, Noventa F; DOAC-PTS Investigators. The risk of post-thrombotic syndrome in patients with proximal deep vein thrombosis treated with the direct oral anticoagulants. *Intern Emerg Med*. 2020;15:447–452. doi: 10.1007/s11739-019-02215-z
85. Centers for Disease Control and Prevention and National Center for Health Statistics. National Ambulatory Medical Care Survey (NAMCS) public use data files. Accessed April 1, 2023. https://cdc.gov/nchs/ahcd/datasets_documentation_related.htm#data
86. Stein PD, Matta F, Hughes MJ. Site of deep venous thrombosis and age in the selection of patients in the emergency department for hospitalization versus home treatment. *Am J Cardiol*. 2021;146:95–98. doi: 10.1016/j.amjcard.2021.01.024
87. Dore RK, Antonova JN, Burudpakdee C, Chang L, Gorritz M, Genovese MC. The incidence, prevalence, and associated costs of anemia, malignancy, venous thromboembolism, major adverse cardiovascular events, and infections in rheumatoid arthritis patients by treatment history in the United States. *ACR Open Rheumatol*. 2022;4:473–482. doi: 10.1002/acr2.11376
88. Setyawan J, Mu F, Zichlin ML, Billmyer E, Downes N, Yang H, Azimi N, Strand V, Yarur A. Risk of thromboembolic events and associated healthcare costs in patients with inflammatory bowel disease. *Adv Ther*. 2022;39:738–753. doi: 10.1007/s12325-021-01973-7
89. Khoury H, Lyons R, Sanaiha Y, Rudasill S, Shemin RJ, Benharash P. Deep venous thrombosis and pulmonary embolism in cardiac surgical patients. *Ann Thorac Surg*. 2020;109:1804–1810. doi: 10.1016/j.athoracsur.2019.09.055
90. RIETE Registry. Death within 30 days: venous thromboembolism. Accessed February 28, 2023. https://rieteregistry.com/graphics-interactives/dead-30-days/
91. Kurata S, Miyayama N, Ogawa K, Watanabe K, Asano K, Fujii T. Thromboembolic events in hospitalised patients with COVID-19: ecological assessment with a scoping review. *BMJ Open*. 2023;13:e066218. doi: 10.1136/bmjopen-2022-066218
92. Cires-Drouet RS, Fangyang L, Rosenberger S, Startzel M, Kidwell M, Yokemick J, McDonald T, Carlin M, Sharma J, Sorkin JD, et al. High prevalence of chronic venous disease among health care workers in the United States. *J Vasc Surg Venous Lymphat Disord*. 2020;8:224–230. doi: 10.1016/j.jvsv.2019.10.017
93. Pappas PJ, Pappas SF, Nguyen KQ, Lakhanpal S. Racial disparities in the outcomes of superficial vein treatments for chronic venous insufficiency. *J Vasc Surg Venous Lymphat Disord*. 2020;8:789–798.e3. doi: 10.1016/j.jvsv.2019.12.076

94. DeCarlo C, Boitano LT, Waller HD, Pendleton AA, Latz CA, Tanious A, Kim Y, Mohapatra A, Dua A. Pregnancy conditions and complications associated with the development of varicose veins. *J Vasc Surg Venous Lymphat Disord*. 2022;10:872–878.e68. doi: 10.1016/j.jvsv.2022.01.003
95. Mok Y, Ishigami J, Sang Y, Kucharska-Newton AM, Salameh M, Schrack JA, Palta P, Coresh J, Windham BG, Lutsey PL, et al. Clinically recognized varicose veins and physical function in older individuals: the ARIC study. *J Gerontol A Biol Sci Med Sci*. 2022;77:1637–1643. doi: 10.1093/gerona/glab287
96. Galanaud JP, Monreal M, Kahn SR. Epidemiology of the post-thrombotic syndrome. *Thromb Res*. 2018;164:100–109. doi: 10.1016/j.thromres.2017.07.026
97. Nishimoto Y, Yamashita Y, Morimoto T, Saga S, Amano H, Takase T, Hiramori S, Kim K, Oi M, Akao M, et al; COMMAND VTE Registry Investigators. Risk factors for post-thrombotic syndrome in patients with deep vein thrombosis: from the COMMAND VTE registry. *Heart Vessels*. 2019;34:669–677. doi: 10.1007/s00380-018-1277-3
98. Rabinovich A, Ducruet T, Kahn SR, Shapiro S, Tagalakis V, Johri M, Chagnon I, Solymoss S, Opatrny L, Miron MJ, et al. Development of a clinical prediction model for the postthrombotic syndrome in a prospective cohort of patients with proximal deep vein thrombosis. *J Thromb Haemost*. 2018;16:262–270. doi: 10.1111/jth.13909
99. Dronkers CEA, Mol GC, Maraziti G, Van De Ree MA, Huisman MV, Becattini C, Klok FA. Predicting post-thrombotic syndrome with ultrasonographic follow-up after deep vein thrombosis: a systematic review and meta-analysis. *Thromb Haemost*. 2018;118:1428–1438. doi: 10.1055/s-0038-1666859
100. Natour AK, Rteil A, Corcoran P, Weaver M, Ahsan S, Kabbani L. Socioeconomic status and clinical stage of patients presenting for treatment of chronic venous disease. *Ann Vasc Surg*. 2022;83:305–312. doi: 10.1016/j.avsg.2021.12.010
101. Fiebig A, Krusche P, Wolf A, Krawczak M, Timm B, Nikolaus S, Frings N, Schreiber S. Heritability of chronic venous disease. *Hum Genet*. 2010;127:669–674. doi: 10.1007/s00439-010-0812-9
102. Slonkova V, Slonkova V Jr, Vasku A, Vasku V. Genetic predisposition for chronic venous insufficiency in several genes for matrix metalloproteinases (MMP-2, MMP-9, MMP-12) and their inhibitor TIMP-2. *J Eur Acad Dermatol Venereol*. 2017;31:1746–1752. doi: 10.1111/jdv.14447
103. Raffetto JD, Ligi D, Maniscalco R, Khalil RA, Mannello F. Why venous leg ulcers have difficulty healing: overview on pathophysiology, clinical consequences, and treatment. *J Clin Med*. 2020;10:29. doi: 10.3390/jcm10010029
104. Shadrina AS, Sharapov SZ, Shashkova TI, Tsepilov YA. Varicose veins of lower extremities: insights from the first large-scale genetic study. *PLoS Genet*. 2019;15:e1008110. doi: 10.1371/journal.pgen.1008110
105. Karathanos C, Nana P, Spanos K, Kouvelos G, Brotis A, Matsagas M, Giannoukas A. Efficacy of rivaroxaban in prevention of post-thrombotic syndrome: a systematic review and meta-analysis. *J Vasc Surg Venous Lymphat Disord*. 2021;9:1568–1576.e1. doi: 10.1016/j.jvsv.2021.04.016
106. Ten Cate-Hoek AJ, Amin EE, Bouman AC, Meijer K, Tick LW, Middeldorp S, Mostard GJM, Ten Wolde M, van den Heiligenberg SM, van Wissen S, et al; IDEAL DVT investigators. Individualised versus standard duration of elastic compression therapy for prevention of post-thrombotic syndrome (IDEAL DVT): a multicentre, randomised, single-blind, allocation-concealed, non-inferiority trial. *Lancet Haematol*. 2018;5:e25–e33. doi: 10.1016/S2352-3026(17)30227-2
107. Amin EE, Joore MA, ten Cate H, Meijer K, Tick LW, Middeldorp S, Mostard GJM, ten Wolde M, van den Heiligenberg SM, van Wissen S, et al. Clinical and economic impact of compression in the acute phase of deep vein thrombosis. *J Thromb Haemost*. 2018;16:1555–1563.
108. Whing J, Nandhra S, Nesbitt C, Stansby G. Interventions for great saphenous vein incompetence. *Cochrane Database Syst Rev*. 2021;8:CD005624. doi: 10.1002/14651858.CD005624.pub4
109. Deol ZK, Lakhanpal S, Franzon G, Pappas PJ. Effect of obesity on chronic venous insufficiency treatment outcomes. *J Vasc Surg Venous Lymphat Disord*. 2020;8:617–628.e1. doi: 10.1016/j.jvsv.2020.04.006
110. Obi AT, Afridi S, Lurie F. Management and treatment outcomes of patients undergoing endovenous ablation are significantly different between Intersocietal Accreditation Commission-accredited and nonaccredited vein centers. *J Vasc Surg Venous Lymphat Disord*. 2021;9:346–351. doi: 10.1016/j.jvsv.2020.07.007
111. Cher BAY, Brown CS, Obi AT, Wakefield TW, Henke PK, Osborne NH. Women benefit from endovenous ablation with fewer complications: analysis of the Vascular Quality Initiative Varicose Vein Registry. *J Vasc Surg Venous Lymphat Disord*. 2022;10:1229–1237.e2. doi: 10.1016/j.jvsv.2022.05.013
112. Martinez-Zapata MJ, Vernooij RW, Simancas-Racines D, Uriona Tuma SM, Stein AT, Moreno Carriles RMM, Vargas E, Bonfill Cosp X. Phlebotonics for venous insufficiency. *Cochrane Database Syst Rev*. 2020;11:CD003229. doi: 10.1002/14651858.CD003229.pub4
113. Westby D, Ghoneim BM, Nolan F, Elsharkawi M, Maguire S, Walsh SR. Varicose veins as a risk factor for venous thromboembolism in arthroplasty patients: meta-analysis. *Phlebology*. 2023;38:150–156. doi: 10.1177/02683555221150563
114. Schul MW, Melin MM, Keaton TJ. Venous leg ulcers and prevalence of surgically correctable reflux disease in a national registry. *J Vasc Surg Venous Lymphat Disord*. 2023;11:511–516. doi: 10.1016/j.jvsv.2022.11.005
115. Shi C, Dumville JC, Cullum N, Connaughton E, Norman G. Compression bandages or stockings versus no compression for treating venous leg ulcers. *Cochrane Database Syst Rev*. 2021;7:CD013397. doi: 10.1002/14651858.CD013397.pub2
116. Kolluri R, Lugli M, Villalba L, Varcoe R, Maleti O, Gallardo F, Black S, Forgues F, Lichtenberg M, Hinahara J, et al. An estimate of the economic burden of venous leg ulcers associated with deep venous disease. *Vasc Med*. 2022;27:63–72. doi: 10.1177/1358863X211028298
117. Zheng H, Magee GA, Tan TW, Armstrong DG, Padula WV. Cost-effectiveness of compression therapy with early endovenous ablation in venous ulceration for a Medicare population. *JAMA Netw Open*. 2022;5:e2248152. doi: 10.1001/jamanetworkopen.2022.48152
118. Homs-Romero E, Romero-Collado A, Verdu J, Blanch J, Rascon-Hernan C, Marti-Lluch R. Validity of chronic venous disease diagnoses and epidemiology using validated electronic health records from primary care: a real-world data analysis. *J Nurs Scholarsh*. 2021;53:296–305. doi: 10.1111/jnu.12639
119. Silva MJ, Louzada ACS, da Silva MFA, Portugal MFC, Teivelis MP, Wolosker N. Epidemiology of 869,220 varicose vein surgeries over 12 years in Brazil: trends, costs and mortality rate. *Ann Vasc Surg*. 2022;82:1–6. doi: 10.1016/j.avsg.2021.11.016
120. Rabe E, Regnier C, Goron F, Salmat G, Pannier F. The prevalence, disease characteristics and treatment of chronic venous disease: an international web-based survey. *J Comp Eff Res*. 2020;9:1205–1218. doi: 10.2217/cer-2020-0158
121. Kirsten N, Mohr N, Gensel F, Alhumam A, Bruning G, Augustin M. Population-based epidemiologic study in venous diseases in Germany: prevalence, comorbidity, and medical needs in a cohort of 19,104 workers. *Vasc Health Risk Manag*. 2021;17:679–687. doi: 10.2147/VHRM.S323084
122. Didden E-M, Lee E, Wyckmans J, Quinn D, Perchenet L. Time to diagnosis of pulmonary hypertension and diagnostic burden: a retrospective analysis of nationwide US healthcare data. *Pulm Circ*. 2023;13:e12188. doi: 10.1002/pul2.12188
123. Wilcox SR, Faridi MK, Camargo CA Jr. Demographics and outcomes of pulmonary hypertension patients in United States emergency departments. *West J Emerg Med*. 2020;21:714–721. doi: 10.5811/westjem.2020.2.45187
124. Lutsey PL, Evensen LH, Thenappan T, Prins KW, Walker RF, Farley JF, MacLehose RF, Alonso A, Zakai NA. Incidence and risk factors of pulmonary hypertension after venous thromboembolism: an analysis of a large health care database. *J Am Heart Assoc*. 2022;11:e024358. doi: 10.1161/JAHA.121.024358
125. Chaturvedi A, Kanwar M, Chandrika P, Thenappan T, Raina A, Benza RL. Data on clinical and economic burden associated with pulmonary arterial hypertension related hospitalizations in the United States. *Data Brief*. 2020;32:106303. doi: 10.1016/j.dib.2020.106303
126. Lentine KL, Lam NN, Caliskan Y, Xiao H, Axelrod DA, Costa SP, Levine DJ, Runo JR, Te HS, Rangaswami J, et al. Incidence, clinical correlates, and outcomes of pulmonary hypertension after kidney transplantation: analysis of linked US registry and Medicare billing claims. *Transplantation*. 2022;106:666–675. doi: 10.1097/TP.0000000000003783
127. Munshi RF, Pellegrini JR Jr, Patel P, Kashin M, Kang J, Sexton R, Russe JR, Makaryus AN, Patel P, Thakkar S, et al. Impact of pulmonary hypertension in patients with acute exacerbation of chronic obstructive pulmonary disease and its effect on healthcare utilization. *Pulm Circ*. 2021;11:20458940211046838. doi: 10.1177/20458940211046838
128. Frost AE, Zhao C, Farber HW, Benza R, Yen J, Selej M, Elliott CG. Smoking history and pulmonary arterial hypertension: demographics, onset, and outcomes. *J Heart Lung Transplant*. 2022;42:377–389. doi: 10.1016/j.healun.2022.10.007

129. Kolaitis NA, Zamanian RT, de Jesus Perez VA, Badesch DB, Benza RL, Burger CD, Chakinala MM, Elwing JM, Feldman J, Lammi MR, et al; Pulmonary Hypertension Association Registry Investigators. Clinical differences and outcomes between methamphetamine-associated and idiopathic pulmonary arterial hypertension in the Pulmonary Hypertension Association Registry. *Ann Am Thorac Soc*. 2021;18:613–622. doi: 10.1513/AnnalsATS.202007-774OC
130. Bernardo RJ, Lu D, Ramirez RL 3rd, Hedlin H, Kawut SM, Bull T, De Marco T, Ford HJ, Grinnan D, Klinger JR, et al. Hispanic ethnicity and social determinants of health in pulmonary arterial hypertension: the Pulmonary Hypertension Association Registry. *Ann Am Thorac Soc*. 2022;19:1459–1468. doi: 10.1513/AnnalsATS.202109-1051OC
131. Gillmeyer KR, Rinne ST, Qian SX, Maron BA, Johnson SW, Klings ES, Wiener RS. Socioeconomically disadvantaged veterans experience treatment delays for pulmonary arterial hypertension. *Pulm Circ*. 2022;12:e12171. doi: 10.1002/pul2.12171
132. Dodson MW, Allen-Brady K, Brown LM, Elliott CG, Cannon-Albright LA. Chronic thromboembolic pulmonary hypertension cases cluster in families. *Chest*. 2019;155:384–390. doi: 10.1016/j.chest.2018.10.004
133. Gamou S, Kataoka M, Aimi Y, Chiba T, Momose Y, Isobe S, Hirayama T, Yoshino H, Fukuda K, Satoh T. Genetics in pulmonary arterial hypertension in a large homogeneous Japanese population. *Clin Genet*. 2018;94:70–80. doi: 10.1111/cge.13154
134. Yaoita N, Satoh K, Satoh T, Shimizu T, Saito S, Sugimura K, Tatebe S, Yamamoto S, Aoki T, Kikuchi N, et al. Identification of the novel variants in patients with chronic thromboembolic pulmonary hypertension. *J Am Heart Assoc*. 2020;9:e015902. doi: 10.1161/JAHA.120.015902
135. Rhodes CJ, Batai K, Bleda M, Haimel M, Southgate L, Germain M, Pauciulo MW, Hadinnapola C, Aman J, Girerd B, et al; UK NIHR BioResource Rare Diseases Consortium; UK PAH Cohort Study Consortium; US PAH Biobank Consortium. Genetic determinants of risk in pulmonary arterial hypertension: international genome-wide association studies and meta-analysis. *Lancet Respir Med*. 2019;7:227–238. doi: 10.1016/S2213-2600(18)30409-0
136. Zhu N, Pauciulo MW, Welch CL, Lutz KA, Coleman AW, Gonzaga-Jauregui C, Wang J, Grimes JM, Martin LJ, He H, et al; PAH Biobank Enrolling Centers' Investigators. Novel risk genes and mechanisms implicated by exome sequencing of 2572 individuals with pulmonary arterial hypertension. *Genome Med*. 2019;11:69. doi: 10.1186/s13073-019-0685-z
137. Yan L, Shi W, Liu Z, Zhao Z, Luo Q, Zhao Q, Jin Q, Zhang Y, Li X, Duan A. The benefit of exercise-based rehabilitation programs in patients with pulmonary hypertension: a systematic review and meta-analysis of randomized controlled trials. *Pulm Circ*. 2021;11:20458940211007810. doi: 10.1177/20458940211007810
138. Burger CD, Pruett JA, Lickert CA, Berger A, Murphy B, Drake W. Prostacyclin use among patients with pulmonary arterial hypertension in the United States: a retrospective analysis of a large health care claims database. *J Manag Care Spec Pharm*. 2018;24:291–302. doi: 10.18553/jmcp.2017.17228
139. Barnes H, Brown Z, Burns A, Williams T. Phosphodiesterase 5 inhibitors for pulmonary hypertension. *Cochrane Database Syst Rev*. 2019;1:CD012621. doi: 10.1002/14651858.CD012621.pub2
140. Liu C, Chen J, Gao Y, Deng B, Liu K. Endothelin receptor antagonists for pulmonary arterial hypertension. *Cochrane Database Syst Rev*. 2021;3:CD004434. doi: 10.1002/14651858.CD004434.pub6
141. Hoeper MM, Al-Hiti H, Benza RL, Chang SA, Corris PA, Gibbs JSR, Grunig E, Jansa P, Klinger JR, Langleben D, et al; REPLACE Investigators. Switching to riociguat versus maintenance therapy with phosphodiesterase-5 inhibitors in patients with pulmonary arterial hypertension (REPLACE): a multicentre, open-label, randomised controlled trial. *Lancet Respir Med*. 2021;9:573–584. doi: 10.1016/S2213-2600(20)30532-4
142. Barnes H, Yeoh HL, Fothergill T, Burns A, Humbert M, Williams T. Prostacyclin for pulmonary arterial hypertension. *Cochrane Database Syst Rev*. 2019;5:CD012785. doi: 10.1002/14651858.CD012785.pub2
143. Garry JD, Kolaitis NA, Kronmal R, Thenappan T, Hemnes A, Grinnan D, Bull T, Chakinala MM, Horn E, Simon MA, et al; Pulmonary Hypertension Association Registry Investigators. Anticoagulation in pulmonary arterial hypertension: association with mortality, healthcare utilization, and quality of life: the Pulmonary Hypertension Association Registry (PHAR). *J Heart Lung Transplant*. 2022;41:1808–1818. doi: 10.1016/j.healun.2022.08.019
144. Kerr KM, Elliott CG, Chin K, Benza RL, Channick RN, Davis RD, He F, LaCroix A, Madani MM, McLaughlin VV, et al. Results from the United States Chronic Thromboembolic Pulmonary Hypertension Registry: enrollment characteristics and 1-year follow-up. *Chest*. 2021;160:1822–1831. doi: 10.1016/j.chest.2021.05.052
145. Gillmeyer KR, Miller DR, Glickman ME, Qian SX, Klings ES, Maron BA, Hanlon JT, Rinne ST, Wiener RS. Outcomes of pulmonary vasodilator use in Veterans with pulmonary hypertension associated with left heart disease and lung disease. *Pulm Circ*. 2021;11:20458940211001714. doi: 10.1177/20458940211001714
146. Trammell AW, Shah AJ, Phillips LS, Michael Hart C. Mortality in US veterans with pulmonary hypertension: a retrospective analysis of survival by subtype and baseline factors. *Pulm Circ*. 2019;9:2045894019825763. doi: 10.1177/2045894019825763
147. Chang KY, Duval S, Badesch DB, Bull TM, Chakinala MM, De Marco T, Frantz RP, Hemnes A, Mathai SC, Rosenzweig EB, et al; PHAR Investigators. Mortality in pulmonary arterial hypertension in the modern era: early insights from the Pulmonary Hypertension Association Registry. *J Am Heart Assoc*. 2022;11:e024969. doi: 10.1161/JAHA.121.024969
148. Kim NH, Fisher M, Poch D, Zhao C, Shah M, Bartolome S. Long-term outcomes in pulmonary arterial hypertension by functional class: a meta-analysis of randomized controlled trials and observational registries. *Pulm Circ*. 2020;10:2045894020935291. doi: 10.1177/2045894020935291
149. Heresi GA, Rao Y. Follow-up functional class and 6-minute walk distance identify long-term survival in pulmonary arterial hypertension. *Lung*. 2020;198:933–938. doi: 10.1007/s00408-020-00402-w
150. Billings CG, Lewis R, Hurdman JA, Condliffe R, Elliot CA, Thompson AAR, Smith IA, Austin M, Armstrong IJ, Hamilton N, et al. The incremental shuttle walk test predicts mortality in non-group 1 pulmonary hypertension: results from the ASPIRE Registry. *Pulm Circ*. 2019;9:2045894019848649. doi: 10.1177/2045894019848649
151. Low TT, Guron N, Ducas R, Yamamura K, Charla P, Granton J, Silversides CK. Pulmonary arterial hypertension in pregnancy: a systematic review of outcomes in the modern era. *Pulm Circ*. 2021;11:20458940211013671. doi: 10.1177/20458940211013671
152. Rohlfing AB, Bischoff KE, Kolaitis NA, Kronmal RA, Kime NA, Gray MP, Bartolome S, Chakinala MM, Frantz RP, Ventetuolo CE, et al; PHAR Investigators. Palliative care referrals in patients with pulmonary arterial hypertension: the Pulmonary Hypertension Association Registry. *Respir Med*. 2023;206:107066. doi: 10.1016/j.rmed.2022.107066
153. Macias CG, Wharam JF, Maron BA, Ong MS. Urban-rural disparities in pulmonary hypertension mortality. *Ann Am Thorac Soc*. 2020;17:1168–1171. doi: 10.1513/AnnalsATS.202003-234RL
154. Studer S, Hull M, Pruett J, Koep E, Tsang Y, Drake W. Treatment patterns, healthcare resource utilization, and healthcare costs among patients with pulmonary arterial hypertension in a real-world US database. *Pulm Circ*. 2019;9:2045894018816294. doi: 10.1177/2045894018816294
155. Saunders H, Helgeson SA, Abdelrahim A, Rottman-Pietrzak K, Reams V, Zeiger TK, Moss JE, Burger CD. Comparing diagnosis and treatment of pulmonary hypertension patients at a pulmonary hypertension center versus community centers. *Diseases*. 2022;10:5. doi: 10.3390/diseases10010005
156. Emmons-Bell S, Johnson C, Boon-Dooley A, Corris PA, Leary PJ, Rich S, Yacoub M, Roth GA. Prevalence, incidence, and survival of pulmonary arterial hypertension: a systematic review for the global burden of disease 2020 study. *Pulm Circ*. 2022;12:e12020. doi: 10.1002/pul2.12020
157. Wijeratne DT, Lajkosz K, Brogly SB, Lougheed MD, Jiang L, Housin A, Barber D, Johnson A, Doliszny KM, Archer SL. Increasing incidence and prevalence of world health organization groups 1 to 4 pulmonary hypertension. *Circulation*. 2018;11:e003973. doi: 10.1161/CIRCOUTCOMES.117.003973
158. Hoeper MM, Humbert M, Souza R, Idrees M, Kawut SM, Sliwa-Hahnle K, Jing ZC, Gibbs JS. A global view of pulmonary hypertension. *Lancet Respir Med*. 2016;4:306–322. doi: 10.1016/S2213-2600(15)00543-3
159. Martinez C, Wallenhorst C, Teal S, Cohen AT, Peacock AJ. Incidence and risk factors of chronic thromboembolic pulmonary hypertension following venous thromboembolism, a population-based cohort study in England. *Pulm Circ*. 2018;8:2045894018791358. doi: 10.1177/2045894018791358
160. Pang W, Zhang Z, Wang Z, Zhen K, Zhang M, Zhang Y, Gao Q, Zhang S, Tao X, Wan J, et al. Higher incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism in Asians than in Europeans: a meta-analysis. *Front Med (Lausanne)*. 2021;8:721294. doi: 10.3389/fmed.2021.721294
161. Gall H, Hoeper MM, Richter MJ, Cacheris W, Hinzmann B, Mayer E. An epidemiological analysis of the burden of chronic thromboembolic pulmonary hypertension in the USA, Europe and Japan. *Eur Respir Rev*. 2017;26:160121. doi: 10.1183/16000617.0121-2016

# 25. PERIPHERAL ARTERY DISEASE AND AORTIC DISEASES

***ICD-9 440.20 to 440.24, 440.30 to 440.32, 440.4, 440.9, 443.9, 445.02; ICD-10 I70.2, I70.9, I73.9, I74.3, I74.4.***

***See Tables 25-1 through 25-3 and Charts 25-1 through 25-5***

Click here to return to the Table of Contents

Click here to return to the Abbreviations

## Peripheral Artery Disease

### *Prevalence*

### *(See Charts 25-1 and 25-2)*

- Population-based estimates indicate that ≈6.5 million individuals (5.8%) ≥40 years of age have PAD, defined as an ABI <0.9, on the basis of the most contemporary pooled data from 7 US cohorts obtained between the 1970s and 2000s and extrapolated from the 2000 US census.[1] Estimates of PAD prevalence by age, sex, and race and ethnicity are shown in Charts 25-1 and 25-2.
  - PAD prevalence increases with age, approximately doubling per decade.[1,2]
  - PAD prevalence in males and females varies by age, race, and ethnicity.[1]
  - PAD prevalence is greater in Black compared with NH White individuals, particularly after 50 and 60 years of age in males and females, respectively.[1,2]
- Approximately 8.5 million adults (7.2%) ≥40 years of age have PAD when individuals with borderline ABI values of 0.90 to 0.99 are included in the aforementioned analysis.[1]

### *Incidence*

- Among individuals >40 years of age, the annual incidence of PAD and CLTI was 2.69% and 0.35%, respectively, when defined with *ICD* codes extracted from nationwide claims data from large employers' health plans and from Medicare and Medicaid programs between 2003 and 2008.[3]
- Among 77 041 individuals in the Veterans Affairs Birth Cohort born between 1945 and 1965 with normal baseline ABIs, risk of incident PAD, defined as subsequent ABI <0.90, surgical or percutaneous revascularization, or nontraumatic amputation, varied by sex and race.[4]
  - Females were at lower risk of incident PAD compared with males (multivariable-adjusted HR, 0.49 [95% CI, 0.41–0.59]).
  - Black participants had an increased risk of incident PAD compared with White participants (multivariable-adjusted HR, 1.09 [95% CI, 1.02–1.16]). This increased overall risk was attributed to a greater risk of amputation (multivariable-adjusted HR, 1.20 [95% CI, 1.06–1.36]) without an increased risk of revascularization (multivariable-adjusted HR, 1.10 [95% CI, 0.98–1.23]) or subsequent ABI <0.90 (multivariable-adjusted HR, 1.04 [95% CI, 0.95–1.13]).

### *Lifetime Risk and Cumulative Incidence*

- The lifetime risk (80-year horizon) of PAD, defined as an ABI <0.90, was estimated at ≈19%, 22%, and 30% in White, Hispanic, and Black individuals, respectively, with the use of pooled data from 6 US community-based cohorts.[5]

### *Secular Trends*

### *(See Table 25-1)*

- Between 2011 and 2019, the prevalence of PAD, defined as an ABI ≤0.9, was 5.56% with a higher prevalence in high- compared with low- to middle-income countries (7.37% versus 5.09%, respectively).[6]
- From 2011 to 2017, the proportion of hospitalizations for PAD increased from 4.5% to 8.9% ($P_{trend}$<0.0001) according to NIS data.[7]
- Similarly, from 2011 to 2017, the proportion of hospitalizations for CLTI increased from 0.9% to 1.4% ($P_{trend}$<0.0001) in the NIS.[7]
- From 2010 to 2020, principal discharge diagnosis for PAD decreased from 134 308 to 69 390 (HCUP, unpublished NHLBI tabulation; Table 25-1).
- Between 2011 and 2017, the annual rate of endovascular lower-extremity peripheral artery interventions increased from 464.47 to 509.99 per 100 000 individuals among Medicare beneficiaries.[8]
- Between 2005 and 2014, the proportion of patients hospitalized for CLTI who underwent endovascular-only treatment within 90 days increased from 11.2% to 18.4% compared with an increase in surgical-only treatment from 23.8% to 26.4%.[9]
- Rates of lower-extremity amputation are also increasing.
  - Between 2009 and 2015, a 50% increase in the rate of nontraumatic lower-extremity amputation was observed in adults with diabetes according to NIS data.[10]

The 2024 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2024. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

– Among patients in the Veterans Affairs health care system, rates of lower-extremity amputation increased from 12.89 (95% CI, 12.53–13.25) per 10 000 individuals to 18.12 (95% CI, 17.70–18.54) per 10 000 individuals from 2008 to 2018.[11]

### *Risk Factors*

- Modifiable PAD risk factors largely parallel those for atherosclerosis in other vascular beds such as CAD and include smoking, diabetes, hypertension, and atherogenic dyslipidemia.[2,5,6,12]
  - Current or former smoking is among the strongest PAD risk factors, with ORs ranging from 1.3 to 5.4 (all $P<0.05$) and relatively greater risk among current smokers.[2,5]
    Heavy smoking, defined by pack-years, smoking duration, or smoking intensity, is a stronger risk factor for PAD compared with CAD (all $P<0.05$).[13]
  - Diabetes is associated with increased risk for PAD, with ORs ranging from 1.38 to 1.89.[5,6]
  - Hypertension, defined as BP ≥140/90 mm Hg, is associated with ≈50% increased odds of PAD (OR, 1.67 [95% CI, 1.50–1.86]).[6]
    - Each 20–mm Hg increase in SBP was associated with an OR of 1.27 (95% CI, 1.22–1.32) for PAD.[5]
    - Among patients treated for hypertension, SBP is more strongly associated with incident PAD (HR per 1-SD increase in SBP, 1.46 [95% CI, 1.29–1.65]) than DBP (HR per 1-SD increase in DBP, 1.12 [95% CI, 0.97–1.30]).[14]
  - In both ARIC and WHS, each 1-SD increase in both TC and LDL-C was not associated with incident PAD (all $P>0.05$) but was associated with incident CAD.[15,16]
    - In contrast, each 1-SD decrease in HDL-C is strongly associated with incident PAD (HR, 1.39 [95% CI, 1.16–1.67] and 1.92 [95% CI, 1.49–2.50], respectively).[15,16]
    - Further lipid subfraction analyses suggest that markers of atherogenic dyslipidemia, including elevated concentrations of triglyceride-rich lipoproteins such as small LDL particles (HR, 2.17 [95% CI, 1.10–4.27]) and total HDL particles (HR, 0.29 [95% CI, 0.16–0.52]), are independently associated with PAD.[15–18]
    - With the use of mendelian randomization, apolipoprotein B–lowering therapy was predicted to have a greater reduction in CAD risk (per 1-SD reduction: OR, 0.66 [95% CI, 0.63–0.69]; $P=4\times10^{-73}$) than PAD risk (per 1-SD reduction: OR, 0.87 [95% CI, 0.84–0.91]; $P=9\times10^{-9}$).[19]
    - Mendelian randomization also suggests a causal link between lipoprotein(a) and PAD among individuals of both European (per 1-SD increase: OR, 1.22 [95% CI, 1.11–1.34]; $P=2.97\times10^{-5}$) and African (per 1-SD increase: OR, 1.16 [95% CI, 1.01–1.33]; $P=0.034$) ancestries.[20]
  - Smoking, type 2 diabetes, hypertension, and hypercholesterolemia accounted for 75% (95% CI, 64%–87%) of risk associated with the development of clinical PAD in the HPFS of males.[21]
  - MetS was associated with increased risk for incident PAD according to data from the CHS (HR, 1.47 [95% CI, 1.11–1.94]) and WHS (HR, 1.48 [95% CI, 1.00–2.19]).[22,23]
- Other possible PAD risk factors include sedentary lifestyle, inflammation, hypertension in pregnancy, and CKD.[12,22,24,25]
- Mediterranean diet compared with counseling for a low-fat diet was associated with a lower risk of incident PAD according to a secondary analysis of a randomized feeding trial conducted in Spain between 2003 and 2010.[26]

### *Social Determinants of Health/Health Equity*

- Lower income and lower education are associated with greater incidence and prevalence of PAD according to ARIC and NHANES (1999–2004) data, respectively.[27,28]
- Lower SES is associated with greater risk for amputation (HR, 1.12 [95% CI, 1.06–1.17]).[29]
- Among patients with PAD requiring revascularization or amputation in the Vascular Quality Initiative, neighborhood social disadvantage, measured with the area deprivation index, was associated with later presentation and a lower likelihood of limb salvage.[30]
  - Compared with those in the lowest quintile of the area deprivation index, those in the highest quintile were more likely to present with rest pain compared with claudication (RR, 2.0 [95% CI, 1.8–2.2]; $P<0.001$) or tissue loss compared with claudication (RR, 1.4 [95% CI, 1.3–1.6]; $P<0.001$).
  - Compared with those in the lowest quintile of the area deprivation index, those in the highest quintile were also less likely to undergo attempts at revascularization (RR, 0.59 [95% CI, 0.51–0.70]; $P<0.001$).
- The rate of lower-extremity amputation varies geographically within the United States and may be influenced by patient rurality and race.[31]
  - Among Medicare beneficiaries, zip codes in the top quartile of amputation rates had a larger mean proportion of Black residents than zip codes in the bottom quartile (17.5% versus 4.4%; $P<0.001$).[31]
  - Data from the Vascular Quality Initiative suggest that individuals from underrepresented racial and

ethnic groups living in rural areas have a 52% greater odds of amputation than people from underrepresented racial and ethnic groups living in urban areas (95% CI, 1.19–1.94).[32]

### Risk Prediction

- Models for predicting the probability of an ABI <0.9 have been developed from NHANES data.[5,33] Included variables were age, sex, race, pulse pressure, TC and HDL (or their ratio), and smoking status, with a C statistic of 0.76 (95% CI, 0.72–0.79).[33] Another model with NHANES data additionally included diabetes and history of CAD or stroke, which yielded a similar C statistic of 0.75.[5,34]

### Genetics/Family History

- Atherosclerotic PAD is heritable. Monozygotic twins compared with dizygotic twins had a greater risk for PAD with an OR of 17.7 (95% CI, 11.7–26.6) and 5.7 (95% CI, 4.1–7.9), respectively, in the Swedish Twin Registry, with heritable factors accounting for 58% of phenotypic variance between twins.[35] Chip-based genetic analyses similarly suggest that the heritability of PAD is 55%.[36]
- GWASs have identified genetic loci associated with common atherosclerotic PAD, including the CHD-associated chromosome 9p21 genetic locus associated with PAD, AAA, and intracranial aneurysm.[37]
  - Other common PAD-associated genetic loci include SNPs on chromosome 9 near the *CDKN2B*, *DAB21P*, and *CYBA* genes.[38]
  - A large-scale GWAS in >31 000 cases with PAD and >211 000 controls from the Million Veteran Program and the UK Biobank identified 18 new PAD loci. Eleven of the loci were associated with atherosclerotic disease in 3 vascular beds, including *LDLR*, *LPA*, and *LPL*, whereas 4 of the variants were specific for PAD (including variants in *TCF7L2* and *F5*).[39]
  - Given this overlap between genetic risk factors between different vascular beds, a GRS composed of genetic variants associated with CAD has been shown to be associated with PAD in the UK Biobank (OR, 1.28 [95% CI, 1.23–1.32]).[40] In another study, targeted sequencing of 41 genome regions associated with CAD performed in 1749 cases with PAD and 1855 controls found overlap of several genes between CAD and PAD.[41]
- Mendelian randomization has been used to examine evidence of causality for several putative PAD risk factors, including hemostatic measures, lipoproteins, smoking, and BP phenotypes. These studies reported that genetically determined increases in factor VIII, von Willebrand factor, apolipoprotein B, very low-density lipoprotein, smoking, SBP, DBP, and pulse pressure increased PAD risk.[19,42–44]
- One GWAS of 449 548 participants of European ancestry (12 086 PAD cases) examined evidence of SNP-by-smoking and SNP–by–type 2 diabetes interaction on PAD.[36] The authors reported a lead variant at *CCSER1* that showed genome-wide significant evidence of association with PAD in the total population ($P$=2.5×10$^{-8}$) and genome-wide suggestive evidence of interaction with type 2 diabetes ($P$=5.3×10$^{-7}$).
- The proportion of variance that 2 traits share attributable to genetic causes (ie, genetic correlation) of PAD with CAD, BMI, HDL-C, LDL-C, triglycerides, type 2 diabetes, and SBP has been reported.[36] Strong genetic correlation between PAD and CAD was reported ($r_g$=0.58). BMI, type 2 diabetes, LDL-C, triglycerides, and SBP also showed evidence of positive genetic correlation with PAD. HDL-C showed evidence of negative genetic correlation with PAD, suggesting that SNPs associated with higher levels of HDL-C are associated with lower PAD risk.

### Prevention (Primary)

- Approaches to primary prevention of PAD extrapolate from recommendations for prevention of atherosclerotic disease with a focus on optimization of healthy lifestyle behaviors (healthy diet, PA, and never-smoking), avoidance of the development of modifiable risk factors, and control of the modifiable risk factors if present.[45]

### Awareness, Treatment, and Control

#### Awareness

- Awareness of PAD, its risk factors, and its complications is relatively low.
  - In a US-based survey of 2501 adults ≥50 years of age in 2006, 25% of individuals expressed familiarity with PAD compared with 67.1% for CAD and 73.9% for stroke.[46]
    - Of those familiar with PAD, ≈50% were aware of smoking, diabetes, hypertension, and dyslipidemia as PAD risk factors.[46]
    - Approximately 25% to 28% knew that PAD is associated with increased risk of MI and stroke, with 14% awareness of amputation or death as a PAD-related complication.[46]
    - Income and education levels were positively associated with all knowledge domain levels.[46]
  - Physicians may underappreciate and undertreat PAD.
    - Patients with PAD receive optimal medical therapy less frequently than patients with CAD. Data from the MarketScan and Medicare databases showed that only 33.9% of patients with PAD were prescribed statins compared with 51.7% of patients with CAD.[47]

- Similarly, only 24.5% of patients with PAD in the MarketScan database achieved a target LDL-C <70 mg/dL.[48]

### *Treatment*

- Treatment of patients with lower-extremity PAD is summarized in the 2016 AHA/ACC guideline and includes addressing modifiable risk factors such as PA, smoking cessation, dyslipidemia, BP and glycemic control, and revascularization approaches.[45]
  - Optimal exercise programs for patients with PAD are summarized in a 2019 AHA scientific statement.[50]
  - In a 2017 Cochrane review with meta-analysis, aerobic exercise compared with usual care was associated with the following[51]:
    - Increased pain-free walk distance (mean difference, 82 m [95% CI, 72–92])
    - Increased maximum walk distance (mean difference, 120 m [95% CI, 51–190])
  - In a randomized trial of optimal medical care, supervised exercise training, and iliac artery stent placement, supervised exercise resulted in superior treadmill walking time at 6 months compared with stenting (mean increase from baseline, 5.8±4.6 minutes versus 3.7±4.9 minutes; *P*=0.04). Results in the exercise group and stent group were superior to results in the group with optimal medical care alone (1.2±2.6 minutes).[52]
  - Smoking cessation compared with continued smoking is associated with lower risks of death (HR, 0.33 [95% CI, 0.13–0.80]), MI (11% versus 53% at 10-year follow-up; *P*=0.043), and amputation (HR, 0.40 [95% CI, 0.19–0.83]) among patients with PAD in observational studies.[53,54]
    - In a retrospective analysis of patients with PAD and intermittent claudication undergoing revascularization in the Veterans Affairs health care system, smokers were more likely to experience wound complications (absolute risk difference, 4.05% [95% CI, 2.12%–5.99%]; *P*<0.001) or graft failure (absolute risk difference, 1.50% [95% CI, 0.63%–2.37%]; *P*=0.001) compared with nonsmokers.[55]
  - Lipid-lowering therapy with a high-intensity statin and, in some cases, a PCSK9 inhibitor is recommended for the treatment of PAD.[45,55,56]
    - Among 155 647 patients with incident PAD in the Veterans Affairs health system, high-intensity statin use was associated with a lower risk of both amputation (HR, 0.67 [95% CI, 0.61–0.74]) and mortality (HR, 0.74 [95% CI, 0.70–0.77]).[57]
    - In a subanalysis of the FOURIER trial, compared with placebo, the PCSK9 inhibitor evolocumab reduced the risk of major adverse limb events, including acute limb ischemia, major amputation, and urgent revascularization (HR, 0.58 [95% CI, 0.38–0.88]), in patients with and without existing PAD and already receiving statin therapy.[58]
    - In a subanalysis of the ODYSSEY Outcomes trial, compared with placebo, the PCSK9 inhibitor alirocumab similarly reduced the risk of major adverse limb events, including CLTI, limb revascularization, or amputation (HR, 0.69 [95% CI, 0.54–0.80]).[59]
- The antithrombotic medication rivaroxaban, in addition to aspirin, may reduce the risk of adverse limb outcomes (eg, revascularization or amputation) among patients with PAD.[60]
  - In a subanalysis of the COMPASS trial, among the 6391 subjects with PAD at baseline, compared with aspirin alone, the combination of rivaroxaban 2.5 mg twice daily plus aspirin 100 mg daily was associated with lower risk of major adverse limb events (2.6% versus 1.5%; HR, 0.57 [95% CI, 0.37–0.88]; *P*=0.01).[60]
  - In the VOYAGER trial, among 6564 subjects with PAD who recently underwent lower-extremity revascularization, compared with aspirin alone, the combination of rivaroxaban 2.5 mg twice daily plus aspirin 100 mg daily reduced the risk of a composite of major adverse cardiovascular and limb events (17.3% versus 19.9%; HR, 0.85 [95% CI, 0.76–0.96]; *P*=0.009).[61]
- Glycemic control may be associated with better limb outcomes among patients with PAD according to observational studies[62,63]:
  - In 149 patients with diabetes, 1-year patency after infrapopliteal percutaneous intervention was greater among patients with below- compared with above-median FPG (HR, 1.8 [95% CI, 1.2–2.8]).[62]
  - Among 197 Japanese patients with diabetes who underwent percutaneous transluminal angioplasty for CLTI, an HbA1c ≥6.8% was associated with 2.91 times greater risk for major amputation (95% CI, 1.61–5.26) over a mean follow-up of 1.7 years.[63]
- Surgical revascularization may be superior to endovascular therapy in select patients with CLTI.[64]
  - In the BEST-CLI trial, 1 cohort of 1434 patients with CLTI and an adequate great saphenous vein for grafting underwent randomization to either initial surgical or endovascular revascularization. Initial surgical revascularization was associated with a reduction in the primary outcome of major adverse limb events or death resulting from any cause compared with initial endovascular revascularization (HR, 0.68 [95% CI, 0.59–0.79]; *P*<0.001).[64]

- In a second cohort of 396 patients with CLTI but without an adequate great saphenous vein, initial surgical revascularization did not reduce major adverse limb events or death resulting from any cause compared with initial endovascular revascularization (HR, 0.79 [95% CI, 0.58–1.06]; $P$=0.12).[64]

- Revascularization for patients with claudication or CLTI may be associated with improvement in quality of life and limb preservation. A meta-analysis of 10 studies found that revascularization was associated with improved quality of life on the basis of a 6.1-point improvement (95% CI, 3.0–9.2) in the Short Form-36 physical functioning domain.[65]
  - Similarly, in a propensity-matched sample from the PORTRAIT registry, those who underwent early invasive management for claudication had a greater improvement in health status at 1 year compared with those treated noninvasively according to the Peripheral Artery Questionnaire ($P$<0.001 for all questionnaire domains).[66]

## Mortality

### (See Table 25-1)

- In 2021, PAD was the underlying cause in 11 549 deaths. The number of any-mention deaths attributable to PAD was 62 431 (Table 25-1; unpublished NHLBI tabulation using NVSS[67] and CDC WONDER).[68]
- In 2021, the overall any-mention age-adjusted death rate for PAD was 15.5 per 100 000 (unpublished NHLBI tabulation using CDC WONDER).[68]
  - Any mention-death rates were 13.2 for NH White females, 16.0 for NH Black females, 5.6 for NH Asian females, 7.9 for NH Native Hawaiian or Other Pacific Islander females, 13.9 for NH American Indian or Alaska Native females, and 9.9 for Hispanic females.
  - Any mention-death rates were 19.3 for NH White males, 24.5 for NH Black males, 7.0 for NH Asian males, 11.6 for NH Native Hawaiian or Other Pacific Islander males, 20.9 for NH American Indian or Alaska Native males, and 15.0 for Hispanic males.
- A meta-analysis of 16 cohorts including a total of 48 294 individuals (48% female) demonstrated a continuous association between ABI and mortality. Increased all-cause and cardiovascular mortality risk began at an ABI ≤1.1, whereas individuals with an ABI between 1.11 and 1.40 had the lowest risk.[69]
  - ABI ≤0.9 was associated with approximately triple the risk of all-cause death compared with ABI of 1.11 to 1.40 in both males (RR, 3.33 [95% CI, 2.74–4.06]) and females (RR, 2.71 [95% CI, 2.03–3.62]).[69]
- In EUCLID, females with symptomatic PAD were at lower risk of both all-cause and cardiovascular mortality (HR, 0.61 [95% CI, 0.53–0.71], $P$<0.001; HR, 0.65 [95% CI, 0.54–0.78], $P$<0.001, respectively).[70]
  - In contrast, based on data from 2011 to 2017 in the NIS, in-hospital mortality for patients with CLTI was higher for females compared with males (OR, 1.13 [95% CI, 1.11–1.14]).[7]

## Complications

### Cardiovascular Disease

- Individuals with PAD are at heightened risk for other types of CVD.
  - In EUCLID, participants with PAD had a cumulative incidence of stroke and TIA of 0.87 per 100 patient-years and 0.27 per 100-patient years, respectively.[71]
  - Similarly, the incidence of type 1 MI in EUCLID was 2.4 events per 100 patient-years.[72]

### Tissue (Limb) Loss

- Among 6 493 141 veterans followed up from 2008 to 2018, PAD was independently associated with an increased risk of lower-limb amputation (HR, 3.04 [95% CI, 2.95–3.13]).[11]
- Risk factors for amputation were evaluated in 2 730 742 Medicare beneficiaries ≥65 years of age with PAD using data from 2000 to 2008[73]:
  - Black versus White race and diabetes each accounted for ≈30% of the multivariable-adjusted logistic model for predicting lower-extremity amputation and had an OR of 2.90 (95% CI, 2.83–2.90) and 2.40 (95% CI, 2.38–2.43), respectively. Dementia (OR, 2.09 [95% CI, 2.05–2.13]), CKD (OR, 1.63 [95% CI, 1.61–1.65]), cerebrovascular disease (OR, 1.49 [95% CI, 1.47-1.50]), and HF (OR, 1.47 [95% CI, 1.46-1.49]) were the next strongest factors associated with increased risk of amputation. CAD (OR, 0.67 [95% CI, 0.66–0.68]), cancer (OR, 0.82 [95% CI, 0.80-0.83]), and Asian versus White race (OR, 0.89 [95% CI, 0.83-0.95]) were associated with significantly lower risk of amputation. Smoking status was not included in the models.
- In an analysis of 393 017 patients in the Premier Healthcare Database who underwent lower-extremity arterial revascularization, 50 750 patients (12.9%) had at least 1 subsequent hospitalization for major adverse limb events.[74]
- Among Medicare beneficiaries who underwent peripheral vascular interventions from 2016 to 2018, the age- and sex-adjusted incidence of death or major amputation was greater among Black compared with White individuals (25.03% [95% CI, 24.45%–25.61%] versus 18.62% [95% CI, 18.39%–18.85%]).[75]

- Patients with microvascular disease, defined as retinopathy, neuropathy, and nephropathy, were at increased risk for amputation (HR, 3.7 [95% CI, 3.0–4.6]), independently of traditional risk factors and prevalent PAD, among 125 674 patients in the Veterans Aging Cohort Study.[76]
- Mortality by 1 year after major lower-extremity amputation was estimated at 48.3% among 186 338 Medicare patients ≥65 years of age with PAD.[77]

#### *Impaired Quality of Life*

- Even individuals with borderline ABI (0.90–0.99) are at risk for mobility loss, defined as the loss of ability to walk one-quarter of a mile or up and down 1 flight of stairs independently (HR, 3.07 [95% CI, 1.21–7.84]).[78]
- Among patients with PAD, lower PA levels are associated with faster rates of functional decline measured by 6-minute walk distance performance, 4-m walking velocity, and the Short Performance Physical Battery (all $P<0.05$).[79]

#### *Health Care Use: Hospital Discharges and Ambulatory Care Visits*

- In 2019, primary diagnosis of PAD accounted for 1 377 000 physician office visits (NAMCS,[80] unpublished NHLBI tabulation) and, in 2020, 69 390 hospital discharges (HCUP[81] unpublished NHLBI tabulation) and 56 630 ED visits (HCUP[81] unpublished NHLBI tabulation).

#### *Cost*

- Among patients with PAD hospitalized in 2014, median hospitalization costs were $15 755 (95% CI, $8972–$27 800) in 2017 US dollars.[82] This corresponded to an annual cost of hospitalization for PAD of approximately $6.31 billion dollars.
- Among 25 695 patients with PAD between 2009 and 2016 in the Optum Integrated Database, the health care costs incurred over 1 year were substantially higher in those who had a MACE (mean difference, $44 659) or major limb event (mean difference, $34 216) compared with patients without these events.[83]
- In 72 199 Medicare beneficiaries admitted to the hospital in 2011 with CLTI, the average annual health care cost ranged from $49 200 to $55 700.[84]
- In a cohort of 22 203 patients with PAD in Minnesota, total health care costs were approximately $18 000 (2011 US dollars) greater among tobacco users (9.0%) compared with nonusers ($64 041 versus $45 918) over 1 year.[85]

#### *Global Burden*

##### *Prevalence*

*(See Table 25-2 and Charts 25-3)*

- In 2015, an estimated 237 million people worldwide had PAD according to a systematic review of 116 studies.[6]
- Approximately 6.6% of the Chinese population >35 years of age, or 45 million individuals, have PAD according to a population-based survey in China conducted between 2012 and 2015.[86]
- PAD estimates in sub-Saharan Africa range from 3.1% to 24% in adults ≥50 years of age, with the variability possibly due to differences in the prevalence of cardiovascular risk factors in the communities surveyed.[87]
- Based on 204 countries and territories in the GBD Study 2021[88]:
  - PAD affected 113.70 (95% UI, 100.63–129.25) million individuals (Table 25-2).
  - PAD age-standardized prevalence was highest in high-income North America followed by Western Europe and southern Latin America (Chart 25-3).

##### *Mortality*

*(See Table 25-2 and Chart 25-4)*

- In the GBD Study 2021,[88] the age-standardized mortality estimated for PAD was 0.85 (95% UI, 0.75–0.92) per 100 000 individuals (Table 25-2).
  - PAD age-standardized mortality was highest in Central and Eastern Europe and lowest in East and Southeast Asia and Oceania (Chart 25-4).

## Aortic Diseases

### *ICD-9* 440, 441, 444, and 447; *ICD-10* I70, I71, I74, I77, and I79.

#### *Aortic Aneurysm and Acute Aortic Syndromes*

#### *ICD-9 441; ICD-10 I71.*

##### *Prevalence*

- Estimating the prevalence of TAA is challenging because of the relatively few studies in which screening has been performed in the general population.
  - Among 5662 patients who underwent chest CT imaging for any reason in 2016, 121 (2.14%) were incidentally found to have an ascending aorta measuring at least 4.0 cm.[89]
- AAA is more common in males than females, and its prevalence increases with age.[90,91]
  - AAA is ≈4 times more common in males than females on the basis of data from an ultrasound screening study of 125 722 veterans 50 to 79 years of age conducted between 1992 and 1997.[92,93]
    - Approximately 1% of males between 55 and 64 years of age have an AAA ≥4.0 cm, and every decade thereafter, the prevalence increases by 2% to 4%.[94,95]
    - Based on a meta-analysis of data from 19 countries, the global prevalence of AAA measuring at least 3.0 cm in people 30 to 79 years of age was 0.92% (95% CI, 0.65%–1.30%).[96]

### Incidence

- In 2010, the estimated annual incidence rate of AAA per 100 000 individuals was 0.83 (95% CI, 0.61–1.11) and 164.57 (95% CI, 152.20–178.78) in individuals 40 to 44 and 75 to 79 years of age, respectively, according to a meta-analysis of 26 studies.[97]

### Lifetime Risk and Cumulative Incidence

- Between 1995 and 2015, the cumulative incidence of hospitalizations for aortic aneurysm and aortic dissection was ≈0.74% and 0.09%, respectively, on the basis of *ICD* codes from Swedish National Health Register databases.[98]

### Secular Trends

- Between 1995 and 2015, the incidence of aortic dissection, intramural hematoma, or penetrating aortic ulcer remained stable at 10.2 (males) and 5.7 (females) per 100 000 person-years according to data from the Rochester Epidemiology Project.[99]
- Between 1999 and 2016, deaths attributable to ruptured TAA and AAA declined significantly from 5.5 to 1.8 (TAA) and 26.3 to 7.9 (AAA) per million, respectively, according to US NVSS data.[100]

### Risk Factors

- TAAs in younger individuals are more likely caused by heritable thoracic aortic disease or congenital conditions, the prototype examples being Marfan syndrome and bicuspid aortic valve disease. In older individuals 60 to 74 years of age, male sex (OR, 1.9 [95% CI, 1.1–3.1]), hypertension (OR, 1.8 [95% CI, 1.5–2.1]), and family history (OR, 1.6 [95% CI, 1.1–2.2]) contribute to the risk of TAA.[101]
- In a mendelian randomization analysis from the UK Biobank and MVP, genetically predicted SBP, DBP, and mean arterial pressure were all associated with increased ascending thoracic aortic diameter (all $P<0.05$).[102]
- In a meta-analysis of 4 563 501 patients, patients with a history of hypertension were more likely to have aortic dissection than those without hypertension (RR, 3.07 [95% CI, 2.15–4.38]).[103]
- Inflammatory conditions such as giant-cell arteritis, Takayasu arteritis, or infectious aortitis also may cause TAA.
  - Giant-cell arteritis is associated with a 2-fold higher risk for developing a thoracoabdominal aortic aneurysm (sub-HR, 1.92 [95% CI, 1.52–2.41]) even after adjustment for competing risks according to data from the United Kingdom.[104]
- Risk factors for AAA were assessed in a retrospective analysis of 3.1 million patients between 2003 and 2008.[105] Male sex (OR, 5.71 [95% CI, 5.57–5.85]), family history (OR, 3.80 [95% CI, 3.66–3.95]), and hypertension (OR, 1.25 [95% CI, 1.21–1.28]) were strongly associated with developing AAA. Individuals of all groups ≥55 years of age were at greater risk of developing AAA compared with those <55 years of age (all $P<0.0001$).
- Mendelian randomization suggests that genetically predicted height and pulse pressure are associated with infrarenal aortic diameter (all $P<0.05$).[106]
- Data suggest that lipoprotein(a) is linked to AAA risk. In ARIC, individuals with baseline lipoprotein(a) measures in the top quartile were at greater risk of incident AAA than those in the bottom quartile (HR, 1.57 [95% CI, 1.19–2.08]).[107]
  - Mendelian randomization analyses also suggest a causal link between genetically determined lipoprotein(a) levels and AAA in individuals of European (per 1-SD increase: OR, 1.28 [95% CI, 1.17–1.40]) and African (per 1-SD increase: OR, 1.34 [95% CI, 1.11–1.62]) ancestries.[20]
- Diabetes may be associated with lower risk of aortic aneurysmal disease.[101,108,109] A 2014 systematic review of 17 community-based observational studies demonstrated a consistent, inverse association between diabetes and prevalent AAA (OR, 0.80 [95% CI, 0.70–0.90]).[108]
- Evidence suggests that there may be a temporal relationship between fluoroquinolone use and aortic disease. A study analyzing >9 million fluoroquinolone prescriptions showed an increased risk of newly diagnosed AAA in patients >35 years of age prescribed a fluoroquinolone compared with other antibiotics (HR, 1.31 [95% CI, 1.25–1.37]).[110]
  - In a case-crossover analysis of patients in Taiwan, fluoroquinolone use was associated with an increased risk of aortic dissection or aneurysm (OR, 2.71 [95% CI, 1.14–6.46]), and there was a greater risk with more prolonged fluoroquinolone exposure.[111]

### Social Determinants of Health/Health Equity

- Few data exist on social determinants of health for TAA.
- In a retrospective study of 60 784 patients who underwent thoracic aortic repair procedures between 2005 and 2008, thoracic endovascular aortic repair was more common than open surgical repair among individuals who were Black (OR, 1.71 [95% CI, 1.37–2.13]), Hispanic (OR, 1.70 [95% CI, 1.22–2.37]), and Native American (OR, 2.37 [95% CI, 1.44–3.91]) compared with White individuals. Those with a mean annual income below $25 000 were also more likely to undergo endovascular rather than open surgical repair than those with a mean annual income exceeding $35 000 (OR, 1.24 [95% CI, 1.03–1.62]).[112]
- Lower SES is associated with a greater risk of 90-day readmission after AAA repair (OR, 1.18

[95% CI, 1.10–1.23]) on the basis of multistate US administrative claims data for 92 028 patients between 2007 and 2014.[113]
- Geographic variation in the approach to AAA appears to be present. In a comparison of AAA management between the United Kingdom and United States, the United States demonstrated a higher rate of AAA repair, smaller AAA diameter at the time of repair, and lower rates of AAA rupture and AAA-related death (all $P<0.0001$).[114]

### *Subclinical/Unrecognized Disease*

- TAAs typically expand slowly, increasing in size at rates of 0.1 and 0.3 cm/y in the ascending and descending aorta, respectively.[115,116] TAAs with familial and genetic causes may display faster rates of expansion ($P<0.0001$).[117]
- One-time screening for AAA in males 65 to 80 years of age had a number needed to screen of 350 to prevent a single AAA-related death over 7 to 15 years in a meta-analysis of 4 randomized trials.[118] In a nationwide Swedish program targeting males ≥65 years of age, the initiation of an AAA screening program found a number needed to screen of 667 to prevent a single premature death.[119]
- A meta-analysis of 15 475 individuals from 18 studies on small AAAs (3.0–5.4 cm) demonstrated a mean aneurysm growth rate of 0.22 cm/y, which did not vary significantly by age and sex.[120]
  - Growth rates were higher in smokers versus former or never-smokers (by 0.35 mm/y) and lower in people with diabetes than in those without diabetes (by 0.51 mm/y).[120]

### *Genetics/Family History*

- Aortic dissection is heritable. In a study using the Taiwan National Health Insurance database of >23 000 patients, a family history of aortic dissection in first-degree relatives was associated with an RR of aortic dissection of 6.82 (95% CI, 5.12–9.07) with an estimated heritability of 57.0% for genetic factors.[121]
- In a study of UK Biobank participants, a PRS for aortic diameter was associated with an increased risk of TAA (HR, 1.42 per SD [95% CI, 1.34–1.50]).[122]
- There are syndromic thoracic aortic diseases caused by rare genetic variants, including Marfan syndrome (caused primarily by variants in the *FBN1* gene), Loeys-Dietz syndrome (TGF-β pathway–related genes, including *TGFBR1*, *TGFBR2*, *SMAD3*, *TGFB2*, and *TGFB3*), vascular Ehlers-Danlos syndrome (*COL3A1*), arterial tortuosity syndrome (*SLC2A10*), and familial TAA syndrome (*ACTA2*, *TGBR2*, and variants in several other genes).
- Genetic variants associated with nonfamilial forms of TAA/dissection include common polymorphisms in *FBN1* (rare variants cause Marfan syndrome), *LRP1* (LDL receptor protein–related 1), and *ULK4* (unc-51–like kinase 4).[123,124]
- AAA is heritable, and twin studies suggest that the degree of heritability ranges from 70% to 77%.[125,126]
- A GWAS of individuals in the Million Veteran Program identified 24 common genetic variants associated with AAA, including a locus on chromosome 9p21, as well as SNPs in *LPA*, *IL6R*, *LDLR*, and *APOE* (all $P<5\times10^{-8}$).[127]
- Genetic variants associated with intracranial aneurysms have been found in several genes, including *RBBP8*, *STRAD13/KL*, *SOX17*, and *CDKN2A/B* (all $P<5\times10^{-8}$).[128] Rare variants in *ANGPTL6* are associated with familial cases of intracranial aneurysms ($P<0.05$).[129]
- GWAS data demonstrate that 16 common genetic variants associated with AAA are also associated with cerebral and lower-extremity arterial aneurysms (all $P<0.05$).[127]
- Genetic associations with nonatherosclerotic arterial diseases such as fibromuscular dysplasia and spontaneous coronary artery dissection have been challenging because of the lower prevalence of disease, but studies of these diseases are ongoing.
  - A noncoding SNP in *PHACTR1* (phosphatase and actin regulator 1) has been associated with fibromuscular dysplasia ($P<10^{-4}$),[130] and functional analyses have demonstrated that this locus regulates endothelin-1 expression.[131]
  - In the UK Biobank, a PRS for AAA was also associated with an increased risk of fibromuscular dysplasia (OR, 1.03 [95% CI, 1.01–1.05]; $P=2.6\times10^{-3}$).[132]
  - A variant at chromosome 1q21.2 that affects *ADAMTSL4* expression and variants in *PHACTR1*, *LRP1*, and *LINC00310* are associated with spontaneous coronary artery dissection (all $P<5\times10^{-8}$).[133]
  - In a case series of patients with spontaneous coronary artery dissection, clinical genetic testing with connective tissue disease panels showed that 8.2% of patients harbored a pathogenic variant, with the most common being for vascular Ehlers-Danlos syndrome, suggesting that genetic testing may be useful in these patients.[134]

### *Awareness, Treatment, and Control*

- Aortic aneurysmal disease is typically asymptomatic until complications occur.
  - Screening for AAA is recommended in males 65 to 75 years of age who currently smoke or have a history of smoking.[135] Awareness of this recommendation, however, appears to be low, with 1.4% of eligible individuals screened on the basis of 2015 estimates from Centers for Medicare & Medicaid Services data.[136]

- Treatment of TAA and AAA is aimed at slowing progression and preventing complications, namely rupture and dissection.
  - Thresholds for surgical repair of TAAs are based on size, rate of growth, presence of syndromic or nonsyndromic heritable thoracic aortic disease, specific genetic variants, and concomitant valve disease and are outlined in the "2022 ACC/AHA Guideline for the Diagnosis and Management of Aortic Disease."[137]
  - In a sample of 12 573 and 2732 Medicare patients from 1998 to 2007, for intact TAA, perioperative mortality was similar for open and endovascular repair (7.1% versus 6.1%; $P$=0.56). In contrast, for ruptured TAA, perioperative mortality was greater for open compared with endovascular repair (45% versus 28%; $P$<0.001), although 5-year survival rates were higher (70% versus 56%; $P$<0.001).[138]
  - Racial disparities in perioperative 30-day mortality after TAA repair are present with open (Black people, 18% versus White people, 10%; $P$<0.001) compared with endovascular (8% versus 9%; $P$=0.54) approaches on the basis of Medicare data from 1999 to 2007.[138]
  - Elective AAA repair is typically not recommended among asymptomatic individuals until the diameter exceeds 5.5 cm or if the annual expansion rate is ≥ 0.5 cm/y because open or endovascular repair of small AAAs (4.0–5.5 cm) did not demonstrate a benefit compared with routine ultrasound surveillance according to results from 4 trials including a total of 3314 participants.[137,139]
    - Procedural volume affects outcomes for ruptured AAA repair. In a meta-analysis of 120 116 patients undergoing ruptured AAA repair, patients treated at low-volume centers had a greater overall mortality risk than those treated at high-volume centers (OR, 1.39 [95% CI, 1.22–1.59]). In multivariable-adjusted models, patients treated at low-volume centers had a greater mortality risk for open repair (OR, 1.68 [95% CI, 1.21–2.33]) but not endovascular repair (OR, 1.42 [95% CI, 0.84–2.41]).[140] In the United States, data from NIS showed that the risk of death after open thoracoabdominal aortic aneurysm repair in low-volume hospitals was significantly greater than at high-volume hospitals (OR, 1.921 [95% CI, 1.458–2.532]; $P$<0.001).[141]
  - After elective AAA repair, survival after endovascular versus open surgical repair varies on the basis of timing since intervention.
    - Among Medicare patients, open versus endovascular AAA repair had a higher risk of all-cause mortality (HR, 1.24 [95% CI, 1.05–1.47]), AAA-related mortality (HR, 4.37 [95% CI, 2.51–7.66]), and complications at 1 year.[142] After 8 years of follow-up, however, survival was similar between the 2 groups ($P$=0.76). The rate of eventual aneurysm rupture was higher with endovascular (5.4%) compared with open (1.4%) repair.[143]
    - Similarly, in the OVER Veterans Affairs Cooperative trial of 881 patients, compared with open repair, endovascular repair was associated with lower mortality at 2 years (HR, 0.63 [95% CI, 0.40–0.98]) and 3 years (HR, 0.72 [95% CI, 0.51–1.00]) but no survival difference in up to 9 years (mean, 5 years) of follow-up (HR, 0.97 [95% CI, 0.77–1.22]).[144]
    - Perioperative mortality of endovascular AAA repair was not associated with surgeon case volume, but outcomes were better in hospitals with higher case volume (eg, 1.9% in hospitals with <10 cases a year versus 1.4% in those with 49–198 cases; $P$<0.01). Perioperative mortality after open repair was inversely associated with case volume for both surgeon (6.4% in ≤3 cases versus 3.8% in 14–62 cases; $P$<0.01) and hospital (6.3% in ≤5 cases versus 3.8% in 14–62 cases; $P$<0.01).[145]
    - Of all AAA repairs, endovascular AAA repair increased from 5% to 74% between 2000 and 2010 despite a stable overall number of AAAs (≈45 000 per year) according to NIS data. Furthermore, associated health care costs rose during this time period despite reductions in in-hospital mortality and length of stay.[146]

### *Mortality*

2021, United States: Underlying cause mortality—10 037. Any-mention mortality—19 025.

- TAA
  - In 2013, type A thoracic aortic dissections were surgically treated in 90% of presenting cases with in-hospital mortality of 22% and surgical mortality of 18% according to data from the IRAD. Type B thoracic aortic dissections were more likely to be treated with endovascular therapies, but mortality rates remained similar between 1996 and 2013.[147]
    - Mesenteric malperfusion with type A acute dissections was present in ≈3.7% of patients in IRAD and associated with greater mortality than among patients without malperfusion (63.2% versus 23.8%; $P$<0.001).[148]
    - Among patients with acute type B aortic dissection in IRAD, heterogeneous in-hospital outcomes exist. In-hospital mortality was higher (20.0%) among patients with complications

(eg, mesenteric ischemia, renal failure, limb ischemia, or refractory pain) compared with patients without complications (6.1%). Among patients with complications, in-hospital mortality was higher with open surgical (28.6%) compared with endovascular (10.1%) repair ($P$=0.006).[149]

- Among Medicare beneficiaries hospitalized with acute type B aortic dissections from 2011 to 2018, initial thoracic endovascular aortic repair within 30 days was not associated with a decrease in mortality (HR, 0.95 [95% CI, 0.85–1.06]) or aorta-related hospitalizations (HR, 1.12 [95% CI, 0.99–1.27]) compared with initial medical therapy.[150]

- AAA
  - Data from 23 838 patients with ruptured AAAs collected through the NIS 2005 to 2010 demonstrated in-hospital mortality of 53.1% (95% CI, 51.3%–54.9%) with 80.4% of patients (95% CI, 79.0%–81.9%) undergoing intervention for repair. Of individuals who underwent repair, 20.9% (95% CI, 18.6%–23.2%) underwent endovascular repair with a 26.8% (95% CI, 23.7%–30.0%) postintervention mortality rate, and 79.1% (95% CI, 76.8%–81.4%) underwent open repair with a 45.6% (95% CI, 43.6%–47.5%) postintervention mortality rate.[151]
  - In ruptured AAAs, implementation of an endovascular-first protocol was associated with decreased perioperative adverse outcomes and improved long-term prognosis in a retrospective analysis of 88 consecutive patients seen at an academic medical center.[152]
  - A meta-analysis with 619 068 patients who underwent elective AAA repair observed a higher 30-day mortality rate in females compared with males (mortality rate, 0.04 [95% CI, 0.04–0.05] versus 0.02 [95% CI, 0.02–0.03]) despite a lower prevalence of comorbidities.[153]
    - Similarly, in the Vascular Quality Initiative, females undergoing repair of ruptured AAAs had a greater likelihood of in-hospital mortality (OR, 1.36 [95% CI, 1.12–1.66]; $P$=0.002) and mortality at 8 years (HR, 1.25 [95% CI, 1.04–1.50]; $P$=0.02) compared with males.[154]
  - Among 4638 ruptured AAA repairs from 2004 to 2018 in the Vascular Quality Initiative, there was no difference in 5-year survival for endovascular versus open repair (HR, 0.88 [95% CI, 0.69–1.11]; $P$=0.28) for 2004 to 2012. However, from 2013 to 2018, endovascular repair was associated with longer 5-year survival compared with open repair (HR, 0.69 [95% CI, 0.60–0.79]; $P$<0.001).[155]

### *Complications*

Dissection and rupture are the predominant complications of aortic aneurysmal disease, and their risks are proportional to aortic diameter and expansion rate, as well as familial or genetic causes.

TAA:

- At a diameter of 4.0 to 4.9 and >6.0 cm, the annual rate of TAA dissection or rupture is estimated at ≈2% and ≈7%, respectively.[156]
- Most TAA dissections in absolute numbers, however, occur at relatively smaller diameters. In IRAD, 59.1% and 40.9% of dissections occurred at diameters <5.5 and <5.0 cm, respectively.[157]
- Annual age- and sex-adjusted incidences per 100 000 people were estimated at 3.5 (95% CI, 2.2–4.9) for TAA rupture and 3.5 (95% CI, 2.4–4.6) for acute aortic dissection according to data from Olmsted County, Minnesota.[158]

AAA:

- The risk of AAA rupture is also proportionately related to diameter.
  - Rates of rupture of small AAAs (3.0–5.4 cm in diameter) range from 0.71 to 11.03 per 1000 person-years with higher rupture rates in smokers (pooled HR, 2.02 [95% CI, 1.33–3.06]) and females (pooled HR, 3.76 [95% CI, 2.58–5.47]; $P$<0.001).[120]
  - A Canadian registry observed that small AAAs (<5.5 cm for males and <5.0 cm for females) account for only 10% of all ruptured AAAs.[159]

### *Health Care Use: Hospital Discharges and Ambulatory Care Visits*

- In 2020, hospital discharges with aortic aneurysm as principal diagnoses totaled 60 590 (HCUP,[81] unpublished NHLBI tabulation).

### *Cost*

- A study comprising 1207 Medicare patients from the Vascular Quality Initiative showed that the median cost of index endovascular repair of AAA was $25 745 (IQR, $21 131–$28 774), whereas the median cost of subsequent reintervention was $22 165 (IQR, $17 152–$29 605).[160]

### *Global Burden (See Table 25-3 and Chart 25-5)*

- Global mortality attributable to aortic aneurysm by sex according to the GBD Study 2021 of 204 countries and territories is shown in Table 25-3.
  - There were 0.16 (95% UI, 0.14–0.17) million deaths attributable to aortic aneurysm, an increase of 76.62% (95% UI, 65.33%–84.98%) from 1990.
  - The highest age-standardized mortality rates estimated for aortic aneurysm were in high-income

Asia Pacific, tropical Latin America, and Eastern Europe (Chart 25-5).

### *Atherosclerotic Renal Artery Stenosis ICD-9 440.1; ICD-10 I70.1.*

#### *Prevalence*

- The prevalence of renal artery disease by renal duplex ultrasonography was 6.8% in the North Carolina subcohort of the CHS between 1997 and 1998.[161] Among those with renal artery stenoses, 88% were unilateral and 12% were bilateral.
- The prevalence of renal artery stenosis by angiography ranged from 5.4% to 11.7% among patients undergoing coronary angiography on the basis of data ascertained from 2007 to 2008 in Italy (n=1298) and from 2000 to 2002 in Argentina (n=843), respectively.[162,163]

#### *Incidence*

- The incidence rate of renal artery stenosis was estimated at 3.09 per 1000 patient-years on the basis of Medicare claims data between 1992 and 2004.[164]

#### *Lifetime Risk and Cumulative Incidence*

- The lifetime risk and cumulative incidence of renal artery stenosis have not been established.

#### *Secular Trends*

- The risk for a claim for renal artery stenosis was higher in 2004 (HR, 3.35 [95% CI, 3.17–3.55]) compared with 1992 according to Medicare claims data, even with adjustment for demographics and comorbidities.[164]

#### *Risk Factors*

- In a multiple logistic regression analysis of 1298 patients undergoing both coronary and renal artery angiography, PAD (OR, 2.98 [95% CI, 1.76–5.03]), dyslipidemia (OR, 2.82 [95% CI, 1.15–6.88]), eGFR <67 mL·min$^{-1}$·1.73 m$^{-2}$ (OR, 2.63 [95% CI, 1.54–4.47]), age >66 years (OR, 2.20 [95% CI, 1.26–3.85]), and multivessel CAD (OR, 1.82 [95% CI, 1.06–3.13]) were all associated with ≥50% renal artery stenosis (all $P<0.05$).[163]

#### *Risk Prediction*

- On the basis of data from a retrospective single-center study of 4177 patients in Iran who underwent renal angiography between 2002 and 2016, a predictive model for the presence of renal artery stenosis, defined by ≥70% stenosis (prevalence, 14.1%), that included age, sex, history of hypertension, BMI, and eGFR had an AUC of 0.70 (95% CI, 0.67–0.72).[165]

#### *Awareness, Treatment, and Control*

- Optimal medical therapy is the first-line treatment in the management of renal artery stenosis.[166] In CORAL, a randomized clinical trial of 943 patients with renal artery stenosis and either hypertension requiring ≥2 medications or CKD recruited between 2005 and 2010, renal artery stenting plus optimal medical therapy was not superior to optimal medical therapy alone for the reduction of the composite of MACEs or major renal events over a median follow-up of 43 months (HR, 0.94 [95% CI, 0.76–1.17]).[167]

#### *Mortality*

- An Irish study reported that among a total of 3987 patients undergoing coronary angiography, the presence of renal artery stenosis conferred a great risk of mortality (HR, 2.01 [95% CI, 1.51–2.67]).[168]

#### *Complications*

- The main long-term complications of renal artery stenosis are decline in renal function and a heightened risk of CVD.
  - In the CHS, renal artery stenosis was associated with an increased risk of CHD (HR, 1.96 [95% CI, 1.00–3.83]).[169]
  - In an analysis of Medicare recipients, patients with atherosclerotic renal artery stenosis were at higher risk of incident congestive HF, stroke, death, and need for renal replacement therapy (all $P<0.0001$).[164]

**Table 25-1. PAD in the United States**

| Population group | Mortality, 2021, all ages* | Hospital discharges, 2020, all ages |
|---|---|---|
| Both sexes | 11 549 | 69 390 |
| Males | 5532 (47.8%)† | |
| Females | 6017 (52.2%)† | |
| NH White males | 4257 | … |
| NH White females | 4648 | … |
| NH Black males | 734 | … |
| NH Black females | 802 | … |
| Hispanic males | 371 | … |
| Hispanic females | 365 | … |
| NH Asian males | 93‡ | … |
| NH Asian females | 123‡ | … |
| NH American Indian/Alaska Native | 62 | … |
| NH Native Hawaiian or Pacific Islander | Suppressed§ | |

Ellipses (…) indicate data not available; NH, non-Hispanic; and PAD, peripheral artery disease.

*Mortality for Hispanic, American Indian or Alaska Native, Asian, and Native Hawaiian or Other Pacific Islander people should be interpreted with caution because of inconsistencies in reporting Hispanic origin or race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native, Asian, Pacific Islander, and Hispanic decedents, as well as undercounts of these groups in censuses.

†These percentages represent the portion of total mortality attributable to PAD that is for males vs females.

‡Includes Chinese, Filipino, Japanese, and other Asian people.

§Suppressed due to confidentiality constraints because there were <10 deaths.

Sources: Mortality (for underlying cause of PAD): Unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using National Vital Statistics System.[67] Hospital discharges (with a principal discharge of PAD): Unpublished NHLBI tabulation using Hospital Cost and Utilization Project.[81]

**Table 25-2. Global Mortality and Prevalence of Lower-Extremity PAD, by Sex, 2021**

| | Both sexes combined | | Males | | Females | |
|---|---|---|---|---|---|---|
| | Death (95% UI) | Prevalence (95% UI) | Death (95% UI) | Prevalence (95% UI) | Death (95% UI) | Prevalence (95% UI) |
| Total number (millions), 2021 | 0.07 (0.06 to 0.07) | 113.70 (100.63 to 129.25) | 0.03 (0.03 to 0.04) | 37.53 (33.09 to 42.97) | 0.04 (0.03 to 0.04) | 76.16 (67.37 to 86.55) |
| Percent change in total number, 1990–2021 | 76.23 (69.12 to 82.75) | 101.99 (99.75 to 103.63) | 76.17 (65.53 to 87.81) | 112.42 (110.02 to 115.33) | 76.29 (63.55 to 86.24) | 97.22 (94.50 to 99.10) |
| Percent change in total number, 2010–2021 | 17.08 (13.19 to 21.15) | 33.99 (32.90 to 35.21) | 18.78 (13.59 to 26.56) | 36.05 (34.56 to 37.87) | 15.49 (9.06 to 20.46) | 32.99 (31.96 to 34.24) |
| Rate per 100 000, age standardized, 2021 | 0.85 (0.75 to 0.92) | 1334.95 (1181.21 to 1512.02) | 0.97 (0.89 to 1.09) | 959.60 (848.44 to 1094.93) | 0.74 (0.62 to 0.81) | 1652.98 (1463.13 to 1877.18) |
| Percent change in rate, age standardized, 1990–2021 | −37.19 (−39.03 to −35.07) | −12.37 (−13.50 to −11.38) | −38.49 (−41.63 to −34.61) | −10.31 (−11.53 to −9.23) | −37.09 (−40.94 to −33.61) | −12.01 (−13.33 to −10.91) |
| Percent change in rate, age standardized, 2010–2021 | −22.81 (−25.37 to −19.83) | −2.23 (−2.92 to −1.59) | −21.21 (−24.18 to −16.29) | −1.22 (−2.13 to −0.11) | −23.88 (−28.21 to −20.66) | −2.36 (−3.13 to −1.69) |

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Disease; PAD, peripheral artery disease; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[88]

**Table 25-3. Global Mortality of Aortic Aneurysm, by Sex, 2021**

| | Both sexes (95% UI) | Males (95% UI) | Females (95% UI) |
|---|---|---|---|
| Total number (millions), 2021 | 0.16 (0.14 to 0.17) | 0.10 (0.09 to 0.10) | 0.06 (0.05 to 0.07) |
| Percent change in total number, 1990–2021 | 76.62 (65.33 to 84.98) | 65.08 (56.00 to 74.61) | 98.14 (79.74 to 112.19) |
| Percent change in total number, 2010–2021 | 26.88 (22.76 to 31.00) | 23.48 (18.95 to 28.15) | 32.56 (25.53 to 38.08) |
| Rate per 100 000, age standardized, 2021 | 1.87 (1.68 to 2.00) | 2.54 (2.34 to 2.71) | 1.30 (1.13 to 1.43) |
| Percent change in rate, age standardized, 1990–2021 | −27.70 (−32.04 to −24.70) | −35.75 (−38.95 to −32.48) | −19.07 (−25.77 to −14.04) |
| Percent change in rate, age standardized, 2010–2021 | −11.13 (−14.05 to −8.60) | −14.58 (−17.61 to −11.52) | −7.64 (−12.52 to −4.09) |

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Disease; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[88]

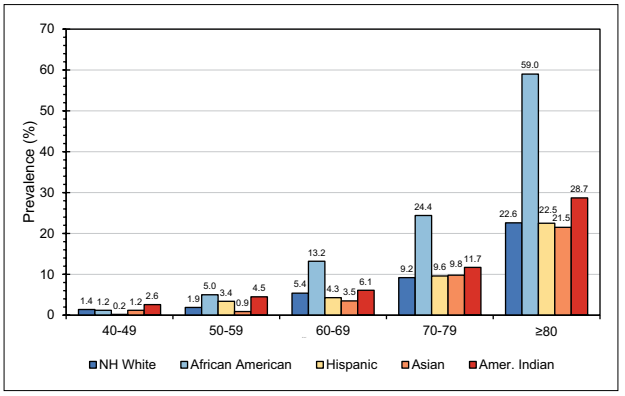



**Chart 25-1. Estimates of prevalence of PAD in males, by age and ethnicity, United States, 2000.**

Amer. indicates American; NH, non-Hispanic; and PAD, peripheral artery disease.

Source: Data derived from Allison et al.[1]

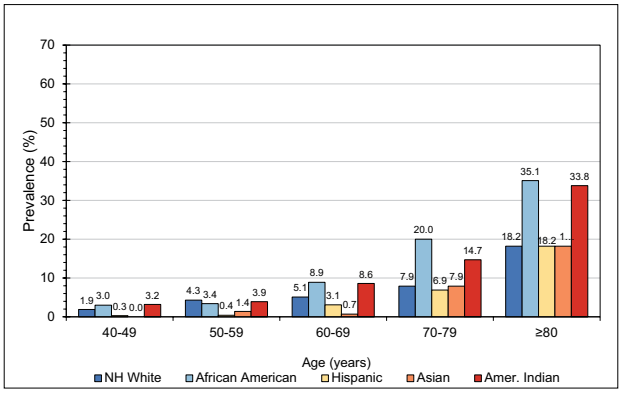



**Chart 25-2. Estimates of prevalence of PAD in females, by age and ethnicity, United States, 2000.**

Amer. indicates American; NH, non-Hispanic; and PAD, peripheral artery disease.

Source: Data derived from Allison et al.[1]

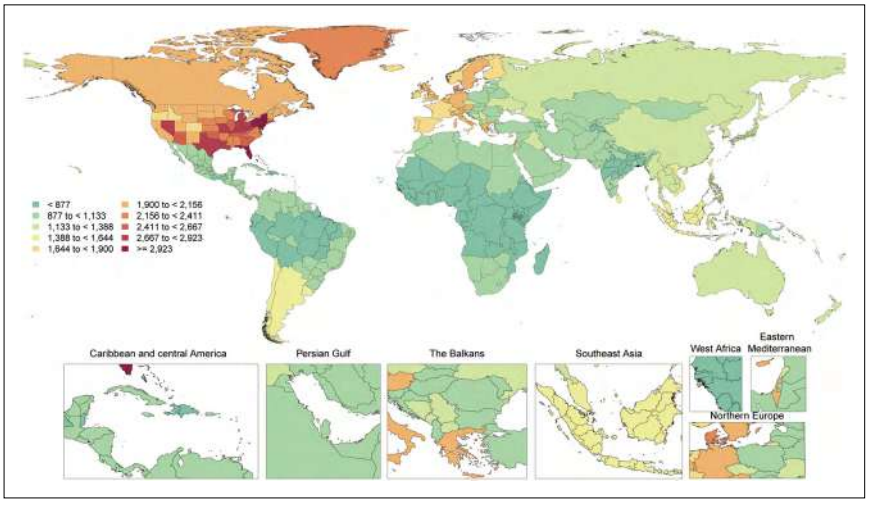



**Chart 25-3. Age-standardized global prevalence of lower-extremity PAD per 100 000, both sexes, 2021.**

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Disease; and PAD, peripheral artery disease.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[88]

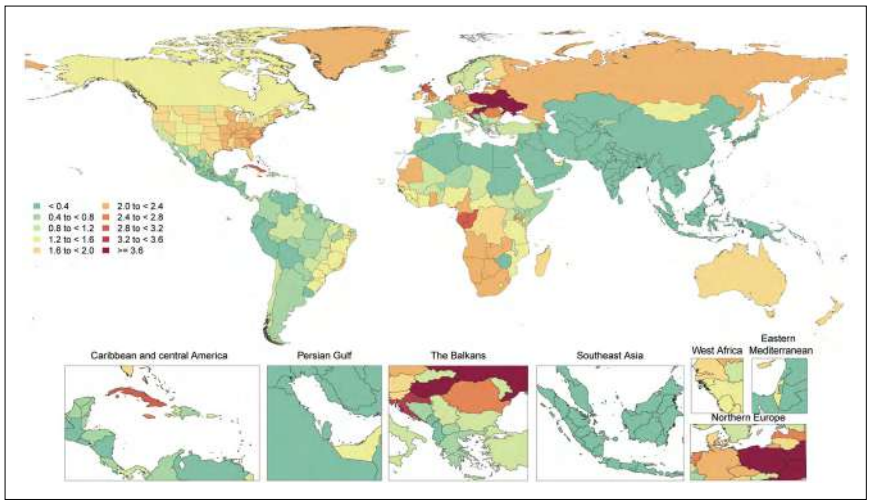



**Chart 25-4. Age-standardized global mortality rates of lower-extremity PAD per 100 000, both sexes, 2021.**
During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.
GBD indicates Global Burden of Disease; and PAD, peripheral artery disease.
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[88]

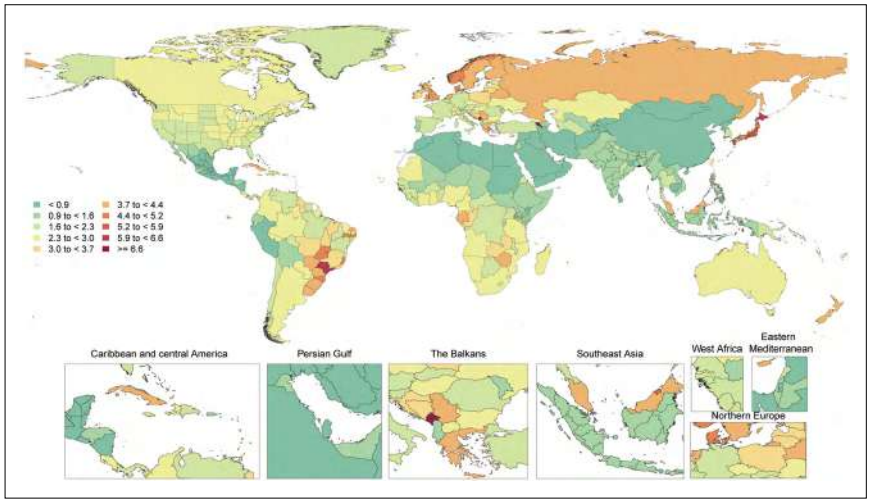



**Chart 25-5. Age-standardized global mortality rates of aortic aneurysm per 100 000, both sexes, 2021.**
During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.
GBD indicates Global Burden of Disease.
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.[88]

## REFERENCES


1. Allison MA, Ho E, Denenberg JO, Langer RD, Newman AB, Fabsitz RR, Criqui MH. Ethnic-specific prevalence of peripheral arterial disease in the United States. *Am J Prev Med*. 2007;32:328–333. doi: 10.1016/j.amepre.2006.12.010
2. Eraso LH, Fukaya E, Mohler ER, Xie D, Sha D, Berger JS. Peripheral arterial disease, prevalence and cumulative risk factor profile analysis. *Eur J Prev Cardiol*. 2014;21:704–711. doi: 10.1177/2047487312452968
3. Nehler MR, Duval S, Diao L, Annex BH, Hiatt WR, Rogers K, Zakharyan A, Hirsch AT. Epidemiology of peripheral arterial disease and critical limb ischemia in an insured national population. *J Vasc Surg*. 2014;60:686–695. e2. doi: 10.1016/j.jvs.2014.03.290
4. Aday AW, Duncan MS, Patterson OV, DuVall SL, Alba PR, Alcorn CW, Tindle HA, Creager MA, Bonaca MP, Damrauer SM, et al. Association of sex and race with incident peripheral artery disease among veterans with normal ankle-brachial indices. *JAMA Netw Open*. 2022;5:e2240188. doi: 10.1001/jamanetworkopen.2022.40188
5. Matsushita K, Sang Y, Ning H, Ballew SH, Chow EK, Grams ME, Selvin E, Allison M, Criqui M, Coresh J, et al. Lifetime risk of lower-extremity peripheral artery disease defined by ankle-brachial index in the United States. *J Am Heart Assoc*. 2019;8:e012177. doi: 10.1161/JAHA.119.012177
6. Song P, Rudan D, Zhu Y, Fowkes FJI, Rahimi K, Fowkes FGR, Rudan I. Global, regional, and national prevalence and risk factors for peripheral artery disease in 2015: an updated systematic review and analysis. *Lancet Glob Health*. 2019;7:e1020–e1030. doi: 10.1016/S2214-109X(19)30255-4
7. Anantha-Narayanan M, Doshi RP, Patel K, Sheikh AB, Llanos-Chea F, Abbott JD, Shishehbor MH, Guzman RJ, Hiatt WR, Duval S, et al. Contemporary trends in hospital admissions and outcomes in patients with critical limb ischemia: an analysis from the National Inpatient Sample database. *Circ Cardiovasc Qual Outcomes*. 2021;14:e007539. doi: 10.1161/CIRCOUTCOMES.120.007539
8. Schramm KM, DeWitt PE, Dybul S, Rochon PJ, Patel P, Hieb RA, Rogers RK, Ryu RK, Wolhauer M, Hong K, et al. Recent trends in clinical setting and provider specialty for endovascular peripheral artery disease interventions for the Medicare population. *J Vasc Interv Radiol*. 2020;31:614–621. e2. doi: 10.1016/j.jvir.2019.10.025
9. Mentias A, Qazi A, McCoy K, Wallace R, Vaughan-Sarrazin M, Girotra S. Trends in hospitalization, management, and clinical outcomes among veterans with critical limb ischemia. *Circ Cardiovasc Interv*. 2020;13:e008597. doi: 10.1161/CIRCINTERVENTIONS.119.008597
10. Geiss LS, Li Y, Hora I, Albright A, Rolka D, Gregg EW. Resurgence of diabetes-related nontraumatic lower-extremity amputation in the young and middle-aged adult US population. *Diabetes Care*. 2019;42:50–54. doi: 10.2337/dc18-1380
11. Cai M, Xie Y, Bowe B, Gibson AK, Zayed MA, Li T, Al-Aly Z. Temporal trends in incidence rates of lower extremity amputation and associated risk factors among patients using Veterans Health Administration services from 2008 to 2018. *JAMA Netw Open*. 2021;4:e2033953. doi: 10.1001/jamanetworkopen.2020.33953
12. Berger JS, Hochman J, Lobach I, Adelman MA, Riles TS, Rockman CB. Modifiable risk factor burden and the prevalence of peripheral artery disease in different vascular territories. *J Vasc Surg*. 2013;58:673–681.e1. doi: 10.1016/j.jvs.2013.01.053
13. Ding N, Sang Y, Chen J, Ballew SH, Kalbaugh CA, Salameh MJ, Blaha MJ, Allison M, Heiss G, Selvin E, et al. Cigarette smoking, smoking cessation, and long-term risk of 3 major atherosclerotic diseases. *J Am Coll Cardiol*. 2019;74:498–507. doi: 10.1016/j.jacc.2019.05.049

14. Lu Y, Ballew SH, Tanaka H, Szklo M, Heiss G, Coresh J, Matsushita K. 2017 ACC/AHA blood pressure classification and incident peripheral artery disease: the Atherosclerosis Risk in Communities (ARIC) study. *Eur J Prev Cardiol*. 2020;27:51–59. doi: 10.1177/2047487319865378
15. Kou M, Ding N, Ballew SH, Salameh MJ, Martin SS, Selvin E, Heiss G, Ballantyne CM, Matsushita K, Hoogeveen RC. Conventional and novel lipid measures and risk of peripheral artery disease. *Arterioscler Thromb Vasc Biol*. 2021;41:1229–1238. doi: 10.1161/ATVBAHA.120.315828
16. Aday AW, Lawler PR, Cook NR, Ridker PM, Mora S, Pradhan AD. Lipoprotein particle profiles, standard lipids, and peripheral artery disease incidence. *Circulation*. 2018;138:2330–2341. doi: 10.1161/CIRCULATIONAHA.118.035432
17. Duran EK, Aday AW, Cook NR, Buring JE, Ridker PM, Pradhan AD. Triglyceride-rich lipoprotein cholesterol, small dense LDL cholesterol, and incident cardiovascular disease. *J Am Coll Cardiol*. 2020;75:2122–2135. doi: 10.1016/j.jacc.2020.02.059
18. Dikilitas O, Satterfield BA, Kullo IJ. Risk factors for polyvascular involvement in patients with peripheral artery disease: a mendelian randomization study. *J Am Heart Assoc*. 2020;9:e017740. doi: 10.1161/JAHA.120.017740
19. Levin MG, Zuber V, Walker VM, Klarin D, Lynch J, Malik R, Aday AW, Bottolo L, Pradhan AD, Dichgans M, et al. Prioritizing the role of major lipoproteins and subfractions as risk factors for peripheral artery disease. *Circulation*. 2021;144:353–364. doi: 10.1161/CIRCULATIONAHA.121.053797
20. Satterfield BA, Dikilitas O, Safarova MS, Clarke SL, Tcheandjieu C, Zhu X, Bastarache L, Larson EB, Justice AE, Shang N, et al. Associations of genetically predicted Lp(a) (lipoprotein [a]) levels with cardiovascular traits in individuals of European and African ancestry. *Circ Genom Precis Med*. 2021;14:e003354. doi: 10.1161/CIRCGEN.120.003354
21. Joosten MM, Pai JK, Bertoia ML, Rimm EB, Spiegelman D, Mittleman MA, Mukamal KJ. Associations between conventional cardiovascular risk factors and risk of peripheral artery disease in men. *JAMA*. 2012;308:1660–1667. doi: 10.1001/jama.2012.13415
22. Garg PK, Biggs ML, Carnethon M, Ix JH, Criqui MH, Britton KA, Djousse L, Sutton-Tyrrell K, Newman AB, Cushman M, et al. Metabolic syndrome and risk of incident peripheral artery disease: the Cardiovascular Health Study. *Hypertension*. 2014;63:413–419. doi: 10.1161/HYPERTENSIONAHA.113.01925
23. Conen D, Rexrode KM, Creager MA, Ridker PM, Pradhan AD. Metabolic syndrome, inflammation, and risk of symptomatic peripheral artery disease in women: a prospective study. *Circulation*. 2009;120:1041–1047. doi: 10.1161/CIRCULATIONAHA.109.863092
24. Matsushita K, Ballew SH, Coresh J, Arima H, Arnlov J, Cirillo M, Ebert N, Hiramoto JS, Kimm H, Shlipak MG, et al; Chronic Kidney Disease Prognosis Consortium. Measures of chronic kidney disease and risk of incident peripheral artery disease: a collaborative meta-analysis of individual participant data. *Lancet Diabetes Endocrinol*. 2017;5:718–728. doi: 10.1016/S2213-8587(17)30183-3
25. Weissgerber TL, Turner ST, Bailey KR, Mosley TH Jr, Kardia SL, Wiste HJ, Miller VM, Kullo IJ, Garovic VD. Hypertension in pregnancy is a risk factor for peripheral arterial disease decades after pregnancy. *Atherosclerosis*. 2013;229:212–216. doi: 10.1016/j.atherosclerosis.2013.04.012
26. Ruiz-Canela M, Estruch R, Corella D, Salas-Salvado J, Martinez-Gonzalez MA. Association of Mediterranean diet with peripheral artery disease: the PREDIMED randomized trial. *JAMA*. 2014;311:415–417. doi: 10.1001/jama.2013.280618
27. Pande RL, Creager MA. Socioeconomic inequality and peripheral artery disease prevalence in US adults. *Circ Cardiovasc Qual Outcomes*. 2014;7:532–539. doi: 10.1161/CIRCOUTCOMES.113.000618
28. Vart P, Coresh J, Kwak L, Ballew SH, Heiss G, Matsushita K. Socioeconomic status and incidence of hospitalization with lower-extremity peripheral artery disease: Atherosclerosis Risk in Communities Study. *J Am Heart Assoc*. 2017;6:e004995. doi: 10.1161/JAHA.116.004995
29. Arya S, Binney Z, Khakharia A, Brewster LP, Goodney P, Patzer R, Hockenberry J, Wilson PWF. Race and socioeconomic status independently affect risk of major amputation in peripheral artery disease. *J Am Heart Assoc*. 2018;7:e007425. doi: 10.1161/JAHA.117.007425
30. Mota L, Marcaccio CL, Zhu M, Moreira CC, Rowe VL, Hughes K, Liang P, Schermerhorn ML. Impact of neighborhood social disadvantage on the presentation and management of peripheral artery disease. *J Vasc Surg*. 2023;77:1477–1485. doi: 10.1016/j.jvs.2022.12.062
31. Fanaroff AC, Yang L, Nathan AS, Khatana SAM, Julien H, Wang TY, Armstrong EJ, Treat-Jacobson D, Glaser JD, Wang G, et al. Geographic and socioeconomic disparities in major lower extremity amputation rates in metropolitan areas. *J Am Heart Assoc*. 2021;10:e021456. doi: 10.1161/JAHA.121.021456
32. Minc SD, Goodney PP, Misra R, Thibault D, Smith GS, Marone L. The effect of rurality on the risk of primary amputation is amplified by race. *J Vasc Surg*. 2020;72:1011–1017. doi: 10.1016/j.jvs.2019.10.090
33. Zhang Y, Huang J, Wang P. A prediction model for the peripheral arterial disease using NHANES data. *Medicine (Baltimore)*. 2016;95:e3454. doi: 10.1097/MD.0000000000003454
34. Matsushita K, Sang Y, Ning H, Ballew SH, Chow EK, Grams ME, Selvin E, Allison M, Criqui M, Coresh J, et al. Online calculator for lifetime risk and prevalence of lower extremity peripheral artery disease (PAD). 2019. Accessed March 15, 2023. http://ckdpcrisk.org/padrisk/
35. Wahlgren CM, Magnusson PK. Genetic influences on peripheral arterial disease in a twin population. *Arterioscler Thromb Vasc Biol*. 2011;31:678–682. doi: 10.1161/ATVBAHA.110.210385
36. van Zuydam NR, Stiby A, Abdalla M, Austin E, Dahlstrom EH, McLachlan S, Vlachopoulou E, Ahlqvist E, Di Liao C, Sandholm N, et al; GoLEAD Consortium, SUMMIT Consortium. Genome-wide association study of peripheral artery disease. *Circ Genom Precis Med*. 2021;14:e002862. doi: 10.1161/CIRCGEN.119.002862
37. Helgadottir A, Thorleifsson G, Magnusson KP, Gretarsdottir S, Steinthorsdottir V, Manolescu A, Jones GT, Rinkel GJ, Blankensteijn JD, Ronkainen A, et al. The same sequence variant on 9p21 associates with myocardial infarction, abdominal aortic aneurysm and intracranial aneurysm. *Nat Genet*. 2008;40:217–224. doi: 10.1038/ng.72
38. Murabito JM, White CC, Kavousi M, Sun YV, Feitosa MF, Nambi V, Lamina C, Schillert A, Coassin S, Bis JC, et al. Association between chromosome 9p21 variants and the ankle-brachial index identified by a meta-analysis of 21 genome-wide association studies. *Circ Cardiovasc Genet*. 2012;5:100–112. doi: 10.1161/CIRCGENETICS.111.961292
39. Klarin D, Lynch J, Aragam K, Chaffin M, Assimes TL, Huang J, Lee KM, Shao Q, Huffman JE, Natarajan P, et al; VA Million Veteran Program. Genome-wide association study of peripheral artery disease in the Million Veteran Program. *Nat Med*. 2019;25:1274–1279. doi: 10.1038/s41591-019-0492-5
40. Ntalla I, Kanoni S, Zeng L, Giannakopoulou O, Danesh J, Watkins H, Samani NJ, Deloukas P, Schunkert H; UK Biobank CardioMetabolic Consortium CHD Working Group. Genetic risk score for coronary disease identifies predispositions to cardiovascular and noncardiovascular diseases. *J Am Coll Cardiol*. 2019;73:2932–2942. doi: 10.1016/j.jacc.2019.03.512
41. Safarova MS, Fan X, Austin EE, van Zuydam N, Hopewell J, Schaid DJ, Kullo IJ. Targeted sequencing study to uncover shared genetic susceptibility between peripheral artery disease and coronary heart disease: brief report. *Arterioscler Thromb Vasc Biol*. 2019;39:1227–1233. doi: 10.1161/ATVBAHA.118.312128
42. Levin MG, Klarin D, Walker VM, Gill D, Lynch J, Hellwege JN, Keaton JM, Lee KM, Assimes TL, Natarajan P, et al; VA Million Veteran Program. Association between genetic variation in blood pressure and increased lifetime risk of peripheral artery disease. *Arterioscler Thromb Vasc Biol*. 2021;41:2027–2034. doi: 10.1161/ATVBAHA.120.315482
43. Small AM, Huffman JE, Klarin D, Sabater-Lleal M, Lynch JA, Assimes TL, Sun YV, Miller D, Freiberg MS, Morrison AC, et al; Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Hemostasis Working Group and the VA Million Veteran Program. Mendelian randomization analysis of hemostatic factors and their contribution to peripheral artery disease: brief report. *Arterioscler Thromb Vasc Biol*. 2021;41:380–386. doi: 10.1161/ATVBAHA.119.313847
44. Levin MG, Klarin D, Assimes TL, Freiberg MS, Ingelsson E, Lynch J, Natarajan P, O'Donnell C, Rader DJ, Tsao PS, et al; VA Million Veteran Program. Genetics of smoking and risk of atherosclerotic cardiovascular diseases: a mendelian randomization study. *JAMA Netw Open*. 2021;4:e2034461. doi: 10.1001/jamanetworkopen.2020.34461
45. Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, Fleisher LA, Fowkes FG, Hamburg NM, Kinlay S, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published correction appears in Circulation. 2017;135:e791–e792]. *Circulation*. 2017;135:e726–e779. doi: 10.1161/CIR.0000000000000471
46. Hirsch AT, Murphy TP, Lovell MB, Twillman G, Treat-Jacobson D, Harwood EM, Mohler ER 3rd, Creager MA, Hobson RW 2nd, Robertson RM, et al; Peripheral Arterial Disease Coalition. Gaps in public knowledge of peripheral arterial disease: the first national PAD public awareness survey. *Circulation*. 2007;116:2086–2094. doi: 10.1161/CIRCULATIONAHA.107.725101
47. Colantonio LD, Hubbard D, Monda KL, Mues KE, Huang L, Dai Y, Jackson EA, Brown TM, Rosenson RS, Woodward M, et al. Atherosclerotic risk and

statin use among patients with peripheral artery disease. *J Am Coll Cardiol*. 2020;76:251–264. doi: 10.1016/j.jacc.2020.05.048
48. Hess CN, Cannon CP, Beckman JA, Goodney PP, Patel MR, Hiatt WR, Mues KE, Orroth KK, Shannon E, Bonaca MP. Effectiveness of blood lipid management in patients with peripheral artery disease. *J Am Coll Cardiol*. 2021;77:3016–3027. doi: 10.1016/j.jacc.2021.04.060
49. Deleted in proof
50. Treat-Jacobson D, McDermott MM, Bronas UG, Campia U, Collins TC, Criqui MH, Gardner AW, Hiatt WR, Regensteiner JG, Rich K; on behalf of the American Heart Association Council on Peripheral Vascular Disease; Council on Quality of Care and Outcomes Research; and Council on Cardiovascular and Stroke Nursing. Optimal exercise programs for patients with peripheral artery disease: a scientific statement from the American Heart Association. *Circulation*. 2019;139:e10–e33. doi: 10.1161/CIR.0000000000000623
51. Lane R, Harwood A, Watson L, Leng GC. Exercise for intermittent claudication. *Cochrane Database Syst Rev*. 2017;12:CD000990. doi: 10.1002/14651858.CD000990.pub4
52. Murphy TP, Cutlip DE, Regensteiner JG, Mohler ER, Cohen DJ, Reynolds MR, Massaro JM, Lewis BA, Cerezo J, Oldenburg NC, et al; CLEVER Study Investigators. Supervised exercise versus primary stenting for claudication resulting from aortoiliac peripheral artery disease: six-month outcomes from the Claudication: Exercise Versus Endoluminal Revascularization (CLEVER) study. *Circulation*. 2012;125:130–139. doi: 10.1161/CIRCULATIONAHA.111.075770
53. Armstrong EJ, Wu J, Singh GD, Dawson DL, Pevec WC, Amsterdam EA, Laird JR. Smoking cessation is associated with decreased mortality and improved amputation-free survival among patients with symptomatic peripheral artery disease. *J Vasc Surg*. 2014;60:1565–1571. doi: 10.1016/j.jvs.2014.08.064
54. Jonason T, Bergstrom R. Cessation of smoking in patients with intermittent claudication: effects on the risk of peripheral vascular complica-tions, myocardial infarction and mortality. *Acta Med Scand*. 1987;221:253–260.
55. Reitz KM, Althouse AD, Meyer J, Arya S, Goodney PP, Shireman PK, Hall DE, Tzeng E. Association of smoking with postprocedural complications following open and endovascular interventions for intermittent claudication. *JAMA Cardiol*. 2022;7:45–54. doi: 10.1001/jamacardio.2021.3979
56. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol [published corrections appear in *Circulation*. 2019;139:e1182–e1186 and *Circulation*. 2023;148:e5]. *Circulation*. 2019;139:e1082–e1143. doi: 10.1161/CIR.0000000000000625
57. Arya S, Khakharia A, Binney ZO, DeMartino RR, Brewster LP, Goodney PP, Wilson PWF. Association of statin dose with amputation and survival in patients with peripheral artery disease. *Circulation*. 2018;137:1435–1446. doi: 10.1161/CIRCULATIONAHA.117.032361
58. Bonaca MP, Nault P, Giugliano RP, Keech AC, Pineda AL, Kanevsky E, Kuder J, Murphy SA, Jukema JW, Lewis BS, et al. Low-density lipoprotein cholesterol lowering with evolocumab and outcomes in patients with peripheral artery disease: insights from the FOURIER trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk). *Circulation*. 2018;137:338–350. doi: 10.1161/CIRCULATIONAHA.117.032235
59. Schwartz GG, Steg PG, Szarek M, Bittner VA, Diaz R, Goodman SG, Kim Y-U, Jukema JW, Pordy R, Roe MT, et al; ODYSSEY OUTCOMES Committees and Investigators. Peripheral artery disease and venous thromboembolic events after acute coronary syndrome. *Circulation*. 2020;141:1608–1617. doi: 10.1161/CIRCULATIONAHA.120.046524
60. Anand SS, Caron F, Eikelboom JW, Bosch J, Dyal L, Aboyans V, Abola MT, Branch KRH, Keltai K, Bhatt DL, et al. Major adverse limb events and mortality in patients with peripheral artery disease: the COMPASS trial. *J Am Coll Cardiol*. 2018;71:2306–2315. doi: 10.1016/j.jacc.2018.03.008
61. Bonaca MP, Bauersachs RM, Anand SS, Debus ES, Nehler MR, Patel MR, Fanelli F, Capell WH, Diao L, Jaeger N, et al. Rivaroxaban in peripheral artery disease after revascularization. *N Engl J Med*. 2020;382:1994–2004. doi: 10.1056/NEJMoa2000052
62. Singh S, Armstrong EJ, Sherif W, Alvandi B, Westin GG, Singh GD, Amsterdam EA, Laird JR. Association of elevated fasting glucose with lower patency and increased major adverse limb events among patients with diabetes undergoing infrapopliteal balloon angioplasty. *Vasc Med*. 2014;19:307–314. doi: 10.1177/1358863X14538330
63. Takahara M, Kaneto H, Iida O, Gorogawa S, Katakami N, Matsuoka TA, Ikeda M, Shimomura I. The influence of glycemic control on the prognosis of Japanese patients undergoing percutaneous transluminal angioplasty for critical limb ischemia. *Diabetes Care*. 2010;33:2538–2542. doi: 10.2337/dc10-0939
64. Farber A, Menard MT, Conte MS, Kaufman JA, Powell RJ, Choudhry NK, Hamza TH, Assmann SF, Creager MA, Cziraky MJ, et al; BEST-CLI Investigators. Surgery or endovascular therapy for chronic limb-threatening ischemia. *N Engl J Med*. 2022;387:2305–2316. doi: 10.1056/NEJMoa2207899
65. Vemulapalli S, Dolor RJ, Hasselblad V, Subherwal S, Schmit KM, Heidenfelder BL, Patel MR, Schuyler Jones W. Comparative effectiveness of medical therapy, supervised exercise, and revascularization for patients with intermittent claudication: a network meta-analysis. *Clin Cardiol*. 2015;38:378–386. doi: 10.1002/clc.22406
66. Angraal S, Hejjaji V, Tang Y, Gosch KL, Patel MR, Heyligers J, White CJ, Tutein Nolthenius R, Mena-Hurtado C, Aronow HD, et al. One-year health status outcomes following early invasive and noninvasive treatment in symptomatic peripheral artery disease. *Circ Cardiovasc Interv*. 2022;15:e011506. doi: 10.1161/CIRCINTERVENTIONS.121.011506
67. Centers for Disease Control and Prevention and National Center for Health Statistics. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death micro-data files. Accessed April 8, 2023. https://cdc.gov/nchs/nvss/mortality_public_use_data.htm
68. Centers for Disease Control and Prevention and National Center for Health Statistics. Multiple cause of death, CDC WONDER online database. Accessed April 1, 2023. https://wonder.cdc.gov/mcd-icd10.html
69. Fowkes FG, Murray GD, Butcher I, Heald CL, Lee RJ, Chambless LE, Folsom AR, Hirsch AT, Dramaix M, deBacker G, et al; Ankle Brachial Index Collaboration. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. *JAMA*. 2008;300:197–208. doi: 10.1001/jama.300.2.197
70. Haine A, Kavanagh S, Berger JS, Hess CN, Norgren L, Fowkes FGR, Katona BG, Mahaffey KW, Blomster JI, Patel MR, et al; International Steering Committee and Investigators of the EUCLID Trial. Sex-specific risks of major cardiovascular and limb events in patients with symptomatic peripheral artery disease. *J Am Coll Cardiol*. 2020;75:608–617. doi: 10.1016/j.jacc.2019.11.057
71. Kolls BJ, Sapp S, Rockhold FW, Jordan JD, Dombrowski KE, Fowkes FGR, Mahaffey KW, Berger JS, Katona BG, Blomster JI, et al. Stroke in patients with peripheral artery disease. *Stroke*. 2019;50:1356–1363. doi: 10.1161/STROKEAHA.118.023534
72. Olivier CB, Mulder H, Hiatt WR, Jones WS, Fowkes FGR, Rockhold FW, Berger JS, Baumgartner I, Held P, Katona BG, et al. Incidence, characteristics, and outcomes of myocardial infarction in patients with peripheral artery disease: insights from the EUCLID trial. *JAMA Cardiol*. 2019;4:7–15. doi: 10.1001/jamacardio.2018.4171
73. Jones WS, Patel MR, Dai D, Subherwal S, Stafford J, Calhoun S, Peterson ED. Temporal trends and geographic variation of lower-extremity amputation in patients with peripheral artery disease: results from US Medicare 2000-2008. *J Am Coll Cardiol*. 2012;60:2230–2236. doi: 10.1016/j.jacc.2012.08.983
74. Hess CN, Wang TY, Weleski Fu J, Gundrum J, Allen LaPointe NM, Rogers RK, Hiatt WR. Long-term outcomes and associations with major adverse limb events after peripheral artery revascularization. *J Am Coll Cardiol*. 2020;75:498–508. doi: 10.1016/j.jacc.2019.11.050
75. Krawisz AK, Natesan S, Wadhera RK, Chen S, Song Y, Yeh RW, Jaff MR, Giri J, Julien H, Secemsky EA. Differences in comorbidities explain Black-White disparities in outcomes after femoropopliteal endovascular intervention. *Circulation*. 2022;146:191–200. doi: 10.1161/CIRCULATIONAHA.122.058998
76. Beckman JA, Duncan MS, Damrauer SM, Wells QS, Barnett JV, Wasserman DH, Bedimo RJ, Butt AA, Marconi VC, Sico JJ, et al. Microvascular disease, peripheral artery disease, and amputation. *Circulation*. 2019;140:449–458. doi: 10.1161/CIRCULATIONAHA.119.040672
77. Jones WS, Patel MR, Dai D, Vemulapalli S, Subherwal S, Stafford J, Peterson ED. High mortality risks after major lower extremity amputation in Medicare patients with peripheral artery disease. *Am Heart J*. 2013;165:809–815.e1. doi: 10.1016/j.ahj.2012.12.002
78. McDermott MM, Liu K, Greenland P, Guralnik JM, Criqui MH, Chan C, Pearce WH, Schneider JR, Ferrucci L, Celic L, et al. Functional decline in peripheral arterial disease: associations with the ankle brachial index and leg symptoms. *JAMA*. 2004;292:453–461. doi: 10.1001/jama.292.4.453
79. Garg PK, Tian L, Criqui MH, Liu K, Ferrucci L, Guralnik JM, Tan J, McDermott MM. Physical activity during daily life and mortality in patients with peripheral arterial disease. *Circulation*. 2006;114:242–248. doi: 10.1161/CIRCULATIONAHA.105.605246

80. Centers for Disease Control and Prevention and National Center for Health Statistics. National Ambulatory Medical Care Survey (NAMCS) public use data files. Accessed April 1, 2023. https://cdc.gov/nchs/ahcd/datasets_documentation_related.htm#data
81. Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project (HCUP). Accessed April 1, 2023. http://hcupnet.ahrq.gov/
82. Kohn CG, Alberts MJ, Peacock WF, Bunz TJ, Coleman CI. Cost and inpatient burden of peripheral artery disease: findings from the National Inpatient Sample. *Atherosclerosis*. 2019;286:142–146. doi: 10.1016/j.atherosclerosis.2019.05.026
83. Berger A, Simpson A, Bhagnani T, Leeper NJ, Murphy B, Nordstrom B, Ting W, Zhao Q, Berger JS. Incidence and cost of major adverse cardiovascular events and major adverse limb events in patients with chronic coronary artery disease or peripheral artery disease. *Am J Cardiol*. 2019;123:1893–1899. doi: 10.1016/j.amjcard.2019.03.022
84. Mustapha JA, Katzen BT, Neville RF, Lookstein RA, Zeller T, Miller LE, Jaff MR. Determinants of long-term outcomes and costs in the management of critical limb ischemia: a population-based cohort study. *J Am Heart Assoc*. 2018;7:e009724. doi: 10.1161/JAHA.118.009724
85. Duval S, Long KH, Roy SS, Oldenburg NC, Harr K, Fee RM, Sharma RR, Alesci NL, Hirsch AT. The contribution of tobacco use to high health care utilization and medical costs in peripheral artery disease: a state-based cohort analysis. *J Am Coll Cardiol*. 2015;66:1566–1574. doi: 10.1016/j.jacc.2015.06.1349
86. Wang Z, Wang X, Hao G, Chen Z, Zhang L, Shao L, Tian Y, Dong Y, Zheng C, Kang Y, et al; China Hypertension Survey Investigators. A national study of the prevalence and risk factors associated with peripheral arterial disease from China: the China Hypertension Survey, 2012-2015. *Int J Cardiol*. 2019;275:165–170. doi: 10.1016/j.ijcard.2018.10.047
87. Johnston LE, Stewart BT, Yangni-Angate H, Veller M, Upchurch GR Jr, Gyedu A, Kushner AL. Peripheral arterial disease in sub-Saharan Africa: a review. *JAMA Surg*. 2016;151:564–572. doi: 10.1001/jamasurg.2016.0446
88. Global Burden of Disease Study and Institute for Health Metrics and Evaluation. University of Washington. Accessed August 2, 2023. http://ghdx.healthdata.org/
89. Mori M, Bin Mahmood SU, Yousef S, Shioda K, Faggion Vinholo T, Mangi AA, Elefteriades JA, Geirsson A. Prevalence of incidentally identified thoracic aortic dilations: insights for screening criteria. *Can J Cardiol*. 2019;35:892–898. doi: 10.1016/j.cjca.2019.03.023
90. Scott RA, Ashton HA, Kay DN. Abdominal aortic aneurysm in 4237 screened patients: prevalence, development and management over 6 years. *Br J Surg*. 1991;78:1122–1125. doi: 10.1002/bjs.1800780929
91. Newman AB, Arnold AM, Burke GL, O'Leary DH, Manolio TA. Cardiovascular disease and mortality in older adults with small abdominal aortic aneurysms detected by ultrasonography: the Cardiovascular Health Study. *Ann Intern Med*. 2001;134:182–190. doi: 10.7326/0003-4819-134-3-200102060-00008
92. Lederle FA, Johnson GR, Wilson SE; Aneurysm Detection and Management Veterans Affairs Cooperative Study. Abdominal aortic aneurysm in women. *J Vasc Surg*. 2001;34:122–126. doi: 10.1067/mva.2001.115275
93. Lederle FA, Johnson GR, Wilson SE, Chute EP, Hye RJ, Makaroun MS, Barone GW, Bandyk D, Moneta GL, Makhoul RG. The Aneurysm Detection and Management Study Screening Program: validation cohort and final results: Aneurysm Detection and Management Veterans Affairs Cooperative Study Investigators. *Arch Intern Med*. 2000;160:1425–1430. doi: 10.1001/archinte.160.10.1425
94. Singh K, Bonaa KH, Jacobsen BK, Bjork L, Solberg S. Prevalence of and risk factors for abdominal aortic aneurysms in a population-based study: the Tromso Study. *Am J Epidemiol*. 2001;154:236–244. doi: 10.1093/aje/154.3.236
95. Powell JT, Greenhalgh RM. Clinical practice: small abdominal aortic aneurysms. *N Engl J Med*. 2003;348:1895–1901. doi: 10.1056/NEJMcp012641
96. Song P, He Y, Adeloye D, Zhu Y, Ye X, Yi Q, Rahimi K, Rudan I; Global Health Epidemiology Research Group (GHERG). The global and regional prevalence of abdominal aortic aneurysms: a systematic review and modelling analysis. *Ann Surg*. 2022;277:912–919. doi: 10.1097/SLA.0000000000005716
97. Sampson UK, Norman PE, Fowkes FG, Aboyans V, Song Y, Harrell FE Jr, Forouzanfar MH, Naghavi M, Denenberg JO, McDermott MM, et al. Estimation of global and regional incidence and prevalence of abdominal aortic aneurysms 1990 to 2010. *Glob Heart*. 2014;9:159–170. doi: 10.1016/j.gheart.2013.12.009
98. Avdic T, Franzen S, Zarrouk M, Acosta S, Nilsson P, Gottsater A, Svensson AM, Gudbjornsdottir S, Eliasson B. Reduced long-term risk of aortic aneurysm and aortic dissection among individuals with type 2 diabetes mellitus: a nationwide observational study. *J Am Heart Assoc*. 2018;7:e007618. doi: 10.1161/JAHA.117.007618
99. DeMartino RR, Sen I, Huang Y, Bower TC, Oderich GS, Pochettino A, Greason K, Kalra M, Johnstone J, Shuja F, et al. Population-based assessment of the incidence of aortic dissection, intramural hematoma, and penetrating ulcer, and its associated mortality from 1995 to 2015. *Circ Cardiovasc Qual Outcomes*. 2018;11:e004689. doi: 10.1161/CIRCOUTCOMES.118.004689
100. Abdulameer H, Al Taii H, Al-Kindi SG, Milner R. Epidemiology of fatal ruptured aortic aneurysms in the United States (1999-2016). *J Vasc Surg*. 2019;69:378–384.e2. doi: 10.1016/j.jvs.2018.03.435
101. Obel LM, Diederichsen AC, Steffensen FH, Frost L, Lambrechtsen J, Busk M, Urbonaviciene G, Egstrup K, Karon M, Rasmussen LM, et al. Population-based risk factors for ascending, arch, descending, and abdominal aortic dilations for 60-74-year-old individuals. *J Am Coll Cardiol*. 2021;78:201–211. doi: 10.1016/j.jacc.2021.04.094
102. DePaolo J, Levin MG, Tcheandjieu C, Priest JR, Gill D, Burgess S, Damrauer SM, Chirinos JA. Relationship between ascending thoracic aortic diameter and blood pressure: a mendelian randomization study. *Arterioscler Thromb Vasc Biol*. 2023;43:359–366. doi: 10.1161/ATVBAHA.122.318149
103. Hibino M, Otaki Y, Kobeissi E, Pan H, Hibino H, Taddese H, Majeed A, Verma S, Konta T, Yamagata K, et al. Blood pressure, hypertension, and the risk of aortic dissection incidence and mortality: results from the J-SCH Study, the UK Biobank Study, and a meta-analysis of cohort studies. *Circulation*. 2022;145:633–644. doi: 10.1161/CIRCULATIONAHA.121.056546
104. Robson JC, Kiran A, Maskell J, Hutchings A, Arden N, Dasgupta B, Hamilton W, Emin A, Culliford D, Luqmani RA. The relative risk of aortic aneurysm in patients with giant cell arteritis compared with the general population of the UK. *Ann Rheum Dis*. 2015;74:129–135. doi: 10.1136/annrheumdis-2013-204113
105. Kent KC, Zwolak RM, Egorova NN, Riles TS, Manganaro A, Moskowitz AJ, Gelijns AC, Greco G. Analysis of risk factors for abdominal aortic aneurysm in a cohort of more than 3 million individuals. *J Vasc Surg*. 2010;52:539–548. doi: 10.1016/j.jvs.2010.05.090
106. Portilla-Fernandez E, Klarin D, Hwang SJ, Biggs ML, Bis JC, Weiss S, Rospleszcz S, Natarajan P, Hoffmann U, Rogers IS, et al; VA Million Veteran Program. Genetic and clinical determinants of abdominal aortic diameter: genome-wide association studies, exome array data and mendelian randomization study. *Hum Mol Genet*. 2022;31:3566–3579. doi: 10.1093/hmg/ddac051
107. Kubota Y, Folsom AR, Ballantyne CM, Tang W. Lipoprotein(a) and abdominal aortic aneurysm risk: the Atherosclerosis Risk in Communities study. *Atherosclerosis*. 2018;268:63–67. doi: 10.1016/j.atherosclerosis.2017.10.017
108. De Rango P, Farchioni L, Fiorucci B, Lenti M. Diabetes and abdominal aortic aneurysms. *Eur J Vasc Endovasc Surg*. 2014;47:243–261. doi: 10.1016/j.ejvs.2013.12.007
109. Prakash SK, Pedroza C, Khalil YA, Milewicz DM. Diabetes and reduced risk for thoracic aortic aneurysms and dissections: a nationwide case-control study. *J Am Heart Assoc*. 2012;1:e000323. doi: 10.1161/JAHA.111.000323
110. Newton ER, Akerman AW, Strassle PD, Kibbe MR. Association of fluoroquinolone use with short-term risk of development of aortic aneurysm. *JAMA Surg*. 2021;156:264–272. doi: 10.1001/jamasurg.2020.6165
111. Lee CC, Lee MG, Hsieh R, Porta L, Lee WC, Lee SH, Chang SS. Oral fluoroquinolone and the risk of aortic dissection. *J Am Coll Cardiol*. 2018;72:1369–1378. doi: 10.1016/j.jacc.2018.06.067
112. Johnston WF, LaPar DJ, Newhook TE, Stone ML, Upchurch GR Jr, Ailawadi G. Association of race and socioeconomic status with the use of endovascular repair to treat thoracic aortic diseases. *J Vasc Surg*. 2013;58:1476–1482. doi: 10.1016/j.jvs.2013.05.095
113. Perlstein MD, Gupta S, Ma X, Rong LQ, Askin G, White RS. abdominal aortic aneurysm repair readmissions and disparities of socioeconomic status: a multistate analysis, 2007-2014. *J Cardiothorac Vasc Anesth*. 2019;33:2737–2745. doi: 10.1053/j.jvca.2019.03.020
114. Karthikesalingam A, Vidal-Diez A, Holt PJ, Loftus IM, Schermerhorn ML, Soden PA, Landon BE, Thompson MM. Thresholds for abdominal aortic aneurysm repair in England and the United States. *N Engl J Med*. 2016;375:2051–2059. doi: 10.1056/NEJMoa1600931
115. Coady MA, Davies RR, Roberts M, Goldstein LJ, Rogalski MJ, Rizzo JA, Hammond GL, Kopf GS, Elefteriades JA. Familial

patterns of thoracic aortic aneurysms. *Arch Surg*. 1999;134:361–367. doi: 10.1001/archsurg.134.4.361
116. Shang EK, Nathan DP, Sprinkle SR, Vigmostad SC, Fairman RM, Bavaria JE, Gorman RC, Gorman JH, Chandran KB, Jackson BM. Peak wall stress predicts expansion rate in descending thoracic aortic aneurysms. *Ann Thorac Surg*. 2013;95:593–598. doi: 10.1016/j.athoracsur.2012.10.025
117. Albornoz G, Coady MA, Roberts M, Davies RR, Tranquilli M, Rizzo JA, Elefteriades JA. Familial thoracic aortic aneurysms and dissections: incidence, modes of inheritance, and phenotypic patterns. *Ann Thorac Surg*. 2006;82:1400–1405. doi: 10.1016/j.athoracsur.2006.04.098
118. Eckstein HH, Bockler D, Flessenkamper I, Schmitz-Rixen T, Debus S, Lang W. Ultrasonographic screening for the detection of abdominal aortic aneurysms. *Dtsch Arztebl Int*. 2009;106:657–663. doi: 10.3238/arztebl.2009.0657
119. Wanhainen A, Hultgren R, Linne A, Holst J, Gottsater A, Langenskiold M, Smidfelt K, Bjorck M, Svensjö S; Swedish Aneurysm Screening Study Group (SASS). Outcome of the Swedish nationwide abdominal aortic aneurysm screening program. *Circulation*. 2016;134:1141–1148. doi: 10.1161/CIRCULATIONAHA.116.022305
120. Sweeting MJ, Thompson SG, Brown LC, Powell JT; RESCAN Collaborators. Meta-analysis of individual patient data to examine factors affecting growth and rupture of small abdominal aortic aneurysms. *Br J Surg*. 2012;99:655–665. doi: 10.1002/bjs.8707
121. Chen SW, Kuo CF, Huang YT, Lin WT, Chien-Chia Wu V, Chou AH, Lin PJ, Chang SH, Chu PH. Association of family history with incidence and outcomes of aortic dissection. *J Am Coll Cardiol*. 2020;76:1181–1192. doi: 10.1016/j.jacc.2020.07.028
122. Nekoui M, Pirruccello JP, Di Achille P, Choi SH, Friedman SN, Nauffal V, Ng K, Batra P, Ho JE, Philippakis AA, et al. Spatially distinct genetic determinants of aortic dimensions influence risks of aneurysm and stenosis. *J Am Coll Cardiol*. 2022;80:486–497. doi: 10.1016/j.jacc.2022.05.024
123. Guo DC, Grove ML, Prakash SK, Eriksson P, Hostetler EM, LeMaire SA, Body SC, Shalhub S, Estrera AL, Safi HJ, et al; GenTAC Investigators, BAVCon Investigators. Genetic variants in *LRP1* and *ULK4* are associated with acute aortic dissections. *Am J Hum Genet*. 2016;99:762–769. doi: 10.1016/j.ajhg.2016.06.034
124. LeMaire SA, McDonald ML, Guo DC, Russell L, Miller CC 3rd, Johnson RJ, Bekheirnia MR, Franco LM, Nguyen M, Pyeritz RE, et al. Genome-wide association study identifies a susceptibility locus for thoracic aortic aneurysms and aortic dissections spanning *FBN1* at 15q211. *Nat Genet*. 2011;43:996–1000. doi: 10.1038/ng.934
125. Wahlgren CM, Larsson E, Magnusson PK, Hultgren R, Swedenborg J. Genetic and environmental contributions to abdominal aortic aneurysm development in a twin population. *J Vasc Surg*. 2010;51:3–7. doi: 10.1016/j.jvs.2009.08.036
126. Joergensen TM, Christensen K, Lindholt JS, Larsen LA, Green A, Houlind K. Editor's choice: high heritability of liability to abdominal aortic aneurysms: a population based twin study. *Eur J Vasc Endovasc Surg*. 2016;52:41–46. doi: 10.1016/j.ejvs.2016.03.012
127. Klarin D, Verma SS, Judy R, Dikilitas O, Wolford BN, Paranjpe I, Levin MG, Pan C, Tcheandjieu C, Spin JM, et al; Veterans Affairs Million Veteran Program. Genetic architecture of abdominal aortic aneurysm in the Million Veteran Program. *Circulation*. 2020;142:1633–1646. doi: 10.1161/CIRCULATIONAHA.120.047544
128. Yasuno K, Bilguvar K, Bijlenga P, Low SK, Krischek B, Auburger G, Simon M, Krex D, Arlier Z, Nayak N, et al. Genome-wide association study of intracranial aneurysm identifies three new risk loci. *Nat Genet*. 2010;42:420–425. doi: 10.1038/ng.563
129. Bourcier R, Le Scouarnec S, Bonnaud S, Karakachoff M, Bourcereau E, Heurtebise-Chretien S, Menguy C, Dina C, Simonet F, Moles A, et al; ICAN Study Group. Rare coding variants in *ANGPTL6* are associated with familial forms of intracranial aneurysm. *Am J Hum Genet*. 2018;102:133–141. doi: 10.1016/j.ajhg.2017.12.006
130. Kiando SR, Tucker NR, Castro-Vega LJ, Katz A, D'Escamard V, Treard C, Fraher D, Albuisson J, Kadian-Dodov D, Ye Z, et al. *PHACTR1* is a genetic susceptibility locus for fibromuscular dysplasia supporting its complex genetic pattern of inheritance. *PLoS Genet*. 2016;12:e1006367. doi: 10.1371/journal.pgen.1006367
131. Gupta RM, Hadaya J, Trehan A, Zekavat SM, Roselli C, Klarin D, Emdin CA, Hilvering CRE, Bianchi V, Mueller C, et al. A genetic variant associated with five vascular diseases is a distal regulator of endothelin-1 gene expression. *Cell*. 2017;170:522–533.e15. doi: 10.1016/j.cell.2017.06.049
132. Katz AE, Yang ML, Levin MG, Tcheandjieu C, Mathis M, Hunker K, Blackburn S, Eliason JL, Coleman DM, Fendrikova-Mahlay N, et al; VA Million Veteran Program. Fibromuscular dysplasia and abdominal aortic aneurysms are dimorphic sex-specific diseases with shared complex genetic architecture. *Circ Genom Precis Med*. 2022;15:e003496. doi: 10.1161/CIRCGEN.121.003496
133. Saw J, Yang M-L, Trinder M, Tcheandjieu C, Xu C, Starovoytov A, Birt I, Mathis MR, Hunker KL, Schmidt EM, et al. Chromosome 1q212 and additional loci influence risk of spontaneous coronary artery dissection and myocardial infarction. *Nat Commun*. 2020;11:4432. doi: 10.1038/s41467-020-17558-x
134. Kaadan MI, MacDonald C, Ponzini F, Duran J, Newell K, Pitler L, Lin A, Weinberg I, Wood MJ, Lindsay ME. Prospective cardiovascular genetics evaluation in spontaneous coronary artery dissection. *Circ Genom Precis Med*. 2018;11:e001933. doi: 10.1161/CIRCGENETICS.117.001933
135. Owens DK, Davidson KW, Krist AH, Barry MJ, Cabana M, Caughey AB, Doubeni CA, Epling JW Jr, Kubik M, Landefeld CS, et al; US Preventive Services Task Force. Screening for abdominal aortic aneurysm: US Preventive Services Task Force recommendation statement. *JAMA*. 2019;322:2211–2218. doi: 10.1001/jama.2019.18928
136. Herb J, Strassle PD, Kalbaugh CA, Crowner JR, Farber MA, McGinigle KL. Limited adoption of abdominal aortic aneurysm screening guidelines associated with no improvement in aneurysm rupture rate. *Surgery*. 2018;164:359–364. doi: 10.1016/j.surg.2018.04.009
137. Isselbacher EM, Preventza O, Hamilton Black J 3rd, Augoustides JG, Beck AW, Bolen MA, Braverman AC, Bray BE, Brown-Zimmerman MM, Chen EP, et al. 2022 ACC/AHA guideline for the diagnosis and management of aortic disease: a report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;146:e334–e482. doi: 10.1161/CIR.0000000000001106
138. Goodney PP, Brooke BS, Wallaert J, Travis L, Lucas FL, Goodman DC, Cronenwett JL, Stone DH. Thoracic endovascular aneurysm repair, race, and volume in thoracic aneurysm repair. *J Vasc Surg*. 2013;57:56–63.e1. doi: 10.1016/j.jvs.2012.07.036
139. Filardo G, Powell JT, Martinez MA, Ballard DJ. Surgery for small asymptomatic abdominal aortic aneurysms. *Cochrane Database Syst Rev*. 2015;2015:CD001835. doi: 10.1002/14651858.CD001835.pub4
140. Kontopodis N, Galanakis N, Akoumianakis E, Ioannou CV, Tsetis D, Antoniou GA. Editor's choice: systematic review and meta-analysis of the impact of institutional and surgeon procedure volume on outcomes after ruptured abdominal aortic aneurysm repair. *Eur J Vasc Endovasc Surg*. 2021;62:388–398. doi: 10.1016/j.ejvs.2021.06.015
141. Polanco AR, D'Angelo AM, Shea NJ, Allen P, Takayama H, Patel VI. Increased hospital volume is associated with reduced mortality after thoracoabdominal aortic aneurysm repair. *J Vasc Surg*. 2021;73:451–458. doi: 10.1016/j.jvs.2020.05.027
142. Jackson RS, Chang DC, Freischlag JA. Comparison of long-term survival after open vs endovascular repair of intact abdominal aortic aneurysm among Medicare beneficiaries. *JAMA*. 2012;307:1621–1628. doi: 10.1001/jama.2012.453
143. Schermerhorn ML, Buck DB, O'Malley AJ, Curran T, McCallum JC, Darling J, Landon BE. Long-term outcomes of abdominal aortic aneurysm in the Medicare population. *N Engl J Med*. 2015;373:328–338. doi: 10.1056/NEJMoa1405778
144. Lederle FA, Freischlag JA, Kyriakides TC, Matsumura JS, Padberg FT Jr, Kohler TR, Kougias P, Jean-Claude JM, Cikrit DF, Swanson KM; OVER Veterans Affairs Cooperative Study Group. Long-term comparison of endovascular and open repair of abdominal aortic aneurysm. *N Engl J Med*. 2012;367:1988–1997. doi: 10.1056/NEJMoa1207481
145. Zettervall SL, Schermerhorn ML, Soden PA, McCallum JC, Shean KE, Deery SE, O'Malley AJ, Landon B. The effect of surgeon and hospital volume on mortality after open and endovascular repair of abdominal aortic aneurysms. *J Vasc Surg*. 2017;65:626–634. doi: 10.1016/j.jvs.2016.09.036
146. Dua A, Kuy S, Lee CJ, Upchurch GR Jr, Desai SS. Epidemiology of aortic aneurysm repair in the United States from 2000 to 2010. *J Vasc Surg*. 2014;59:1512–1517. doi: 10.1016/j.jvs.2014.01.007
147. Pape LA, Awais M, Woznicki EM, Suzuki T, Trimarchi S, Evangelista A, Myrmel T, Larsen M, Harris KM, Greason K, et al. Presentation, diagnosis, and outcomes of acute aortic dissection: 17-year trends from the International Registry of Acute Aortic Dissection. *J Am Coll Cardiol*. 2015;66:350–358. doi: 10.1016/j.jacc.2015.05.029
148. Di Eusanio M, Trimarchi S, Patel HJ, Hutchison S, Suzuki T, Peterson MD, Di Bartolomeo R, Folesani G, Pyeritz RE, Braverman AC, et al. Clinical presentation, management, and short-term outcome of patients with type A acute dissection complicated by mesenteric malperfusion: observations from the International Registry of Acute Aortic Dissection. *J Thorac Cardiovasc Surg*. 2013;145:385–390.e1. doi: 10.1016/j.jtcvs.2012.01.042

149. Trimarchi S, Tolenaar JL, Tsai TT, Froehlich J, Pegorer M, Upchurch GR, Fattori R, Sundt TM 3rd, Isselbacher EM, Nienaber CA, et al. Influence of clinical presentation on the outcome of acute B aortic dissection: evidences from IRAD. *J Cardiovasc Surg (Torino)*. 2012;53:161–168.
150. Weissler EH, Osazuwa-Peters OL, Greiner MA, Hardy NC, Kougias P, O'Brien SM, Mark DB, Jones WS, Secemsky EA, Vekstein AM, et al. Initial thoracic endovascular aortic repair vs medical therapy for acute uncomplicated type B aortic dissection. *JAMA Cardiol*. 2023;8:44–53. doi: 10.1001/jamacardio.2022.4187
151. Karthikesalingam A, Holt PJ, Vidal-Diez A, Ozdemir BA, Poloniecki JD, Hinchliffe RJ, Thompson MM. Mortality from ruptured abdominal aortic aneurysms: clinical lessons from a comparison of outcomes in England and the USA. *Lancet*. 2014;383:963–969. doi: 10.1016/S0140-6736(14)60109-4
152. Ullery BW, Tran K, Chandra V, Mell MW, Harris EJ, Dalman RL, Lee JT. Association of an endovascular-first protocol for ruptured abdominal aortic aneurysms with survival and discharge disposition. *JAMA Surg*. 2015;150:1058–1065. doi: 10.1001/jamasurg.2015.1861
153. Tedjawirja VN, de Wit MCJ, Balm R, Koelemay MJW. Differences in comorbidities between women and men treated with elective repair for abdominal aortic aneurysms: a systematic review and meta-analysis. *Ann Vasc Surg*. 2021;76:330–341. doi: 10.1016/j.avsg.2021.03.049
154. Li B, Eisenberg N, Witheford M, Lindsay TF, Forbes TL, Roche-Nagle G. Sex differences in outcomes following ruptured abdominal aortic aneurysm repair. *JAMA Netw Open*. 2022;5:e2211336. doi: 10.1001/jamanetworkopen.2022.11336
155. Varkevisser RRB, Swerdlow NJ, de Guerre L, Dansey K, Stangenberg L, Giles KA, Verhagen HJM, Schermerhorn ML. Five-year survival following endovascular repair of ruptured abdominal aortic aneurysms is improving. *J Vasc Surg*. 2020;72:105–113.e4. doi: 10.1016/j.jvs.2019.10.074
156. Davies RR, Goldstein LJ, Coady MA, Tittle SL, Rizzo JA, Kopf GS, Elefteriades JA. Yearly rupture or dissection rates for thoracic aortic aneurysms: simple prediction based on size. *Ann Thorac Surg*. 2002;73:17–27. doi: 10.1016/s0003-4975(01)03236-2
157. Pape LA, Tsai TT, Isselbacher EM, Oh JK, O'Gara PT, Evangelista A, Fattori R, Meinhardt G, Trimarchi S, Bossone E, et al; International Registry of Acute Aortic Dissection (IRAD) Investigators. Aortic diameter >or = 55 cm is not a good predictor of type A aortic dissection: observations from the International Registry of Acute Aortic Dissection (IRAD). *Circulation*. 2007;116:1120–1127. doi: 10.1161/CIRCULATIONAHA.107.702720
158. Clouse WD, Hallett JW Jr, Schaff HV, Spittell PC, Rowland CM, Ilstrup DM, Melton LJ 3rd. Acute aortic dissection: population-based incidence compared with degenerative aortic aneurysm rupture. *Mayo Clin Proc*. 2004;79:176–180. doi: 10.4065/79.2.176
159. Bellamkonda KS, Nassiri N, Sadeghi MM, Zhang Y, Guzman RJ, Ochoa Chaar CI. Characteristics and outcomes of small abdominal aortic aneurysm rupture in the American College of Surgeons National Surgical Quality Improvement Program database. *J Vasc Surg*. 2021;74:729–737. doi: 10.1016/j.jvs.2021.01.063
160. Columbo JA, Goodney PP, Gladders BH, Tsougranis G, Wanken ZJ, Trooboff SW, Powell RJ, Stone DH. Medicare costs for endovascular abdominal aortic aneurysm treatment in the Vascular Quality Initiative. *J Vasc Surg*. 2021;73:1056–1061. doi: 10.1016/j.jvs.2020.06.109
161. Hansen KJ, Edwards MS, Craven TE, Cherr GS, Jackson SA, Appel RG, Burke GL, Dean RH. Prevalence of renovascular disease in the elderly: a population-based study. *J Vasc Surg*. 2002;36:443–451. doi: 10.1067/mva.2002.127351
162. Cohen MG, Pascua JA, Garcia-Ben M, Rojas-Matas CA, Gabay JM, Berrocal DH, Tan WA, Stouffer GA, Montoya M, Fernandez AD, et al. A simple prediction rule for significant renal artery stenosis in patients undergoing cardiac catheterization. *Am Heart J*. 2005;150:1204–1211. doi: 10.1016/j.ahj.2005.02.019
163. Marcantoni C, Rastelli S, Zanoli L, Tripepi G, Di Salvo M, Monaco S, Sgroi C, Capodanno D, Tamburino C, Castellino P. Prevalence of renal artery stenosis in patients undergoing cardiac catheterization. *Intern Emerg Med*. 2013;8:401–408. doi: 10.1007/s11739-011-0624-5
164. Kalra PA, Guo H, Gilbertson DT, Liu J, Chen SC, Ishani A, Collins AJ, Foley RN. Atherosclerotic renovascular disease in the United States. *Kidney Int*. 2010;77:37–43. doi: 10.1038/ki.2009.406
165. Khatami MR, Jalali A, Zare E, Sadeghian S. Development of a simple risk score model to predict renal artery stenosis. *Nephron*. 2018;140:257–264. doi: 10.1159/000492732
166. Bhalla V, Textor SC, Beckman JA, Casanegra AI, Cooper CJ, Kim ESH, Luther JM, Misra S, Oderich GS; on behalf of the American Heart Association Council on the Kidney in Cardiovascular Disease; Council on Hypertension; Council on Peripheral Vascular Disease; and Council on Cardiovascular Radiology and Intervention. Revascularization for renovascular disease: a scientific statement from the American Heart Association. *Hypertension*. 2022;79:e128–e143. doi: 10.1161/HYP.0000000000000217
167. Cooper CJ, Murphy TP, Cutlip DE, Jamerson K, Henrich W, Reid DM, Cohen DJ, Matsumoto AH, Steffes M, Jaff MR, et al; CORAL Investigators. Stenting and medical therapy for atherosclerotic renal-artery stenosis. *N Engl J Med*. 2014;370:13–22. doi: 10.1056/NEJMoa1310753
168. Conlon PJ, Little MA, Pieper K, Mark DB. Severity of renal vascular disease predicts mortality in patients undergoing coronary angiography. *Kidney Int*. 2001;60:1490–1497. doi: 10.1046/j.1523-1755.2001.00953.x
169. Edwards MS, Craven TE, Burke GL, Dean RH, Hansen KJ. Renovascular disease and the risk of adverse coronary events in the elderly: a prospective, population-based study. *Arch Intern Med*. 2005;165:207–213. doi: 10.1001/archinte.165.2.207

# 26. QUALITY OF CARE

*See Tables 26-1 through 26-8*

Click here to return to the Table of Contents
Click here to return to the Abbreviations

Quality-of-care assessment uses performance measures as explicit standards against which care delivery can be judged.[1] This differs from guidelines, which provide clinical recommendations to inform usual clinical scenarios but ultimately leave decisions to reasonable clinician discretion. Measuring performance requires robust data collection across care settings, rigorous analytics, and timely dissemination. Broadly, there are 2 types of measures: process measures, which focus on tasks that are directly under the control of the clinician (Did patients receive a prescription for a statin after an MI?), and outcomes measures, which focus on endpoints that are meaningful to patients (What proportion of individuals are alive at 30 days after a hospitalization for an MI?).

Decades of outcomes research have helped measure and improve quality of care delivered and, in so doing, improve CVH outcomes. In the United States, much of this body of work has relied on cardiovascular registries, many of which are run by the AHA's GWTG program[2] and the ACC's NCDR program.[3] Increasingly, health care claims data from payers (Medicare, commercial claims) or integrated health care systems (Veterans Affairs, Kaiser Permanente) have also examined quality. Although claims data typically lack the granular phenotyping available in registries, their scale and ability to capture long-term follow-up make them powerful for examining quality of care and outcomes. Last, simulation modeling approaches that systematically integrate data from numerous disparate sources have been used to evaluate the cost-effectiveness of diagnostic tests, drugs, devices, and programs as a measure of the efficiency of health care.

The following sections present illustrative examples of how quality of care is measured in the United States and overseas. These are not meant to be comprehensive given the sheer volume of quality data reported annually. When possible, we report standardized quality indicators drawn from quality-improvement registries using methods that are consistent with performance measures endorsed by the ACC and AHA.[1,4,5] We also provide a few examples of how social determinants of health affect cardiovascular care and outcomes; a more extensive discussion related to health equity is included in individual condition-specific chapters. Of note, the first year of the COVID-19 pandemic saw marked worsening in quality of cardiovascular care and outcomes[6]; although quality of care has recovered in recent years, the recovery has, in some settings, been incomplete and inequitable.[7,8]

## Acute MI

## (See Tables 26-1 and 26-2)

- The ACC's Chest Pain–MI Registry (formerly the ACTION Registry)[9] is currently the largest US-based hospital registry of inpatient AMI care. Tables 26-1 and 26-2 show the latest metrics of AMI quality of care at the time of presentation and at hospital discharge. Rates of prescription of aspirin, β-blocker, and high-intensity statin exceed 95% among hospitals participating in this registry. Referral rates for cardiac rehabilitation after MI increased from 75% in 2010 to 86% in 2022.

### *Quality and Outcomes Across Hospitals*

- With public outcome reporting from 2009 to 2015 across 2751 hospitals, 30-day mortality was highest among baseline poor performers (worst quartile in 2009 and 2010 in public reporting, before value-based payment) but improved more over time compared with other hospitals (from 18.6% in 2009 to 14.6% in 2015 [–0.74%/y; $P<0.001$] versus from 15.7% in 2009 to 14.0% in 2015 [–0.26%/y; $P<0.001$]; $P_{interaction}<0.001$).[5]
- The CMS and Hospital Quality Alliance started to publicly report 30-day mortality measures for AMI and HF in 2007, subsequently expanding to include 30-day readmission rates. According to national Medicare data from July 2015 through June 2016, the median hospital risk-standardized mortality rate for MI was 13.1% (IQR, 12.6%–13.5%), and the median risk-standardized 30-day readmission rate was 15.8% (IQR, 15.5%–16.2%).[10]
- An analysis spanning from April 2011 through December 2017 of patients with AMI from 625 sites using both the NCDR Chest Pain–MI Registry (n=776 890 patients) and CathPCI Registry (n=853 386) explored hospital-level disease-based mortality compared with PCI procedural mortality.[11] There was a moderate correlation between disease-based and procedural mortality (Spearman rank correlation coefficient, 0.53 [95% CI, 0.47–0.58]). Among patients with AMI who had cardiogenic shock or cardiac arrest, procedural mortality

The 2024 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2024. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

was lower than disease-based mortality (mean difference in excess mortality ratio, −0.64% [95% CI, −4.41% to 3.12%]; $P<0.001$), suggesting risk avoidance in this high-risk group.

### Measuring Quality and Outcomes in Medicare Beneficiaries

- In a cohort analysis of 4070 US acute care hospitals, 2820 hospitals had >25 admissions for AMI, CHF, or pneumonia. There was modest but significant correlation in the 30-day risk-standardized readmission rates for patients with traditional Medicare and Medicare Advantage (correlation coefficients, 0.31 for AMI, 0.40 for HF, and 0.41 for pneumonia).[12] The traditional Medicare risk-standardized readmission rate showed a systematic underestimation of risk for AMI and other conditions.
- In a large cohort of Medicare beneficiaries with 642 105 index hospitalizations for AMI, higher 30-day payments were associated with lower 30-day mortality after adjustment for patient characteristics and comorbidities (aOR for additional $1000 payments, 0.986 [95% CI, 0.979–0.992]; $P<0.001$).[4]

### Effect of Health Policy on Quality of AMI Care

- The HRRP announcement in March 2010 was associated with a reduction in 30-day postdischarge mortality in patients with AMI (0.18% pre-HRRP increase versus 0.08% post-HRRP announcement decrease; difference in change, −0.26%; $P=0.01$) that did not change significantly after HRRP implementation.[13]
- A national cross-sectional study highlighted discordance in measurement of quality between AHA/ACC metrics and federal value-based programs.[14] In fiscal year 2018, the analysis included hospitals participating in the HRRP (n=3175 hospitals) or the Hospital Value-Based Purchasing Program (n=2781 hospitals).
  - Hospitals that were recognized with awards for high-quality care from national quality-improvement initiatives of the AHA and ACC were more likely to receive financial penalties from the HRRP compared with other hospitals (419 [85.5%] versus 2112 [78.7%]; $P<0.001$). Award hospitals also were more commonly penalized compared with other hospitals in the Hospital Value-Based Purchasing Program (250 [51.7%] versus 950 [41.4%]; $P<0.001$) with fewer financial rewards (234 [48.4%] versus 1347 [58.6%]; $P<0.001$).
  - Thirty-day AMI mortality at award hospitals was similar to that at other hospitals (13.2% versus 13.2%; $P=0.76$).
- The association of state Medicaid expansion with quality of AMI care and outcomes was investigated in 55 737 patients with low income who were <65 years of age across 765 sites using NCDR data from January 1, 2012, to December 31, 2016.[15] During this period, Medicaid coverage increased from 7.5% to 14.4% in expansion states compared with 6.2% to 6.6% in nonexpansion states ($P<0.001$). In expansion compared with nonexpansion states, there was no change in use of procedures such as PCI for NSTEMI, and delivery of defect-free care increased to a lesser extent in expansion states (aOR, 1.11 [95% CI, 1.02–1.21]). In-hospital mortality improved to a similar extent in expansion and nonexpansion states: 3.2% to 2.8% (aOR, 0.93 [95% CI, 0.77–1.12]) versus 3.3% to 3.0% (aOR, 0.85 [95% CI, 0.73–0.99]; $P_{interaction}=0.48$).

### Social Determinants of Health/Health Equity in AMI Care

- In the ARIC study, 28 732 weighted hospitalizations from 1995 to 2014 for AMI were sampled among patients 35 to 74 years of age. The proportion of AMI hospitalizations occurring in young individuals 35 to 54 years of age increased steadily over the 20-year period, from 27% in 1995 to 1999 to 32% in 2010 to 2014 ($P_{trend}=0.002$). Of note, this increase was seen in young females (from 21% to 31%; $P<0.0001$) but not in young males. Compared with young males, young females with AMI were more often of Black race and presented with a higher comorbidity burden. Young females were less likely to have received guideline-directed medical therapies (RR, 0.87 [95% CI, 0.80–0.94]). However, 1-year all-cause mortality was comparable for females and males (HR, 1.10 [95% CI, 0.83–1.45]).[16]
- Among 237 549 AMI survivors in the US Nationwide Readmissions Database, sex differences in HF hospitalization risk were explored.[17] In a propensity-matched time-to-event analysis, females had a 13% higher risk of 6-month HF readmission compared with males (6.4% versus 5.8%; HR, 1.13 [95% CI, 1.05–1.21]; $P<0.001$).
- An analysis of the Veterans Affairs health care system including 147 600 veteran primary care patients identified sex-related disparities in secondary prevention for IHD.[18] Among patients with premature IHD, females received less antiplatelet (aOR, 0.47 [95% CI, 0.45–0.50]), any statin (aOR, 0.62 [95% CI, 0.59–0.66]), and high-intensity statin (aOR, 0.63 [95% CI, 0.59–0.66]) therapy and had lower adherence to statin therapy than males (mean±SD proportion of days covered, 0.68±0.34 versus 0.73±0.31; β coefficient, −0.02 [95% CI, −0.03 to −0.01]).
- In a health care system cohort of 27 694 patients (52% males, 91% White individuals) examined from January 1, 2011, through December 31, 2018,

area deprivation index as a measure of living in socioeconomically disadvantaged communities was associated with readmission after cardiac hospitalization.[19] Patients with myocardial ischemia living in the areas with the greatest deprivation index had a 2-fold greater hazard of 1-year readmission (HR, 2.04 [95% CI, 1.44–2.91]). In addition, higher area deprivation index was associated with 25% (HR, 1.25 [95% CI, 1.08–1.44]) greater 1-year mortality.

- Among 4667 patients in a study using a North Carolina statewide electronic database of all EMS patient care reports from 2011 to 2017, 62% of EMS encounters met the 11-minute benchmark for response time and 49% met the 15-minute benchmark for scene time.[20]
- NCDR data in 390 692 patients among 586 hospitals from July 2008 to December 2013 were used to examine whether care after an MI varied according to neighborhood socioeconomic disadvantage (defined using an SES summary measure that incorporated information about their neighborhood of residence wealth/income, education, and occupation using US Census data).[21] The study reported longer median arrival-to-angiography time in lower-SES neighborhoods (lowest-SES neighborhood, 8.0 hours; highest-SES neighborhood, 3.4 hours; $P<0.0001$) and a higher proportion of patients with STEMI treated with fibrinolysis (lowest-SES neighborhood, 23.1%; highest-SES neighborhood, 5.9%; $P<0.0001$). Although overall defect-free acute care appeared similar after controlling for covariates, patients from lower-SES neighborhoods had greater independent risk of in-hospital mortality and major bleeding and a lower quality of discharge care. These results indicate further opportunities to improve the quality of AMI care in patients from the most socioeconomically disadvantaged neighborhoods.
- A retrospective cohort study of Medicare patients found that outpatient practices serving the most socioeconomically disadvantaged patients with CAD perform worse on 30-day AMI mortality, despite delivery of guideline-recommended care similar to that of other outpatient practices.[22] Patients at the most socioeconomically disadvantaged–serving outpatient practices had higher 30-day mortality rates after AMI (aOR, 1.31 [95% CI, 1.02–1.68]) compared with patients at other outpatient practices despite similar prescription of guideline-recommended interventions (antiplatelet, antihypertensive, and statin therapy, as well as cardiac rehabilitation). The association was attenuated after additional adjustment for patient-level area deprivation index, suggesting that factors other than guideline-concordant care may influence AMI outcomes.

## Heart Failure

## (See Tables 26-3 and 26-4)

- Current US HF quality data are captured by the widespread but voluntary GWTG-HF program (Tables 26-3 and 26-4) and analyses of health care claims data.

### *Hospitalizations for HF*

- In a cohort study using data from 8 272 270 adult hospitalizations of 5 092 626 unique patients (mean age, 72.1 years; 48.9% females) in the Nationwide Readmission Database from 2010 through 2017, primary HF hospitalization rates per 1000 US adults declined from 4.4 in 2010 to 4.1 in 2013 and then increased to 4.9 in 2017.[23] Similar trends were noted in the rate per 1000 US adults of postdischarge HF readmissions (1.0 in 2010 to 0.9 in 2014 to 1.1 in 2017) and all-cause 30-day readmissions (0.8 in 2010 to 0.7 in 2014 to 0.9 in 2017). The observed increase in the rate of HF hospitalizations in recent years may represent an actual increase in HF hospitalizations, increased detection attributable to rising use of HF biomarkers, the use of more sensitive definitions of HFpEF, or changing coding practices.
- A majority of Medicare beneficiaries are now enrolled in Medicare Advantage Plans compared with fee-for-service Medicare.[24] Thus, it is increasingly important to examine outcomes among beneficiaries enrolled in Medicare Advantage plans in addition to those in traditional fee-for-service Medicare. In 1 study of 262 626 patients hospitalized with HF included in GWTG-HF, patients enrolled in the Medicare Advantage program were more likely to be discharged home compared with patients enrolled in traditional fee-for-service Medicare (aOR, 1.16 [95% CI, 1.13–1.19]; $P<0.001$) and slightly less likely to be discharged within 4 days (aOR, 0.97 [95% CI, 0.93–1.00]; $P=0.04$).[25] In addition, no difference was reported in in-hospital mortality.

### *Effect of Health Policy on HF Hospitalizations*

A number of studies noted a decline in HF readmissions after the implementation of HRRP. However, there is evidence of a potential unintended effect of HRRP on mortality among patients with HF.

- In a longitudinal cohort study of 48 million hospitalizations among 20 million Medicare fee-for-service patients across 3497 hospitals, patients at hospitals subject to penalties under the HRRP had greater reductions in readmission rates than those at nonpenalized hospitals (absolute difference=−1.25 [95% CI, −1.64 to −0.86] percentage point reduction in penalized compared with nonpenalized hospitals).[26]
- Reductions in readmission rates were greater for target versus nontarget conditions for patients at the penalized hospitals but not at nonpenalized

hospitals.[27] Among patients who had multiple admissions at >1 hospital within a given year, the readmission rate was consistently higher among patients admitted to hospitals in the worse-performing quartile than among those admitted to hospitals in a best-performing quartile (absolute difference in readmission rate, 2.0 percentage points [95% CI, 0.4–3.5]).[27]

- In an analysis from 2005 to 2015 including 3.2 million hospitalizations for HF among Medicare fee-for-service beneficiaries, the announcement and implementation of HRRP were associated with an increase in death within 30 days of hospitalization.[13] Compared with this baseline trend, postdischarge mortality increased by 0.49% after the announcement of HRRP ($P$=0.01) and 0.52% after implementation of HRRP ($P$=0.001). The increase in mortality among patients with HF was related to outcomes among patients who were not readmitted but died within 30 days of discharge.
- Readmission reduction efforts may have been associated with an increased number of total hospital visits after discharge when urgent care or emergency room visits are also considered.[28]

### *Alternative Metrics of Care Quality for HF*

- As noted, the increasing enrollment in Medicare Advantage plans necessitates that any quality evaluation includes both fee-for-service and Medicare Advantage patients. A recent study showed that ≈1 in 4 "top-performing" hospitals (based on outcomes among fee-for-service patients) would be reclassified to a lower performance group when Medicare Advantage beneficiaries are included in the evaluation of hospital readmissions and mortality.[29] Between 21.6% and 30.2% were reclassified to a lower-performing quintile, and similar proportions of hospitals were reclassified from the bottom performance quintile to a higher one. The authors concluded that Medicare's current value-based programs provide an incomplete picture of hospital performance.
- Among 106 304 patients hospitalized with HF at 317 centers in the GWTG-HF registry, there was a graded inverse association between 30-day risk-standardized mortality rate and long-term mortality (quartile 1 versus 4 centers: 5-year mortality, 73.7% versus 76.8%). Lower hospital-level 30-day risk-standardized mortality rate was associated with greater 1-, 3-, and 5-year survival for patients with HF. These differences in 30-day survival continued to accrue beyond 30 days and persisted long term, which suggests that 30-day risk-standardized mortality rate could be a useful HF performance metric for centers.[30]
- In 125 595 patients with HF at 342 hospitals in the GWTG-HF registry, hospital volume correlated with process measures but not with 30-day outcomes ($P$=0.26) and only marginally with outcomes in up to 6 months of follow-up ($P$=0.025).[31] Lower-volume hospitals were significantly less likely to be adherent to HF process measures than higher-volume hospitals. On multivariable modeling, higher hospital volume was not associated with differences in in-hospital mortality (OR, 0.99 [95% CI, 0.94–1.05]; $P$=0.78), 30-day mortality (HR, 0.99 [95% CI, 0.97–1.01]; $P$=0.26), or 30-day readmissions (HR, 0.99 [95% CI, 0.97–1.00]; $P$=0.10).
- In data from the GWTG-HF registry from 2007 to 2012, early follow-up visits with a specialist or primary care physician were associated with a reduction in readmissions and mortality for patients with HF. Early visits with subspecialists were associated with lower mortality, particularly for individuals with HF and diabetes (HR, 0.58 [95% CI, 0.34–0.99]). Last, an early follow-up with the cardiologist or primary care physician for those with no comorbidities was associated with a reduction in 90-day mortality (HR, 0.78 [95% CI, 0.63–0.96]).[32]
- Although participation in cardiac rehabilitation improves exercise capacity, quality of life, and clinical outcomes in patients with HFrEF, uptake among eligible Medicare beneficiaries with HFrEF has been low. Among 11 696 Medicare beneficiaries hospitalized for HFrEF from quarter 1 of 2014 to quarter 2 of 2016, the quarterly participation rate within 6 months of discharge was 4.3% with a modest increase over the study period (2.8% in quarter 1 of 2014; 5.0% in quarter 2 of 2016).[33] Factors associated with participation in cardiac rehabilitation among eligible patients with HFrEF included younger age, male sex, race and ethnicity other than Black, previous cardiovascular procedures, and hospitalization at hospitals with cardiac rehabilitation facilities.
- In the GWTG-HF registry, discharge to hospice after HF admissions increased from 2.0% in 2005 to 4.9% in 2014. For individuals discharged to hospice, the median postdischarge survival was 11 days with 34.1% mortality within 3 days and 15.0% survival after 6 months. Among those discharged to hospice, the readmission rate (4.1%) was significantly lower than for other patients with advanced HF (27.2%) or other HF (22.2%) in the registry.[34]
- There has been a continuous trend in the reduction of racial disparities for MI and HF, particularly in safety-net hospitals, before and after HRRP implementation. For example, although Black individuals had 13% higher odds of readmission if treated in safety-net hospitals in 2007, this difference decreased to 5% in 2010.[35]

### Patient-Reported Outcomes for HF

The use of patient-reported outcomes may provide understanding about patient well-being and prognosis.

- In a secondary analysis of the TOPCAT and HF-ACTION trials focused on patient-reported outcomes, the most recent score of a series of Kansas City Cardiomyopathy Questionnaire scores was most strongly associated with subsequent death and cardiovascular hospitalization with a 10% (95% CI, 7%–12%; $P<0.001$) lower risk for subsequent cardiovascular death or HF hospitalization in patients with HFpEF and 7% (95% CI, 3%–11%; $P<0.001$) lower risk for those with HFrEF.[36]

### Cost-Effectiveness and Affordability of HF Therapies

- Simulation modeling studies have examined the cost-effectiveness of sacubitril-valsartan in patients with HFrEF.[37] Among patients with New York Heart Association class II to IV HF and LVEF of ≤40%, the sacubitril-valsartan group gained 0.69 additional life-year and 0.62 additional QALY over a lifetime. Assuming a monthly cost of sacubitril-valsartan to be $380 produced an incremental cost per QALY gained of $47 000. However, sacubitril-valsartan prices have increased substantially in recent years to approximately $660 a month. According to the sensitivity analyses reported in the aforementioned study, the use of sacubitril-valsartan is likely intermediate value per the ACC/AHA value framework (ie, $50 000 to <$150 000 per QALY gained).[38]
- Similarly, simulation modeling studies have found that the use of SGLT-2 inhibitor as a part of guideline-directed medical therapy for HFrEF is of intermediate-value economic value (ie, $50 000 to <150 000 per QALY gained), regardless of the diabetes status of the patient.[39,40] In 1 study,[39] dapagliflozin, at an annual cost of $4192, was projected to add 0.63 QALY at an incremental lifetime cost of $42 800, for an incremental cost-effectiveness ratio of $68 300 per QALY gained (95% UI, $54 600–$117 600 per QALY gained; cost-effective in 94% of probabilistic simulations at a threshold of $100 000 per QALY gained). Findings were similar in individuals with and those without diabetes but were sensitive to drug cost.
- In contrast, the use of an SGLT-2 inhibitor for HFpEF was estimated to be of low economic value in 1 study[41] and low to intermediate value in another study,[42] largely because of the lack of benefit on mortality and small benefit on quality of life.
- A major barrier to accessing novel but effective guideline-directed medical therapies for HF has been the high out-of-pocket costs faced by patients, including Medicare beneficiaries. Two studies suggest that the Inflation Reduction Act of 2022 will lower out-of-pocket costs by 29% to 40% for patients with HFrEF by capping out-of-pocket costs to $2000 starting in 2025.[43] One study evaluated 4137 Medicare Part D plans for out-of-pocket costs associated with comprehensive guideline-directed HFrEF therapy and found that patient costs were projected to decline from $2758 in 2022 to $1954 in 2025 (a 29% reduction).[44] Patients on concurrent DOAC therapy for AF are projected to see an even larger reduction in out-of-pocket costs (from $3259 in 2022 to $2000 in 2025, a 39% reduction).

## Prevention and Risk Factor Modification (See Table 26-5)

- Recent data suggest that Medicaid health maintenance organization patients have better performance on several key preventive measures related to CVD and diabetes than commercial preferred provider organization patients (Table 26-5).
- The National Committee for Quality Assurance Healthcare Effectiveness Data and Information Set consists of established measures of quality of care related to CVD prevention in the United States (Table 26-5).[45]
- In a cross-sectional study of 12 924 adults 20 to 44 years of age from 2009 to 2020, there were increases in the prevalence of diabetes and obesity and no improvement in the prevalence of hypertension. Black young adults had the highest rates of hypertension over the study period, whereas increases in hypertension and diabetes were observed among Hispanic adults.[46]
- In an analysis of the US NHANES from 2001 to 2002 through 2015 to 2016, trends in cardiovascular risk factor control were assessed in 35 416 males and females 20 to 79 years of age.[47] There were improvements in control of hypertension, diabetes, and dyslipidemia over time, but sex differences persisted. In 2013 to 2016, hypertension control in females versus males was observed in 30% versus 22%, diabetes control in 30% versus 20%, and dyslipidemia control in 51% versus 63%.

### Blood Pressure

- Trends in BP control from 1999 to 2000 through 2017 to 2018 in US adults with hypertension were assessed in a serial cross-sectional analysis of NHANES participants.[48] The data were weighted to be representative of US adults and included participants with a mean age of 48±19 years, with 50.1% females, 43.2% NH White adults, 21.6% NH Black adults, 5.3% NH Asian adults, and 26.1% Hispanic adults. In the 18 262 adults with hypertension, the

age-adjusted estimated proportion with controlled BP, defined as BP <140/90 mm Hg, improved from 31.8% (95% CI, 26.9%–36.7%) in 1999 to 2000 to 48.5% (95% CI, 45.5%–51.5%) in 2007 to 2008 ($P_{trend}$<0.001), was similar in 2013 to 2014 (53.8% [95% CI, 48.7%–59.0%]; $P_{trend}$=0.14), and then worsened to 43.7% (95% CI, 40.2%–47.2%) in 2017 to 2018 ($P_{trend}$=0.003).

### Social Determinants of Health/Health Equity in Hypertension

- Disparities in BP control were observed by age, race and ethnicity, insurance status, and health care use. For instance, an analysis of 16 531 nonpregnant US adults in NHANES examined disparities by self-reported race and ethnicity in the cascade of hypertension prevalence, awareness, treatment, and control using data from 2013 to 2018.[49]
  - Compared with White adults, Black adults had a higher prevalence rate (45.3% versus 31.4%; aOR, 2.24 [95% CI, 1.97–2.56]; *P*<0.001) but similar awareness and treatment rates. Hispanic adults had a similar prevalence but lower awareness (71.1% versus 79.1%; aOR, 0.72 [95% CI, 0.58–0.89]; *P*=0.005) and treatment (60.5% versus 67.3%; aOR, 0.78 [95% CI, 0.66–0.94]; *P*=0.010) rates compared with White adults. Asian adults had similar prevalence, lower awareness (72.5% versus 79.1%; aOR, 0.75 [95% CI, 0.58–0.97]; *P*=0.038), and similar treatment rates relative to White adults.
  - Compared with the age-adjusted BP control rate of 49.0% of White adults, BP control rates were lower in Black adults (39.2%; aOR, 0.71 [95% CI, 0.59–0.85]; *P*<0.001), Hispanic adults (40.0%; aOR, 0.71 [95% CI, 0.58–0.88]; *P*=0.003), and Asian adults (37.8%; aOR, 0.68 [95% CI, 0.55–0.84]; *P*=0.001).

### Diabetes

- In 6653 NHANES participants from 1999 to 2018 who were >20 years of age and reported physician-diagnosed diabetes (other than during pregnancy), trends in glycemic control and control of other cardiovascular risk factors were examined.[50]
  - Glycemic control, defined as an HbA1c <7%, improved from 1999 to the early 2010s and then worsened. The percentage of adult NHANES participants with diabetes achieving glycemic control in the 2007 to 2010 period was 57.4% (95% CI, 52.9%–61.8%), worsening to 50.5% (95% CI, 45.8%–55.3%) by 2015 to 2018.
  - Lipid control, defined as non–HDL-C <130 mg/dL, improved in the early 2000s and stalled from 2007 to 2010 (52.3% [95% CI, 49.2%–55.3%]) to 2015 to 2018 (55.7% [95% CI, 50.8%–60.5%]).
  - BP control, defined as BP <140/90 mm Hg, declined from 2011 to 2014 (74.2% [95% CI, 70.7%–77.4%]) to 2015 to 2018 (70.4% [95% CI, 66.7%–73.8%]).
  - Control of all 3 targets plateaued after 2010 and was 22.2% (95% CI, 17.9%–27.3%) in 2015 to 2018. There was no improvement in the use of glucose-lowering or antihypertensive medications after 2010 and in the use of statins after 2014.

### Appropriate Use of Statin Therapy

- In a PINNACLE Registry study of 1 655 723 patients, 57% to 62% of patients were treated with appropriate statin therapy under the ACC/AHA guidelines.[51] Overall, there was a small association of higher income with appropriate statin therapy (point-biserial correlation, 0.026; *P*<0.001). Logistic regression showed an independent association of income with appropriate statin therapy (OR, 1.03 for wealthiest quintile versus poorest quintile [95% CI, 1.01–1.04]).
- In an examination of electronic health record data for patients seen in primary care or cardiology at an urban academic medical center in New York City from October 2018 to January 2020, 7550 patients were eligible for statin therapy on the basis of their 10-year ASCVD risk, but only 3994 (52.9%) were prescribed a statin.[52] After multivariable adjustment, females remained less likely to receive a prescription for statin therapy (aOR, 0.79 [95% CI, 0.71–0.88]).
- Among 24 651 adults >75 years of age (48% females) receiving ASCVD care at a health system in Northern California between 2007 and 2018, prescriptions for moderate- or high-intensity statin therapy increased over time.[53] However, fewer than half of patients (45%) received moderate- or high-intensity statins in 2018. Lower use of statin therapy was observed in females (OR, 0.77 [95% CI, 0.74–0.80]), patients with HF (OR, 0.69 [95% CI, 0.65–0.74]), patients with dementia (OR, 0.88 [95% CI, 0.82–0.95]), and patients with underweight (OR, 0.64 [95% CI, 0.57–0.73]).
- Disparities in statin prescription rates were identified in an analysis of the Vascular Quality Initiative registry of patients undergoing lower-extremity PAD revascularization from January 1, 2014, to December 31, 2019.[54] Among 125 791 patients (mean age, 67.7 years; 62.7% males, 78.7% White individuals) undergoing 172 025 revascularization procedures, the overall proportion of patients receiving a statin prescription after the procedure improved from 75% in 2014 to 87% in 2019. However, only 30% of patients who were not taking a statin at the time of revascularization were newly discharged with a statin prescription.

- An emphasis on short-term risk vastly misses younger individuals at elevated lifetime risk. Recent findings[46] showed a rising prevalence of diabetes, hypertension, and hypercholesterolemia among young individuals 20 to 44 years of age from 2009 to 2020, particularly among Black and Hispanic adults. Taken together, these results support beyond 10-year or short-term risk quantification for improving risk communication, and they provide a baseline for public health efforts aimed at increasing the proportion of Americans with low short-term and low lifetime risk for CVD.

## Atrial Fibrillation

## (See Table 26-6)

### *Prescription of Oral Anticoagulation*

- An analysis of data from the AHA GWTG-AFIB program examined prescription of oral anticoagulation therapy at discharge in 33 235 patients with a $CHA_2DS_2$-VASc score ≥2 hospitalized for AF at 1 of 115 sites from 2013 to 2017. Oral anticoagulation use increased over time from 79.9% to 96.6% in the end of the follow-up period for those with no contraindications, and there was high adherence, with 93.5% of eligible patients without contraindications being prescribed oral anticoagulation therapy for stroke prevention in AF.[55]
- In a cross-sectional analysis spanning 2013 to 2019 and including 34 174 hospitalized patients ≥65 years of age with AF from the GWTG-AFIB registry, overall discharge prescription of anticoagulation was 85.6%.[56] However, higher morbidity burden was associated with lower odds of anticoagulation prescription (aOR, 0.72 for patients with ≥6 comorbidities versus 0–2 comorbidities [95% CI, 0.60–0.86]). In those with ≥6 comorbidities, frequent falls/frailty was the most common reason for nonprescription of anticoagulation (31.0%).
- An AHA GWTG-Stroke study compared outcomes with DOAC therapy (dabigatran, rivaroxaban, or apixaban) versus warfarin in 11 662 patients ≥65 years of age with AF who were anticoagulation naive and discharged from 1041 hospitals after AIS in October 2011 to December 2014. Patients discharged on DOAC therapy had more favorable outcomes compared with those discharged on warfarin, including more days at home during the first year after discharge (mean±SD, 287.2±114.7 days versus 263.0±127.3 days; adjusted difference, 15.6 [99% CI, 9.0–22.1]), fewer MACEs (aHR, 0.89 [99% CI, 0.83–0.96]), and fewer deaths (aHR, 0.88 [95% CI, 0.82–0.95]; $P<0.001$).[57]
- Although there are no trial data comparing the DOACs with each other, high-quality observational studies[58–61] have compared major ischemic and hemorrhagic outcomes in patients with AF treated with rivaroxaban or apixaban. A retrospective cohort study using Medicare fee-for-service claims identified 581 451 patients with AF who began rivaroxaban (n=227 572) or apixaban (n=353 879).[58] Among patients receiving rivaroxaban, the rate of a composite outcome of major ischemic (stroke/systemic embolism) and hemorrhagic (ICH/other intracranial bleeding/fatal extracranial bleeding) events was 16.1 per 1000 person-years versus 13.4 per 1000 person-years for apixaban (HR, 1.18 [95% CI, 1.12–1.24]). The rivaroxaban group had increased risk for both major ischemic events (8.6 versus 7.6 per 1000 person-years; HR, 1.12 [95% CI, 1.04–1.20]) and hemorrhagic events (7.5 versus 5.9 per 1000 person-years; HR, 1.26 [95% CI, 1.16–1.36]). The authors concluded that among Medicare beneficiaries ≥65 years of age with AF, treatment with rivaroxaban compared with apixaban was associated with a significantly increased risk of major ischemic or hemorrhagic events.

### *Adherence to Anticoagulation*

- A systematic review and meta-analysis demonstrated suboptimal adherence and persistence to DOACs in patients with AF.[62] Among 48 observational studies with a combined 594 784 patients with AF (59% male; mean age, 71 years), the pooled mean proportion of days covered/medication possession ratio was 77% (95% CI, 75%–80%), with 66% (95% CI, 63%–70%) showing ≥80% adherence and 69% (95% CI, 65%–72%) showing persistence. Poor adherence to DOAC therapy was associated with greater risk of stroke (HR, 1.39 [95% CI, 1.06–1.81]).
- Using administrative health data from 1996 to 2019 in British Columbia, Canada, a study examined oral anticoagulant adherence trajectories over 5 years in 19 749 patients with AF (mean age, 70.6 years; 56% male; mean $CHA_2DS_2$-VASc score, 2.8).[63] Group-based trajectory modeling identified 74% of patients as having "consistent adherence," defined as a high and steady proportion of days covered by the prescription medication, typically ≈80%), 12% as having "rapid decline and discontinuation," 10% as having "rapid decline and partial recovery," and 4% as having "slow decline and discontinuation."[63] Clinical and demographic characteristics were not able to provide strong performance in predicting these adherence trajectories.

### *Management of AF*

- In a NCDR PINNACLE Registry study, 107 759 of 658 250 patients (16.4%) with AF without CVD were inappropriately prescribed combination antiplatelet and anticoagulant therapy, and 5731 of 150 079 patients (3.8%) with AF with reduced

LVEF received an inappropriate prescription for a nondihydropyridine calcium channel blocker.[64] The adjusted practice-level median OR for inappropriate prescriptions in AF patients was 1.70 (95% CI, 1.61–1.82), consistent with a 70% likelihood of 2 random practices treating identical patients with AF differently.

- In the NCDR Left Atrial Appendage Occlusion Registry, 49 357 patients (mean age, 76.1 years; 41.3% females) with AF undergoing left atrial appendage occlusion with the Watchman device from January 1, 2016, to June 30, 2019, were analyzed.[65] After multivariable adjustment, females had a higher risk of in-hospital adverse events after left atrial appendage occlusion than males (1284 [6.3%] versus 1144 [3.9%]; $P<0.001$; OR, 1.63 [95% CI, 1.49–1.77]; $P<0.001$).
- An economic evaluation of the CABANA trial examined medical resource use data for all trial participants (N=2204), US unit costs of care, and quality-of-life adjustments based on EQ-5D–based utilities measured during the trial.[66] Catheter ablation was associated with an increased lifetime mean cost of $15 516 (95% CI, −$2963 to $35 512) compared with drug therapy with an incremental cost-effectiveness ratio of $57 893 per QALY gained (<$100 000 per QALY in 75% of bootstrap replications). However, the incremental cost-effectiveness ratio rose to $183 318 per life-year gained if one were to assume no quality-of-life gains. The authors concluded that catheter ablation of AF was economically attractive compared with drug therapy on the basis of projected incremental quality-adjusted survival but not survival alone.

### Social Determinants of Health/Health Equity in AF Care

- Health care insurance coverage may influence oral anticoagulant and novel oral anticoagulant use. An analysis of 363 309 patients with prevalent AF from the PINNACLE-AF outpatient registry found considerable variation in oral anticoagulant use across insurance plans.[67] Relative to Medicare, Medicaid insurance was associated with a lower odds of oral anticoagulant prescription (military, 53%; private, 53%; Medicare, 52%; other, 41%; Medicaid, 41%; $P<0.001$) and of novel oral anticoagulant use (military, 24%; private, 19%; Medicare, 17%; other, 17%; Medicaid, 8%; $P<0.001$).

## Stroke

### Prehospital Care

- A retrospective pre-post study examined the effect of a regional prehospital EMS transport policy to triage patients with suspected large-vessel occlusion stroke to CSCs.[68] The outcome was treatment rates before and after implementation of this triage policy in patients with AIS at 15 primary stroke centers and 8 CSCs in Chicago, IL. Among 7709 patients with stroke, the rate of endovascular therapy increased overall among all patients with AIS (from 4.9% [95% CI, 4.1%–5.8%] to 7.4% [95% CI, 7.5%–8.5%]; $P<0.001$) and among EMS-transported patients with AIS within 6 hours of onset (4.8% [95% CI, 3.0%–7.8%] to 13.6% [95% CI, 10.4%–17.6%]; $P<0.001$). The authors concluded that "the implementation of a prehospital transport policy for CSC triage in Chicago was associated with a significant, rapid, and sustained increase in endovascular therapy rate for patients with AIS without deleterious associations with thrombolysis rates or times."[68]

### Acute Stroke Care

### (See Table 26-7)

- The AHA GWTG-Stroke program (Table 26-7) remains the largest stroke quality-improvement program. The US-based program is an ongoing, voluntary hospital registry and performance improvement initiative for acute stroke and supplies most of the quality data for acute stroke care.
- In an analysis comparing individuals presenting with stroke at institutions participating in the GWTG-Stroke program and those at institutions not enrolled in the program, individuals in the GWTG-Stroke program were more likely to receive intravenous tPA (RR, 3.74 [95% CI, 1.65–8.50]), to receive education on risk factors (RR, 1.54 [95% CI, 1.16–2.05]), to be evaluated for swallowing (RR, 1.25 [95% CI, 1.04–1.50]), to receive a lipid evaluation (RR, 1.18 [95% CI, 1.05–1.32]), and to be evaluated by a neurologist (RR, 1.12 [95% CI, 1.05–1.20]).[69]
- In a study from the National Acute Stroke Quality Assessment including 14 666 patients from 202 hospitals, patients admitted to lower-volume centers had higher mortality.[70] However, this association was no longer present once adjusted for stroke severity, suggesting that severity should be accounted for in comparisons of performance across institutions.
- In an analysis from GWTG-Stroke, Asian American individuals presented with more severe strokes, with an OR of 1.35 (95% CI, 1.30–1.40; $P<0.001$) for an NIHSS score >16, and were less likely to receive intravenous tPA (OR, 0.95 [95% CI, 0.91–0.98]; $P=0.003$). They also had higher in-hospital mortality (OR, 1.14 [95% CI, 1.09–1.19]; $P<0.001$) and more symptomatic hemorrhage after tPA (OR, 1.36 [95% CI, 1.20–1.55]; $P<0.001$) than White individuals, although mortality was in fact lower after adjustment for stroke severity (OR, 0.95 [95% CI, 0.91–0.99]; $P=0.008$). In addition, Asian American patients had better adherence to rehabilitation (OR,

1.27 [95% CI, 1.18–1.36]; $P<0.001$) and intensive statin therapy (OR, 1.14 [95% CI, 1.10–1.18]; $P<0.001$).[71]

### Poststroke Care and Outcomes

- A study of 2083 patients with ischemic stroke from 82 hospitals with data in both the AVAIL registry and GWTG-Stroke found that one-third of patients with acute stroke were functionally dependent or dead at 3 months after stroke. Functional rates varied considerably across hospitals, which indicates the need to understand which process measures could be targeted to minimize hospital variation and to improve poststroke functional outcomes.[72]
- A retrospective, difference-in-differences analysis of GWTG-Stroke registry data compared 342 765 first-time ischemic stroke admissions from 2012 to 2018 for patients 19 to 64 years of age in 45 states (27 that expanded Medicaid and 18 that did not).[73] As expected, expansion of Medicaid resulted in an increase in the proportion of stroke admissions covered by Medicaid (from 12.2% to 18.1% in expansion states and from 10.0% to only 10.6% in nonexpansion states). Medicaid expansion was associated with increased odds of discharge to a skilled nursing facility (aOR, 1.33 [95% CI, 1.12–1.59]) and, among eligible patients, transfer to any rehabilitation facility (aOR, 1.24 [95% CI, 1.08–1.41]) and lower odds of discharge home (aOR, 0.89 [95% CI, 0.80–0.98]), but Medicaid expansion was not associated with other outcomes such as stroke severity, use of emergency services, time to acute care, in-hospital mortality, or level of disability.
- Because of the poor survival after stroke, interventions related to improvement in end-of-life care are desirable to improve quality of care for those patients. In a study using GWTG-Stroke data, it was demonstrated that discharge from a Medicare Shared Savings Program hospital or alignment with a related organization was associated with a 16% increase in the odds of hospice enrollment (OR, 1.16 [95% CI, 1.06–1.26]) for patients with high mortality risk with absolute rates of 20% versus 22%. However, a reduction in inpatient comfort measures or hospice enrollment in individuals at lower mortality risk, from 9% to 8%, was noted in the same organizations (OR, 0.82 [95% CI, 0.74–0.91]).[74]

## Transcatheter Aortic Valve Replacement

Since its approval for commercial use in 2011, TAVR has rapidly become the primary modality for the management of aortic stenosis.

### Access

- A multicenter, nationwide cross-sectional analysis of Medicare claims data (2012–2018) examined receipt of TAVR among beneficiaries of fee-for-service Medicare who were ≥66 years of age living in the 25 largest metropolitan core-based statistical areas.[75] When analyzed by zip code, receipt of TAVR was inversely related to median household income, proportion of beneficiaries also enrolled in Medicaid, and increased community-level social deprivation. For instance, for each $1000 decrease in median household income, the number of TAVR procedures performed per 100 000 Medicare beneficiaries declined by 0.2% (95% CI, 0.1%–0.4%). Zip codes with higher proportions of patients of Black race and Hispanic ethnicity had lower rates of TAVR, even after accounting for differences in socioeconomic markers, age, and clinical comorbidities. Disparities in access and outcome were also noted for patients residing in low-population-density areas.[76] In a geospatial study of 6531 patients undergoing TAVR in Florida between 2011 and 2016, those residing in the lowest density category (<50 people per square mile) faced longer unadjusted driving distances and times to their TAVR center (mean extra distance, 43.5 miles [95% CI, 35.6–51.4]; mean extra time, 45.6 minutes [95% CI, 38.3–52.9]). Compared with the highest-population-density regions, the lowest-population-density regions had a 7-fold lower TAVR use rate (7 versus 45 per 100 000; $P<0.001$) and increased in-hospital mortality after TAVR (aOR, 6.13 [95% CI, 1.97–19.1]).

### Clinical Outcomes

- A retrospective cohort study using data from the STS/ACC TVT Registry was used to develop a novel ranked composite performance measure for TAVR quality that incorporated stroke; major, life-threatening, or disabling bleeding; stage III acute kidney injury; and moderate or severe perivalvular regurgitation.[77] When this new outcomes-based metric of TAVR quality was applied to 3-year rolling data, there was significant site-level variation in quality of care in TAVR in the United States, with 25 of 301 sites (8%) performing better than expected, 242 of 301 sites (80%) performing as expected, and 34 of 301 (11%) sites performing worse than expected on the basis of predicted outcomes. However, the reliability of this metric exceeded 0.7 only in sites that performed at least 100 procedures over a 3-year period.

## Resuscitation

### In-Hospital Cardiac Arrests

#### (See Table 26-8)

Quality measures in resuscitation have targeted inpatient care settings. Started in 1999, the AHA GWTG–Resuscitation Registry remains the dominant source of US

quality-improvement data (Table 26-8). GWTG–Resuscitation is a voluntary hospital registry and performance-improvement initiative for IHCA. Process measures for in-hospital resuscitation are generally based on time to correct administration of specific resuscitation and postresuscitation procedures, drugs, or therapies.

- Among 192 adult hospitals in the GWTG–Resuscitation program, risk-standardized survival after IHCA rates (total of 44 477 IHCAs) varied widely between hospitals (median, 24.7%; range, 9.2%–37.5%).[78] Compared with sites without a very active resuscitation champion, hospitals with a very active physician champion were more likely to be in a higher survival quintile (aOR, 3.90 [95% CI, 1.39–10.95]). There was no difference in survival between sites without a very active champion and those with a very active nonphysician champion (aOR, 1.28 [95% CI, 0.62–2.65]).
- In a temporal trend evaluation of survival to discharge after IHCA, there was a significant increase in survival in Black (11.3% in 2000 versus 21.4% in 2014) and White (15.8% versus 23.2%) individuals, and a reduction in the disparity between races was noted ($P_{interaction}$<0.001).[79]
- According to the most updated resuscitation guidelines,[80] only 15% to 30% of patients with IHCA will survive to hospital discharge, and some of these patients will survive with unfavorable functional outcome.[81] They concluded that although an estimated 290 000 IHCAs occur each year in the United States, there is limited evidence to support clinical decision-making. An increased awareness with regard to optimizing clinical care and new research might improve IHCA outcomes.

## Out-of-Hospital Cardiac Arrests

- Recent work within a large US registry demonstrated that Black and Hispanic individuals were less likely to receive bystander CPR at home (38.5%) than White individuals (47.4%; aOR, 0.74 [95% CI, 0.72-0.76]) and less likely to receive bystander CPR in public locations than White individuals (45.6% versus 60.0%; aOR, 0.63 [95% CI, 0.60-0.66])[82] and concluded that significant disparities in bystander CPR exist after controlling for income variables, regardless of the racial and ethnic composition of the location of the arrest.
- In a study comparing OHCAs between 2019 and 2020 to evaluate the impact of the COVD-19 pandemic, a lower proportion of cases receiving bystander CPR in 2020 (61% to 51%; *P*=0.02) and lower use of automated external defibrillators (5% to 1%; *P*=0.02) were seen.[83] The authors also reported longer EMS response time (6.6±2.0 to 7.6±3.0 minutes, respectively; *P*<0.001) and lower survival to hospital discharge (14.7% to 7.9%; *P*=0.02).
- In a study using a large US registry of OHCAs to compare outcomes during the pandemic period of March 16 through April 30, 2020,[84] incidence of OHCA was significantly higher in 2020 compared with 2019, largely in communities with high COVID-19 mortality (adjusted mean difference, 38.6 [95% CI, 37.1–40.1] per 1 million residents) and very high COVID-19 mortality (adjusted mean difference, 28.7 [95% CI, 26.7–30.6] per 1 million residents). However, there was no difference in rates of sustained return of spontaneous circulation or survival to discharge during the prepandemic and peripandemic periods in 2020 versus 2019.

## Implantable Defibrillators and Cardiac Resynchronization Therapy

- In an observational analysis of patients hospitalized with HF and an EF ≤35% without an ICD in the GWTG-HF program (2011–2014), females were less likely than males to receive predischarge ICD counseling (19.3% versus 24.6%; aOR, 0.84 [95% CI, 0.78–0.91]), and individuals from underrepresented racial and ethnic group populations were less likely to receive counseling than patients from White populations (Black, 22.6%; Hispanic, 18.6%; other racial and ethnic groups, 14.4%; versus White, 24.3%; aOR versus White populations, 0.69 [95% CI, 0.63–0.76] for Black individuals; aOR, 0.62 [95% CI, 0.55-0.70] for Hispanic individuals; aOR, 0.53 [95% CI, 0.43-0.65] for other patients).[85] Among patients who were counseled, females and males were similarly likely to receive an ICD (aOR, 1.13 [95% CI, 0.99–1.29]), but compared with White individuals, Black individuals (aOR, 0.70 [95% CI, 0.56–0.88]) and Hispanic individuals (aOR, 0.68 [95% CI, 0.46–1.01]) were less likely to receive an ICD.
- According to data from the ACC's ICD registry, among patients receiving an ICD for primary prevention without indications for pacing, rates of device-related complications were lower among patients receiving a single-chamber ICD compared with patients receiving a dual-chamber ICD (3.51% versus 4.72%; *P*<0.001; risk difference, −1.20 [95% CI, −1.72 to −0.69]), but 1-year mortality was similar in the 2 groups.[86]
- In a multicenter retrospective analysis of 106 individuals ≤21 years or age without prior cardiac disease who received an ICD after SCA, 20 individuals (19%) received appropriate shocks, 16 individuals (15%) received inappropriate shocks (including 3 individuals who had both appropriate and inappropriate shocks), and 73 individuals (69%) received

no shocks over a median follow-up of 3 years.[87] The appropriate use of device therapy was high, regardless of underlying disease.

- Using an antibiotic-eluting envelope during cardiac implantable electronic device procedures reduces the risk of device infection but increases procedural costs. A simulation modeling study examined the cost-effectiveness of using an antibiotic-eluting envelope during cardiac implantable electronic device procedures among patients with HF.[88] Effectiveness was estimated from the World-Wide Randomized Antibiotic Envelope Infection Prevention Trial. Compared with usual care, using an antibiotic-eluting envelope at a cost of $953 per unit during initial implantations produced an incremental cost-effectiveness ratio of $112 000 per QALY gained (39% probability of being cost-effective). In contrast, using an antibiotic-eluting envelope during generator replacement procedures produced an incremental cost-effectiveness ratio of $54 000 per QALY gained (84% probability of being cost-effective). Sensitivity analyses showed that results were sensitive to the underlying rate of infection, cost of the envelope, and durability of effectiveness to prevent infections.

**Table 26-1. Time Trends in the CAD Quality-of-Care Measures in the Chest Pain–MI Registry, United States, 2010 to 2022**

| Quality-of-care measure | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019* | 2020 | 2021 | 2022 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Aspirin within 24 h of arrival† | 97 | 97.6 | 97.8 | 95.4 | 98.1 | 98.6 | 98.5 | 98.5 | 98.7 | 97.6 | 97.4 | 97.7 | 97.6 |
| Aspirin at discharge‡ | 98 | 98.3 | 98.4 | 98.4 | 98.7 | 98.7 | 98.7 | 98.7 | 98.9 | 98.3 | 98.6 | 98.7 | 98.7 |
| β-Blockers at discharge | 96 | 96.7 | 97.1 | 97.1 | 97.6 | 97.5 | 97.5 | 97.4 | 97.4 | 96.3 | 97.0 | 97.2 | 97.1 |
| Statin use at discharge | 92 | 98.4 | 98.8 | 98.8 | 99.1 | 99.2 | 99.4 | 99.4 | 99.5 | 99.4 | NA | NA | NA |
| High-intensity statin at discharge | NA | NA | NA | NA | NA | NA | NA | NA | NA | 88.1 | 92.4 | 94.3 | 95.1 |
| ARB/ACE inhibitor at discharge for patients with LVEF <40% | 86 | 87.8 | 89.7 | 90.0 | 91.2 | 90.2 | 91.0 | 90.3 | 90.9 | 81.4 | 86.3 | 87.7 | 88.5 |
| Adult smoking cessation advice/counseling | 98 | 98.4 | 98.4 | 98.4 | 98.6 | 98.0 | 98.1 | 98.0 | 98.2 | NA | NA | NA | NA |
| Cardiac rehabilitation referral for patients with AMI | 75 | 76.5 | 77.3 | 77.2 | 79.4 | 77.8 | 78.6 | 80.4 | 83.3 | 82.7 | 83.7 | 85.0 | 85.9 |

Values are percentages.

ACE indicates angiotensin-converting enzyme; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; CAD, coronary artery disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; and NA, not available.

*Quality-of-care metrics in 2019 were updated to align with the "AHA [American Heart Association]/ACC [American College of Cardiology] Clinical Performance and Quality Measures for Adults With ST-Elevation and Non–ST-Elevation Myocardial Infarction."[89] These updated measures did not consider a "patient reason" valid for not prescribing guideline medications. Consequently, the registry saw a decline in performance for the following: aspirin within 24 hours of arrival, aspirin at discharge, β-blockers at discharge, statin use at discharge, and ARB/ACE inhibitor at discharge for patients with LVEF <40%. In addition, the registry aligned cardiac rehabilitation referral at discharge with the "ACC/AHA Clinical Performance and Quality Measures for Cardiac Rehabilitation," which has more stringent criteria.[90]

†Effective January 1, 2015, this measure was updated in the Chest Pain–MI Registry to exclude patients taking dabigatran, rivaroxaban, or apixaban (novel oral anticoagulant medications) at home.

‡Effective January 1, 2015, this measure was updated in the Chest Pain–MI Registry to exclude patients who were prescribed dabigatran, rivaroxaban, or apixaban (novel oral anticoagulant medications) at discharge.

Source: Data from the ACC's Chest Pain–MI Registry.[9]

**Table 26-2. Additional Chest Pain–MI Registry Quality-of-Care Metrics for AMI Care, United States, 2018 to 2022**

| Quality metrics | 2018 | 2019 | 2020 | 2021 | 2022 |
|---|---|---|---|---|---|
| ECG within 10 min of arrival* | 68.6 | 64.0 | 59.0 | 56.0 | 55.0 |
| Aspirin within 24 h of arrival | 98.7 | 97.6 | 97.4 | 97.7 | 97.6 |
| STEMI | | | | | |
| PCI within 90 min† | NA | 94.0 | 93.0 | 93.0 | 93.2 |
| Dosing errors | | | | | |
| UFH dose | 43.2 | NA | NA | NA | NA |
| Enoxaparin dose | 9.8 | NA | NA | NA | NA |
| Glycoprotein IIb/IIIa inhibitor dose | 4.3 | NA | NA | NA | NA |
| Discharge | | | | | |
| Aspirin at discharge | 98.9 | 98.3 | 98.6 | 98.7 | 98.7 |
| High-intensity statin at discharge | NA | 88.1 | 92.4 | 94.3 | 95.1 |
| Cardiac rehabilitation referral | 83.3 | 82.7 | 83.7 | 85.0 | 85.9 |
| In-hospital mortality‡ (95% CI) | 4.12 (3.96–4.39) | NA | 5.4 (5.24–5.69) | 5.63 (5.34–6.03) | 5.42 (5.29–5.72) |

Values are percentages. Data reported include data from the first quarter of 2018 to the fourth quarter of 2018.

AMI indicates acute myocardial infarction; MI, myocardial infarction; NA, not available; and UFH, unfractionated heparin.

*Effective January 2019, this metric was updated in the American College of Cardiology's (ACC's) Chest Pain–MI Registry to include patient records in the denominator with incomplete data; consequently, the registry saw a decline in performance (includes all patients with ST-segment–elevation myocardial infarction before hospital admittance and patients with non–ST-segment–elevation myocardial infarction; exclusions are patients with a prehospital ECG, patients transferred in, or patients with a nonsystem reason for delay).

†Excludes transfers and is measuring hospital arrival.

‡Includes all patients. Risk-standardized mortality.

Source: Data from the ACC's Chest Pain–MI Registry.[9]

**Table 26-3. Quality-of-Care Measures in the GWTG-HF Program, United States, 2020 to 2022**

| Quality-of-care measure | 2020 | 2021 | 2022 |
|---|---|---|---|
| ACE inhibitors/ARBs or ARNI at discharge | 90.2 | 91.7 | 92.6 |
| Evidence-based specific β-blockers | 92.0 | 93.4 | 94.2 |
| Measure LV function | 99.0 | 99.2 | 99.2 |
| Postdischarge appointment for patients with HF | 84.9 | 85.5 | 86.2 |

Values are percentages.

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; GWTG, Get With The Guidelines; HF, heart failure; and LV, left ventricular.

Source: Unpublished American Heart Association tabulation, GWTG-HF.

**Table 26-4. Quality of Care by Race and Ethnicity and Sex in the GWTG-HF Program, United States, 2022**

| | Race and ethnicity | | | Sex | |
|---|---|---|---|---|---|
| Quality-of-care measure | White | Black | Hispanic | Males | Females |
| Postdischarge appointment for patients with HF* | 87.1 | 84.2 | 86.4 | 85.9 | 86.6 |
| Measurement of LV function* | 99.3 | 99.2 | 99.4 | 99.2 | 99.3 |
| ACE inhibitors/ARBs or ARNI at discharge* | 91.9 | 93.6 | 93.4 | 92.9 | 91.9 |
| Smoking cessation | 79.9 | 79.3 | 76.7 | 79.4 | 79.7 |
| Evidence-based specific β-blockers* | 93.4 | 95.7 | 94.8 | 94.6 | 93.6 |
| Hydralazine nitrate at discharge | 21.1 | 25.9 | 23 | 27.5 | 23 |
| HF composite (4 achievement measures) | 93.6 | 93.1 | 93.6 | 93.4 | 93.5 |

Values are percentages.

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; GWTG, Get With The Guidelines; HF, heart failure; and LV, left ventricular.

*Indicates the 4 key achievement measures targeted in GWTG-HF.

Source: Unpublished American Heart Association tabulation, GWTG-HF.

**Table 26-5. National Committee for Quality Assurance Healthcare Effectiveness Data and Information Set on CVD, Diabetes, Tobacco, Nutrition, and Lifestyle, United States, 2021**

| | Commercial* | | Medicare* | | Medicaid* |
|---|---|---|---|---|---|
| | HMO | PPO | HMO | PPO | HMO |
| CVD | | | | | |
| β-Blocker persistence after MI† | 85.3 | 85.6 | 80.7 | 88.8 | 89.6 |
| BP control‡ | 60.3 | 50.8 | 58.6 | 70.4 | 70.1 |
| Statin therapy for patients with CVD | 66.1 | 64.5 | 64.7 | 79 | 76.6 |
| Diabetes | | | | | |
| HbA1c testing | 91.1 | 89.4 | 85.3 | 93.9 | 94.2 |
| HbA1c >9.0% | 30.7 | 42.5 | 42.3 | 23.5 | 21.7 |
| Eye examination performed | 51.1 | 48.4 | 50.8 | 71.1 | 69.7 |
| Monitoring nephropathy | NA | NA | NA | 94.9 | 94.9 |
| BP <140/90 mm Hg | 62.9 | 50.6 | 60.3 | 67.9 | 66.3 |
| Statin therapy for patients with diabetes | 72.5 | 76 | 66.2 | 83.6 | 82.8 |
| Tobacco, nutrition, and lifestyle | | | | | |
| Advising smokers and tobacco users to quit | 79.8 | NA | 72.5 | NA | NA |
| BMI percentile assessment in children and adolescents (3–17 y of age) | 72.1 | 60.6 | 76.1 | 72.1 | 60.6 |
| Nutrition counseling (children and adolescents [3–17 y of age]) | 66.5 | 55 | 69.2 | 66.5 | 55 |
| Counseling for PA (children and adolescents [3–17 y of age]) | 63.2 | 52.4 | 65.7 | 63.2 | 52.4 |
| BMI assessment for adults (18–74 y of age) | 84.9§ | 69.7§ | 96.2‖ | 96.3‖ | 88.4§ |
| PA discussion in older adults (≥65 y of age; 2016 data) | 85.9 | | 86.6 | 88.8 | 91.3 |
| PA advice in older adults (≥65 y of age; 2016 data) | 51.8 | | 46.2 | 63.0 | 61.8 |

Values are percentages.

BMI indicates body mass index; BP, blood pressure; CVD, cardiovascular disease; HbA1c, hemoglobin A1c; HMO, health maintenance organization; MI, myocardial infarction; NA, not available; PA, physical activity; and PPO, preferred provider organization.

*Data presented are from 2020 unless otherwise noted.

†β-Blocker persistence: received persistent β-blocker treatment for 6 months after hospital discharge for acute MI.

‡Adults 18 to 59 years of age with BP <140/90 mm Hg, adults 60 to 85 years of age with a diagnosis of diabetes and BP <140/90 mm Hg, and adults 60 to 85 years of age without a diagnosis of diabetes and BP <150/90 mm Hg.

§2019 data.

‖2018 data.

Source: Healthcare Effectiveness Data and Information Set.[45]

**Table 26-6. Quality of Care by Race and Ethnicity and Sex in the GWTG-AFIB Program, United States, 2022**

| | Race and ethnicity | | | Sex | |
|---|---|---|---|---|---|
| Quality-of-care measure | White | Black | Hispanic | Males | Females |
| Discharge HR ≤110 | 94.5 | 95 | 95.7 | 95 | 95.5 |
| Anticoagulation therapy education | 71.9 | 64.4 | 70.2 | 59.7 | 63.4 |
| $CHADS_2$-VASc score documented before discharge | 84.3 | 78.5 | 78.3 | 79.1 | 80 |
| FDA-approved anticoagulation before discharge | 99 | 97 | 97.1 | 98.9 | 98.6 |
| Warfarin at discharge for patients with valvular AF or atrial flutter | 61.4 | 71.9 | 45 | 68.4 | 56.3 |
| DOAC at discharge for patients with nonvalvular AF or atrial flutter | 90.5 | 90.6 | 89.5 | 90.8 | 90.8 |
| PT/INR planned follow-up documented before discharge for warfarin treatment | 90.6 | 88.4 | 83.3 | 82.9 | 83.1 |
| Inappropriate use of DOAC in patients with AF and a mechanical heart valve | 17 | 2.9 | 27.3 | 14.9 | 15.3 |

Values are percentages.

AF indicates atrial fibrillation; DOAC, direct oral anticoagulant; FDA, Food and Drug Administration; GWTG-AFIB, Get With The Guidelines–Atrial Fibrillation; HR, heart rate; INR, international normalized ratio; and PT, prothrombin time.

Source: Unpublished American Heart Association tabulation, GWTG-AFIB.

**Table 26-7. Quality of Care by Race and Ethnicity and Sex in the GWTG-Stroke Program, United States, 2022**

| Quality-of-care measure | Race and ethnicity | | | Sex | |
|---|---|---|---|---|---|
| | White | Black | Hispanic | Males | Females |
| IV tPA in patients who arrived <3.5 h after symptom onset, treated ≤4.5 h* | 92.6 | 92.7 | 94.4 | 92.8 | 92.8 |
| IV tPA door-to-needle time ≤60 min | 86.1 | 85.4 | 86.3 | 87.2 | 85.3 |
| Thrombolytic complications: IV tPA and life-threatening, serious systemic hemorrhage | 7.4 | 6.4 | 5.9 | 6.5 | 7 |
| Antithrombotic agents <48 h after admission | 96.5 | 96.3 | 96.4 | 96.7 | 96.2 |
| VTE prophylaxis by second hospital day | 95 | 95.3 | 95.1 | 95.1 | 95.1 |
| Antithrombotic agents at discharge | 98.5 | 98.8 | 96.9 | 98.7 | 98.4 |
| Anticoagulation for AF/atrial flutter at discharge | 96.8 | 96.8 | 96.9 | 96.9 | 97 |
| Counseling for smoking cessation | 97.5 | 97.6 | 97.5 | 97.6 | 97.4 |
| Lifestyle changes recommended for BMI >25 kg/m$^2$ | 66.7 | 70.4 | 74.7 | 67.9 | 67.6 |
| Composite quality-of-care measure† | 96.1 | 96.3 | 96.1 | 96.3 | 96 |

Values are percentages.

AF indicates atrial fibrillation; BMI, body mass index; GWTG, Get With The Guidelines; IV, intravenous; tPA, tissue-type plasminogen activator; and VTE, venous thromboembolism.

*This measure was changed in 2016 to include in-hospital strokes in the denominator.

†The composite score includes IV thrombolytics arrive by 3.5 hours/treat by 4.5 hours, early antithrombotics, VTE prophylaxis, antithrombotics, anticoagulation for AF/atrial flutter, smoking cessation, and intensive statin therapy.

Source: Unpublished American Heart Association tabulation, GWTG-Stroke.

**Table 26-8. Quality of Care of Patients With IHCA Among GWTG-Resuscitation Hospitals, United States, 2022**

| | Adults | Children |
|---|---|---|
| Event outside critical care setting | 39.6 | 29.0 |
| Hospital survival to discharge for IHCA outside the ICU | 14.6 | 23.0 |
| End-tidal $CO_2$ monitoring used during arrest (all IHCA events) | 17.1 | 34.1 |
| Induced hypothermia used when initial rhythm was shockable (all IHCA events) | 0.9 | 0.5 |
| For IHCA with survival, induced hypothermia initiated | 6.3 | 9.1 |

Values are mean percentages.

GWTG indicates Get With The Guidelines; ICU, intensive care unit; and IHCA, in-hospital cardiac arrest.

Source: Unpublished American Heart Association tabulation, GWTG-Resuscitation.

## REFERENCES


1. Quality of Care and Outcomes Research in CVD and Stroke Working Group. Measuring and improving quality of care: a report from the American Heart Association/American College of Cardiology First Scientific Forum on Assessment of Healthcare Quality in Cardiovascular Disease and Stroke. *Circulation*. 2000;101:1483–1493. doi: 10.1161/01.cir.101.12.1483
2. American Heart Association. Focus on quality. Accessed April 20, 2023. http://heart.org/en/professional/quality-improvement
3. American College of Cardiology Quality Improvement for Institutions. NCDR registries. Accessed April 20, 2023. https://cvquality.acc.org/NCDR-Home/about-ncdr
4. Wadhera RK, Joynt Maddox KE, Wang Y, Shen C, Bhatt DL, Yeh RW. Association between 30-day episode payments and acute myocardial infarction outcomes among Medicare beneficiaries. *Circ Cardiovasc Qual Outcomes*. 2018;11:e004397. doi: 10.1161/CIRCOUTCOMES.117.004397
5. Chatterjee P, Joynt Maddox KE. US national trends in mortality from acute myocardial infarction and heart failure: policy success or failure? *JAMA Cardiol*. 2018;3:336–340. doi: 10.1001/jamacardio.2018.0218
6. Kite TA, Ludman PF, Gale CP, Wu J, Caixeta A, Mansourati J, Sabate M, Jimenez-Quevedo P, Candilio L, Sadeghipour P, et al, International COVID-ACS Registry Investigators. International prospective registry of acute coronary syndromes in patients with COVID-19. *J Am Coll Cardiol*. 2021;77:2466–2476. doi: 10.1016/j.jacc.2021.03.309
7. Varghese MS, Beatty AL, Song Y, Xu J, Sperling LS, Fonarow GC, Keteyian SJ, McConeghy KW, Penko J, Yeh RW, et al. Cardiac rehabilitation and the COVID-19 pandemic: persistent declines in cardiac rehabilitation participation and access among US Medicare beneficiaries. *Circ Cardiovasc Qual Outcomes*. 2022;15:e009618. doi: 10.1161/CIRCOUTCOMES.122.009618
8. De Luca G, Algowhary M, Uguz B, Oliveira DC, Ganyukov V, Zimbakov Z, Cercek M, Jensen LO, Loh PH, Calmac L, et al; ISACS-STEMI COVID-19. COVID-19 pandemic, mechanical reperfusion and 30-day mortality in ST elevation myocardial infarction. *Heart*. 2022;108:458–466. doi: 10.1136/heartjnl-2021-319750
9. American College of Cardiology. The American College of Cardiology's National Cardiovascular Data Registry Chest Pain - MI Registry™. Accessed April 13, 2023. https://cvquality.acc.org/NCDR-Home/registries/hospital-registries/chest-pain-mi-registry

10. Centers for Medicare and Medicaid Services. Medicare Hospital Quality 2017 Chartbook: performance report on outcome measures. Accessed April 13, 2023. https://cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/HospitalQualityInits/OutcomeMeasures.html
11. Nathan AS, Xiang Q, Wojdyla D, Khatana SAM, Dayoub EJ, Wadhera RK, Bhatt DL, Kolansky DM, Kirtane AJ, Rao SV, et al. Performance of hospitals when assessing disease-based mortality compared with procedural mortality for patients with acute myocardial infarction. *JAMA Cardiol*. 2020;5:765–772. doi: 10.1001/jamacardio.2020.0753
12. Panagiotou OA, Voorhies KR, Keohane LM, Kim D, Adhikari D, Kumar A, Rivera-Hernandez M, Rahman M, Gozalo P, Gutman R, et al. Association of inclusion of Medicare Advantage patients in hospitals' risk-standardized readmission rates, performance, and penalty status. *JAMA Netw Open*. 2021;4:e2037320. doi: 10.1001/jamanetworkopen.2020.37320
13. Wadhera RK, Joynt Maddox KE, Wasfy JH, Haneuse S, Shen C, Yeh RW. Association of the Hospital Readmissions Reduction Program with mortality among Medicare beneficiaries hospitalized for heart failure, acute myocardial infarction, and pneumonia. *JAMA*. 2018;320:2542–2552. doi: 10.1001/jama.2018.19232
14. Wadhera RK, Vaduganathan M, Jiang GY, Song Y, Xu J, Shen C, Bhatt DL, Yeh RW, Fonarow GC. Performance in federal value-based programs of hospitals recognized by the American Heart Association and American College of Cardiology for high-quality heart failure and acute myocardial infarction care. *JAMA Cardiol*. 2020;5:515–521. doi: 10.1001/jamacardio.2020.0001
15. Wadhera RK, Bhatt DL, Wang TY, Lu D, Lucas J, Figueroa JF, Garratt KN, Yeh RW, Joynt Maddox KE. Association of state Medicaid expansion with quality of care and outcomes for low-income patients hospitalized with acute myocardial infarction. *JAMA Cardiol*. 2019;4:120–127. doi: 10.1001/jamacardio.2018.4577
16. Arora S, Stouffer GA, Kucharska-Newton AM, Qamar A, Vaduganathan M, Pandey A, Porterfield D, Blankstein R, Rosamond WD, Bhatt DL, et al. Twenty year trends and sex differences in young adults hospitalized with acute myocardial infarction. *Circulation*. 2019;139:1047–1056. doi: 10.1161/CIRCULATIONAHA.118.037137
17. Yandrapalli S, Malik A, Pemmasani G, Aronow W, Shah F, Lanier G, Cooper H, Jain D, Naidu S, Frishman W, et al. Sex differences in heart failure hospitalisation risk following acute myocardial infarction. *Heart*. 2021;107:1657–1663. doi: 10.1136/heartjnl-2020-318306
18. Lee MT, Mahtta D, Ramsey DJ, Liu J, Misra A, Nasir K, Samad Z, Itchhaporia D, Khan SU, Schofield RS, et al. Sex-related disparities in cardiovascular health care among patients with premature atherosclerotic cardiovascular disease. *JAMA Cardiol*. 2021;6:782–790. doi: 10.1001/jamacardio.2021.0683
19. Johnson AE, Zhu J, Garrard W, Thoma FW, Mulukutla S, Kershaw KN, Magnani JW. Area deprivation index and cardiac readmissions: evaluating risk-prediction in an electronic health record. *J Am Heart Assoc*. 2021;10:e020466. doi: 10.1161/JAHA.120.020466
20. Cui ER, Fernandez AR, Zegre-Hemsey JK, Grover JM, Honvoh G, Brice JH, Rossi JS, Patel MD. Disparities in emergency medical services time intervals for patients with suspected acute coronary syndrome: findings from the North Carolina Prehospital Medical Information System. *J Am Heart Assoc*. 2021;10:e019305. doi: 10.1161/JAHA.120.019305
21. Udell JA, Desai NR, Li S, Thomas L, de Lemos JA, Wright-Slaughter P, Zhang W, Roe MT, Bhatt DL. Neighborhood socioeconomic disadvantage and care after myocardial infarction in the National Cardiovascular Data Registry. *Circ Cardiovasc Qual Outcomes*. 2018;11:e004054. doi: 10.1161/CIRCOUTCOMES.117.004054
22. Wadhera RK, Bhatt DL, Kind AJH, Song Y, Williams KA, Maddox TM, Yeh RW, Dong L, Doros G, Turchin A, et al. Association of outpatient practice-level socioeconomic disadvantage with quality of care and outcomes among older adults with coronary artery disease: implications for value-based payment. *Circ Cardiovasc Qual Outcomes*. 2020;13:e005977. doi: 10.1161/CIRCOUTCOMES.119.005977
23. Agarwal MA, Fonarow GC, Ziaeian B. National trends in heart failure hospitalizations and readmissions from 2010 to 2017. *JAMA Cardiol*. 2021;6:952–956. doi: 10.1001/jamacardio.2020.7472
24. MEDPAC. The Medicare Advantage program: status report and mandated report on dual-eligible special needs plans. In: Report to Congress: Medicare Payment Policy. 2022. Accessed April 20, 2023. https://medpac.gov/wp-content/uploads/2022/03/Mar22_MedPAC_ReportToCongress_Ch12_SEC.pdf
25. Figueroa JF, Wadhera RK, Frakt AB, Fonarow GC, Heidenreich PA, Xu H, Lytle B, DeVore AD, Matsouaka R, Yancy CW, et al. Quality of care and outcomes among Medicare Advantage vs fee-for-service Medicare patients hospitalized with heart failure. *JAMA Cardiol*. 2020;5:1349–1357. doi: 10.1001/jamacardio.2020.3638
26. Desai NR, Ross JS, Kwon JY, Herrin J, Dharmarajan K, Bernheim SM, Krumholz HM, Horwitz LI. Association between hospital penalty status under the Hospital Readmission Reduction Program and readmission rates for target and nontarget conditions. *JAMA*. 2016;316:2647–2656. doi: 10.1001/jama.2016.18533
27. Krumholz HM, Wang K, Lin Z, Dharmarajan K, Horwitz LI, Ross JS, Drye EE, Bernheim SM, Normand ST. Hospital-readmission risk: isolating hospital effects from patient effects. *N Engl J Med*. 2017;377:1055–1064. doi: 10.1056/NEJMsa1702321
28. Wadhera RK, Joynt Maddox KE, Kazi DS, Shen C, Yeh RW. Hospital revisits within 30 days after discharge for medical conditions targeted by the Hospital Readmissions Reduction Program in the United States: national retrospective analysis. *BMJ*. 2019;366:l4563. doi: 10.1136/bmj.l4563
29. Oseran AS, Wadhera RK, Orav EJ, Figueroa JF. Effect of Medicare Advantage on hospital readmission and mortality rankings. *Ann Intern Med*. 2023;176:480–488. doi: 10.7326/M22-3165
30. Pandey A, Patel KV, Liang L, DeVore AD, Matsouaka R, Bhatt DL, Yancy CW, Hernandez AF, Heidenreich PA, de Lemos JA, et al. Association of hospital performance based on 30-day risk-standardized mortality rate with long-term survival after heart failure hospitalization: an analysis of the Get With The Guidelines-Heart Failure Registry. *JAMA Cardiol*. 2018;3:489–497. doi: 10.1001/jamacardio.2018.0579
31. Kumbhani DJ, Fonarow GC, Heidenreich PA, Schulte PJ, Lu D, Hernandez A, Yancy C, Bhatt DL. Association between hospital volume, processes of care, and outcomes in patients admitted with heart failure: insights from Get With The Guidelines-Heart Failure. *Circulation*. 2018;137:1661–1670. doi: 10.1161/CIRCULATIONAHA.117.028077
32. Edmonston DL, Wu J, Matsouaka RA, Yancy C, Heidenreich P, Pina IL, Hernandez A, Fonarow GC, DeVore AD. Association of post-discharge specialty outpatient visits with readmissions and mortality in high-risk heart failure patients. *Am Heart J*. 2019;212:101–112. doi: 10.1016/j.ahj.2019.03.005
33. Pandey A, Keshvani N, Zhong L, Mentz RJ, Pina IL, DeVore AD, Yancy C, Kitzman DW, Fonarow GC. Temporal trends and factors associated with cardiac rehabilitation participation among Medicare beneficiaries with heart failure. *JACC Heart Fail*. 2021;9:471–481. doi: 10.1016/j.jchf.2021.02.006
34. Warraich HJ, Xu H, DeVore AD, Matsouaka R, Heidenreich PA, Bhatt DL, Hernandez AF, Yancy CW, Fonarow GC, Allen LA. Trends in hospice discharge and relative outcomes among Medicare patients in the Get With The Guidelines-Heart Failure Registry. *JAMA Cardiol*. 2018;3:917–926. doi: 10.1001/jamacardio.2018.2678
35. Kaplan CM, Thompson MP, Waters TM. How have 30-day readmission penalties affected racial disparities in readmissions? An analysis from 2007 to 2014 in five US states. *J Gen Intern Med*. 2019;34:878–883. doi: 10.1007/s11606-019-04841-x
36. Pokharel Y, Khariton Y, Tang Y, Nassif ME, Chan PS, Arnold SV, Jones PG, Spertus JA. Association of serial Kansas City Cardiomyopathy Questionnaire assessments with death and hospitalization in patients with heart failure with preserved and reduced ejection fraction: a secondary analysis of 2 randomized clinical trials. *JAMA Cardiol*. 2017;2:1315–1321. doi: 10.1001/jamacardio.2017.3983
37. Sandhu AT, Ollendorf DA, Chapman RH, Pearson SD, Heidenreich PA. Cost-effectiveness of sacubitril-valsartan in patients with heart failure with reduced ejection fraction. *Ann Intern Med*. 2016;165:681–689. doi: 10.7326/M16-0057
38. Anderson JL, Heidenreich PA, Barnett PG, Creager MA, Fonarow GC, Gibbons RJ, Halperin JL, Hlatky MA, Jacobs AK, Mark DB, et al. ACC/AHA statement on cost/value methodology in clinical practice guidelines and performance measures: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures and Task Force on Practice Guidelines. *Circulation*. 2014;129:2329–2345. doi: 10.1161/CIR.0000000000000042
39. Isaza N, Calvachi P, Raber I, Liu CL, Bellows BK, Hernandez I, Shen C, Gavin MC, Garan AR, Kazi DS. Cost-effectiveness of dapagliflozin for the treatment of heart failure with reduced ejection fraction. *JAMA Netw Open*. 2021;4:e2114501. doi: 10.1001/jamanetworkopen.2021.14501
40. Parizo JT, Goldhaber-Fiebert JD, Salomon JA, Khush KK, Spertus JA, Heidenreich PA, Sandhu AT. Cost-effectiveness of dapagliflozin for treatment of patients with heart failure with reduced ejection fraction. *JAMA Cardiol*. 2021;6:926–935. doi: 10.1001/jamacardio.2021.1437

41. Zheng J, Parizo JT, Spertus JA, Heidenreich PA, Sandhu AT. Cost-effectiveness of empagliflozin in patients with heart failure with preserved ejection fraction. *JAMA Intern Med*. 2022;182:1278–1288. doi: 10.1001/jamainternmed.2022.5010
42. Cohen LP, Isaza N, Hernandez I, Lewis GD, Ho JE, Fonarow GC, Kazi DS, Bellows BK. Cost-effectiveness of sodium-glucose cotransporter-2 inhibitors for the treatment of heart failure with preserved ejection fraction. *JAMA Cardiol*. 2023;8:419–428. doi: 10.1001/jamacardio.2023.0077
43. Johnson M, Nayak RK, Gilstrap L, Dusetzina SB. Estimation of out-of-pocket costs for guideline-directed medical therapy for heart failure under Medicare Part D and the Inflation Reduction Act. *JAMA Cardiol*. 2023;8:299–301. doi: 10.1001/jamacardio.2022.5033
44. Kazi DS, DeJong C, Chen R, Wadhera RK, Tseng CW. The Inflation Reduction Act and out-of-pocket drug costs for Medicare beneficiaries with cardiovascular disease. *J Am Coll Cardiol*. 2023;81:2103–2111. doi: 10.1016/j.jacc.2023.03.414
45. National Committee for Quality Assurance. Healthcare Effectiveness Data and Information Set (HEDIS) health plan employer data and information set measures of care on cardiovascular disease, diabetes mellitus, tobacco, nutrition, and lifestyle. Accessed April 20, 2023. https://ncqa.org/hedis/measures/
46. Aggarwal R, Yeh RW, Joynt Maddox KE, Wadhera RK. Cardiovascular risk factor prevalence, treatment, and control in US adults aged 20 to 44 years, 2009 to March 2020. *JAMA*. 2023;329:899–909. doi: 10.1001/jama.2023.2307
47. Peters SAE, Muntner P, Woodward M. Sex differences in the prevalence of, and trends in, cardiovascular risk factors, treatment, and control in the United States, 2001 to 2016. *Circulation*. 2019;139:1025–1035. doi: 10.1161/CIRCULATIONAHA.118.035550
48. Muntner P, Hardy ST, Fine LJ, Jaeger BC, Wozniak G, Levitan EB, Colantonio LD. Trends in blood pressure control among US adults with hypertension, 1999-2000 to 2017-2018. *JAMA*. 2020;324:1190–1200. doi: 10.1001/jama.2020.14545
49. Aggarwal R, Chiu N, Wadhera RK, Moran AE, Raber I, Shen C, Yeh RW, Kazi DS. Racial/ethnic disparities in hypertension prevalence, awareness, treatment, and control in the United States, 2013 to 2018. *Hypertension*. 2021;78:1719–1726. doi: 10.1161/HYPERTENSIONAHA.121.17570
50. Fang M, Wang D, Coresh J, Selvin E. Trends in diabetes treatment and control in U.S. adults, 1999-2018. *N Engl J Med*. 2021;384:2219–2228. doi: 10.1056/NEJMsa2032271
51. Tanguturi VK, Kennedy KF, Virani SS, Maddox TM, Armstrong K, Wasfy JH. Association between poverty and appropriate statin prescription for the treatment of hyperlipidemia in the United States: an analysis from the ACC NCDR PINNACLE Registry. *Cardiovasc Revasc Med*. 2020;21:1016–1021. doi: 10.1016/j.carrev.2019.12.026
52. Metser G, Bradley C, Moise N, Liyanage-Don N, Kronish I, Ye S. Gaps and disparities in primary prevention statin prescription during outpatient care. *Am J Cardiol*. 2021;161:36–41. doi: 10.1016/j.amjcard.2021.08.070
53. Spencer-Bonilla G, Chung S, Sarraju A, Heidenreich P, Palaniappan L, Rodriguez F. Statin use in older adults with stable atherosclerotic cardiovascular disease. *J Am Geriatr Soc*. 2021;69:979–985. doi: 10.1111/jgs.16975
54. Singh N, Ding L, Devera J, Magee GA, Garg PK. Prescribing of statins after lower extremity revascularization procedures in the US. *JAMA Netw Open*. 2021;4:e2136014. doi: 10.1001/jamanetworkopen.2021.36014
55. Piccini JP, Xu H, Cox M, Matsouaka RA, Fonarow GC, Butler J, Curtis AB, Desai N, Fang M, McCabe PJ, et al; Get With The Guidelines-AFIB Clinical Working Group and Hospitals. Adherence to guideline-directed stroke prevention therapy for atrial fibrillation is achievable. *Circulation*. 2019;139:1497–1506. doi: 10.1161/CIRCULATIONAHA.118.035909
56. Dalgaard F, Xu H, Matsouaka RA, Russo AM, Curtis AB, Rasmussen PV, Ruwald MH, Fonarow GC, Lowenstern A, Hansen ML, et al. Management of atrial fibrillation in older patients by morbidity burden: insights from Get With The Guidelines-Atrial Fibrillation. *J Am Heart Assoc*. 2020;9:e017024. doi: 10.1161/JAHA.120.017024
57. Xian Y, Xu H, O'Brien EC, Shah S, Thomas L, Pencina MJ, Fonarow GC, Olson DM, Schwamm LH, Bhatt DL, et al. Clinical effectiveness of direct oral anticoagulants vs warfarin in older patients with atrial fibrillation and ischemic stroke: findings from the Patient-Centered Research Into Outcomes Stroke Patients Prefer and Effectiveness Research (PROSPER) Study. *JAMA Neurol*. 2019;76:1192–1202. doi: 10.1001/jamaneurol.2019.2099
58. Ray WA, Chung CP, Stein CM, Smalley W, Zimmerman E, Dupont WD, Hung AM, Daugherty JR, Dickson A, Murray KT. Association of rivaroxaban vs apixaban with major ischemic or hemorrhagic events in patients with atrial fibrillation. *JAMA*. 2021;326:2395–2404. doi: 10.1001/jama.2021.21222
59. Paschke LM, Klimke K, Altiner A, von Stillfried D, Schulz M. Comparing stroke prevention therapy of direct oral anticoagulants and vitamin K antagonists in patients with atrial fibrillation: a nationwide retrospective observational study. *BMC Med*. 2020;18:254. doi: 10.1186/s12916-020-01695-7
60. Mitchell A, Watson MC, Welsh T, McGrogan A. Effectiveness and safety of direct oral anticoagulants versus vitamin K antagonists for people aged 75 years and over with atrial fibrillation: a systematic review and meta-analyses of observational studies. *J Clin Med*. 2019;8:554. doi: 10.3390/jcm8040554
61. Yaghi S, Saldanha IJ, Misquith C, Zaidat B, Shah A, Joudi K, Persaud B, Abdul Khalek F, Shu L, de Havenon A, et al. Direct oral anticoagulants versus Vitamin K antagonists in cerebral venous thrombosis: a systematic review and meta-analysis. *Stroke*. 2022;53:3014–3024. doi: 10.1161/STROKEAHA.122.039579
62. Ozaki AF, Choi AS, Le QT, Ko DT, Han JK, Park SS, Jackevicius CA. Real-world adherence and persistence to direct oral anticoagulants in patients with atrial fibrillation: a systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes*. 2020;13:e005969. doi: 10.1161/CIRCOUTCOMES.119.005969
63. Salmasi S, De Vera MA, Safari A, Lynd LD, Koehoorn M, Barry AR, Andrade JG, Deyell MW, Rush K, Zhao Y, et al. Longitudinal oral anticoagulant adherence trajectories in patients with atrial fibrillation. *J Am Coll Cardiol*. 2021;78:2395–2404. doi: 10.1016/j.jacc.2021.09.1370
64. Hsu JC, Reynolds MR, Song Y, Doros G, Lubitz SA, Gehi AK, Turakhia MP, Maddox TM. Outpatient prescription practices in patients with atrial fibrillation (from the NCDR PINNACLE Registry). *Am J Cardiol*. 2021;155:32–39. doi: 10.1016/j.amjcard.2021.06.011
65. Darden D, Duong T, Du C, Munir MB, Han FT, Reeves R, Saw J, Zeitler EP, Al-Khatib SM, Russo AM, et al. Sex differences in procedural outcomes among patients undergoing left atrial appendage occlusion: insights from the NCDR LAAO Registry. *JAMA Cardiol*. 2021;6:1275–1284. doi: 10.1001/jamacardio.2021.3021
66. Chew DS, Li Y, Cowper PA, Anstrom KJ, Piccini JP, Poole JE, Daniels MR, Monahan KH, Davidson-Ray L, Bahnson TD, et al; CABANA Investigators. Cost-effectiveness of catheter ablation versus antiarrhythmic drug therapy in atrial fibrillation: the CABANA randomized clinical trial. *Circulation*. 2022;146:535–547. doi: 10.1161/CIRCULATIONAHA.122.058575
67. Yong CM, Liu Y, Apruzzese P, Doros G, Cannon CP, Maddox TM, Gehi A, Hsu JC, Lubitz SA, Virani S, et al; ACC PINNACLE Investigators. Association of insurance type with receipt of oral anticoagulation in insured patients with atrial fibrillation: a report from the American College of Cardiology NCDR PINNACLE registry. *Am Heart J*. 2018;195:50–59. doi: 10.1016/j.ahj.2017.08.010
68. Kass-Hout T, Lee J, Tataris K, Richards CT, Markul E, Weber J, Mendelson S, O'Neill K, Sednew RM, Prabhakaran S. Prehospital comprehensive stroke center vs primary stroke center triage in patients with suspected large vessel occlusion stroke. *JAMA Neurol*. 2021;78:1220–1227. doi: 10.1001/jamaneurol.2021.2485
69. Howard G, Schwamm LH, Donnelly JP, Howard VJ, Jasne A, Smith EE, Rhodes JD, Kissela BM, Fonarow GC, Kleindorfer DO, et al. Participation in Get With The Guidelines-Stroke and Its association with quality of care for stroke. *JAMA Neurol*. 2018;75:1331–1337. doi: 10.1001/jamaneurol.2018.2101
70. Lee KJ, Kim JY, Kang J, Kim BJ, Kim SE, Oh H, Park HK, Cho YJ, Park JM, Park KY, et al. Hospital volume and mortality in acute ischemic stroke patients: effect of adjustment for stroke severity. *J Stroke Cerebrovasc Dis*. 2020;29:104753. doi: 10.1016/j.jstrokecerebrovasdis.2020.104753
71. Song S, Liang L, Fonarow GC, Smith EE, Bhatt DL, Matsouaka RA, Xian Y, Schwamm LH, Saver JL. Comparison of clinical care and in-hospital outcomes of Asian American and White patients with acute ischemic stroke. *JAMA Neurol*. 2019;76:430–439. doi: 10.1001/jamaneurol.2018.4410
72. Bettger JP, Thomas L, Liang L, Xian Y, Bushnell CD, Saver JL, Fonarow GC, Peterson ED. Hospital variation in functional recovery after stroke. *Circ Cardiovasc Qual Outcomes*. 2017;10:e002391. doi: 10.1161/CIRCOUTCOMES.115.002391
73. McGee BT, Seagraves KB, Smith EE, Xian Y, Zhang S, Alhanti B, Matsouaka RA, Reeves M, Schwamm LH, Fonarow GC. Associations of Medicaid expansion with access to care, severity, and outcomes for acute ischemic stroke. *Circ Cardiovasc Qual Outcomes*. 2021;14:e007940. doi: 10.1161/CIRCOUTCOMES.121.007940
74. Kaufman BG, O'Brien EC, Stearns SC, Matsouaka RA, Holmes GM, Weinberger M, Schwamm LH, Smith EE, Fonarow GC, Xian Y, et al. Medicare shared savings ACOs and hospice care for ischemic stroke patients. *J Am Geriatr Soc*. 2019;67:1402–1409. doi: 10.1111/jgs.15852
75. Nathan AS, Yang L, Yang N, Eberly LA, Khatana SAM, Dayoub EJ, Vemulapalli S, Julien H, Cohen DJ, Nallamothu BK, et al. Racial, ethnic, and socioeconomic disparities in access to transcatheter aortic valve

replacement within major metropolitan areas. *JAMA Cardiol*. 2022;7:150–157. doi: 10.1001/jamacardio.2021.4641
76. Damluji AA, Fabbro M 2nd, Epstein RH, Rayer S, Wang Y, Moscucci M, Cohen MG, Carroll JD, Messenger JC, Resar JR, et al. Transcatheter aortic valve replacement in low-population density areas: assessing healthcare access for older adults with severe aortic stenosis. *Circ Cardiovasc Qual Outcomes*. 2020;13:e006245. doi: 10.1161/CIRCOUTCOMES.119.006245
77. Desai ND, O'Brien SM, Cohen DJ, Carroll J, Vemulapalli S, Arnold SV, Forrest JK, Thourani VH, Kirtane AJ, O'Neil B, et al. Composite metric for benchmarking site performance in transcatheter aortic valve replacement: results from the STS/ACC TVT Registry. *Circulation*. 2021;144:186–194. doi: 10.1161/CIRCULATIONAHA.120.051456
78. Chan JL, Lehrich J, Nallamothu BK, Tang Y, Kennedy M, Trumpower B, Chan PS; American Heart Association's Get With the Guidelines-Resuscitation Investigators. Association between hospital resuscitation champion and survival for in-hospital cardiac arrest. *J Am Heart Assoc*. 2021;10:e017509. doi: 10.1161/JAHA.120.017509
79. Joseph L, Chan PS, Bradley SM, Zhou Y, Graham G, Jones PG, Vaughan-Sarrazin M, Girotra S; American Heart Association Get With the Guidelines–Resuscitation Investigators. Temporal changes in the racial gap in survival after in-hospital cardiac arrest. *JAMA Cardiol*. 2017;2:976–984. doi: 10.1001/jamacardio.2017.2403
80. Wyckoff MH, Greif R, Morley PT, Ng KC, Olasveengen TM, Singletary EM, Soar J, Cheng A, Drennan IR, Liley HG, et al. International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations: summary from the Basic Life Support; Advanced Life Support; Pediatric Life Support; Neonatal Life Support; Education, Implementation, and Teams; and First Aid Task Forces. *Circulation*. 2022;146:e483–e557. doi: 10.1161/CIR.0000000000001095
81. Andersen LW, Holmberg MJ, Berg KM, Donnino MW, Granfeldt A. In-hospital cardiac arrest: a review. *JAMA*. 2019;321:1200–1210. doi: 10.1001/jama.2019.1696
82. Garcia RA, Spertus JA, Girotra S, Nallamothu BK, Kennedy KF, McNally BF, Breathett K, Del Rios M, Sasson C, Chan PS. Racial and ethnic differences in bystander CPR for witnessed cardiac arrest. *N Engl J Med*. 2022;387:1569–1578. doi: 10.1056/NEJMoa2200798
83. Uy-Evanado A, Chugh HS, Sargsyan A, Nakamura K, Mariani R, Hadduck K, Salvucci A, Jui J, Chugh SS, Reinier K. Out-of-hospital cardiac arrest response and outcomes during the COVID-19 pandemic. *JACC Clin Electrophysiol*. 2021;7:6–11. doi: 10.1016/j.jacep.2020.08.010
84. Chan PS, Girotra S, Tang Y, Al-Araji R, Nallamothu BK, McNally B. Outcomes for out-of-hospital cardiac arrest in the United States during the coronavirus disease 2019 pandemic. *JAMA Cardiol*. 2021;6:296–303. doi: 10.1001/jamacardio.2020.6210
85. Hess PL, Hernandez AF, Bhatt DL, Hellkamp AS, Yancy CW, Schwamm LH, Peterson ED, Schulte PJ, Fonarow GC, Al-Khatib SM. Sex and race/ethnicity differences in implantable cardioverter-defibrillator counseling and use among patients hospitalized with heart failure: findings from the Get With The Guidelines-Heart Failure program. *Circulation*. 2016;134:517–526. doi: 10.1161/CIRCULATIONAHA.115.021048
86. Peterson PN, Varosy PD, Heidenreich PA, Wang Y, Dewland TA, Curtis JP, Go AS, Greenlee RT, Magid DJ, Normand SL, et al. Association of single- vs dual-chamber ICDs with mortality, readmissions, and complications among patients receiving an ICD for primary prevention. *JAMA*. 2013;309:2025–2034. doi: 10.1001/jama.2013.4982
87. Robinson JA, LaPage MJ, Atallah J, Webster G, Miyake CY, Ratnasamy C, Ollberding NJ, Mohan S, Von Bergen NH, Johnsrude CL, et al. Outcomes of pediatric patients with defibrillators following initial presentation with sudden cardiac arrest. *Circ Arrhythm Electrophysiol*. 2021;14:e008517. doi: 10.1161/CIRCEP.120.008517
88. Modi RM, Liu CL, Isaza N, Raber I, Calvachi P, Zimetbaum P, Bellows BK, Kramer DB, Kazi DS. Cost-effectiveness of antibiotic-eluting envelope for prevention of cardiac implantable electronic device infections in heart failure. *Circ Cardiovasc Qual Outcomes*. 2022;15:e008443. doi: 10.1161/CIRCOUTCOMES.121.008443
89. Jneid H, Addison D, Bhatt DL, Fonarow GC, Gokak S, Grady KL, Green LA, Heidenreich PA, Ho PM, Jurgens CY, et al. AHA/ACC clinical performance and quality measures for adults with ST-elevation and non–ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. *Circ Cardiovasc Qual Outcomes*. 2017;10:e000032. doi: 10.1161/HCQ.0000000000000032
90. Thomas RJ, Balady G, Banka G, Beckie TM, Chiu J, Gokak S, Ho PM, Keteyian SJ, King M, Lui K, et al. ACC/AHA clinical performance and quality measures for cardiac rehabilitation: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. *Circ Cardiovasc Qual Outcomes*. 2018;11:e000037. doi: 10.1161/HCQ.0000000000000037

# 27. MEDICAL PROCEDURES

*See Table 27-1 and Charts 27-1 through 27-3*

Click here to return to the Table of Contents
Click here to return to the Abbreviations

## Trends in Operations and Procedures (See Table 27-1 and Chart 27-1)

According to HCUP data from the Agency for Healthcare Research and Quality for the year 2020[1] (Table 27-1):

- There were 434 230 PCIs performed on an inpatient basis in the United States.
- A total of 104 000 inpatient procedures involving CEA or stenting were performed.
- A total of 43 345 left atrial appendage–related procedures were performed.
- A total of 56 395 inpatient peripheral arterial bypass procedures were performed.
- Trends in the numbers of 5 common cardiovascular procedures in the United States from 2016 to 2020 are presented in Chart 27-1. Of the 5 procedures, PCI was the most common procedure for all years presented (Chart 27-1).

## Cardiac Open Heart Surgery in Adults

- Data from the STS Adult Cardiac Surgery Database, which voluntarily collects data from ≈80% of all hospitals that perform CABG in the United States, indicate that a total of 161 816 procedures involved isolated CABG in 2019.[2] CABG made up a little more than half of all adult cardiac surgical procedures performed (N=301 077).
- Among other major procedures in 2019, there were 20 965 isolated aortic valve replacements and 10 748 isolated mitral valve replacements: 12 570 isolated mitral valve repairs, 14 246 procedures involving both aortic valve replacement and CABG, 3441 procedures involving both mitral valve replacement and CABG, 4153 procedures involving both mitral valve repair and CABG, and 2624 procedures involving both mitral valve replacement and aortic valve replacement.[2] A notable trend has been a decrease in the number of procedures involving isolated aortic valve replacement and procedures involving combined aortic valve replacement and CABG.
- Operative mortality for various adult cardiac surgical procedures in 2019 was as follows: isolated CABG, 2.2%; isolated aortic valve replacement, 1.9%; aortic valve replacement plus CABG, 3.6%; mitral valve replacement, 4.6%; mitral valve replacement plus CABG, 8.8%; mitral valve repair, 1.1%; and mitral valve repair plus CABG, 5.0%.[2] Operative mortality for these analyses is defined as "(1) all deaths, regardless of cause, occurring during the hospitalization in which the operation was performed, even if after 30 days (including patients transferred to other acute care facilities); and (2) all deaths, regardless of cause, occurring after discharge from the hospital, but before the end of the 30th postoperative day." [2]
- Median length of stay was 6 days for isolated CABG. It was longest for mitral valve replacement plus CABG (9 days).[2]

## Transcatheter Aortic Valve Replacement

- The STS-ACC TVT Registry collects data on TAVR procedures performed in the Unites States.[3] Between 2011 and 2019, it collected data on 276 316 TAVR procedures in the United States. Some notable findings include the following:
- TAVR volumes continue to grow, with 13 723 TAVR procedures in 2011 to 2013 to 72 991 TAVR procedures in 2019. In 2019, 669 sites were performing TAVR. In 2019, TAVR volumes (n=72 991) exceeded the volumes for all forms of SAVR (n=57 626). The number of intermediate- and low-risk patients receiving TAVR has grown steadily. Similarly, elective or planned valve-in-valve TAVR cases have increased steadily from 305 cases between 2011 and 2013 to 4508 in 2019. The number of sites in the United States performing TAVR was 715 by the end of August 2020.[4] The median age of patients undergoing TAVR in 2019 was 80 years (IQR, 73–85 years) compared with 84 years (IQR, 78–88 years) in the initial years after FDA approval of TAVR.
- In-hospital and 30-day mortality rates of TAVR have improved over time. The in-hospital and 30-day mortality rates were 5.4% and 7.2%, respectively, in 2013 and before, whereas they were 1.3% and 2.5%, respectively, in 2019 ($P<0.0001$). The in-hospital stroke rate decreased from 1.8% before 2013 to 1.6% in 2019 ($P<0.0001$). Need for a pacemaker at 30 days has not changed significantly

The 2024 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2024. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

(10.9% in 2011–2013 and 10.8% in 2019). Median length of stay was 2 days in 2019 (IQR, 1–3 days) with 90.3% of patients discharged home.
- The femoral artery remains the most frequent access site (used in 95.3% of patients undergoing TAVR in 2019).

## Percutaneous Left Atrial Appendage Occlusion

- The NCDR Left Atrial Appendage Occlusion Registry is an FDA-mandated postmarket surveillance registry. Hospitals are required by Centers for Medicare & Medicaid Services to submit data to this registry for Medicare reimbursement.[5] Between January 1, 2016, and December 31, 2018, it collected data on 38 158 percutaneous left atrial appendage occlusion procedures in the United States. According to data from the registry:
  - The mean±SD age of the patients was 76.1± 8.1 years, and 92.7% were ≥65 years of age. Of the patients, 58.9% were male, 92.6% were White, and 4.6% were Black.
  - Of the hospitals that performed percutaneous left atrial appendage occlusion, 37.6% were in the South, 22.7% in the West, 22.2% in the Midwest, and 17.4% in the Northeast. Private/community hospitals and university hospitals performed 77.4% and 21.5% of the procedures, respectively.
  - In-hospital and 45-day mortality rates after discharge were 0.19% and 0.80%, respectively. Risk of any in-hospital major adverse event was 2.16%.[6]

## Congenital Heart Surgery, 2015 to 2018

According to data from the STS Congenital Heart Surgery Database[3]:
- There were 123 777 congenital heart surgeries performed from January 2015 to December 2018. The in-hospital mortality rate was 2.8% during that time period.
- The 5 most common diagnoses were type 2 VSD (6.2%), open sternum with open skin (6.1%), HLHS (5.8%), patent ductus arteriosus (4.0%), and secundum ASD (4.0%).
- The 5 most common primary procedures were delayed sternal closure (8.3%), patch VSD repair (6.4%), mediastinal exploration (3.5%), patch ASD repair (3.2%), and complete atrioventricular canal repair (2.8%).

## Heart Transplantations (See Charts 27-2 and 27-3)

According to data from the Organ Procurement and Transplantation Network[7]:
- In 2022, 4111 heart transplantations were performed in the United States, the most ever (Chart 27-2). A total of 51 combined heart-lung transplantations were performed in 2022 (up from 45 in 2021).
- The highest numbers of heart transplantations were performed in California (547), Texas (363), New York (350), and Florida (263).
- Of the recipients in 2022, 71.2% were males, 55.3% were White people, 26.2% were Black people, 13.1% were Hispanic people, and 3.8% were Asian people. Heart transplantations by recipient age are shown in Chart 27-3. The largest proportion of these patients (41.3%) were between 50 and 64 years of age.
- For transplantations that occurred between 2008 and 2015, the 1-year survival rate was 90.5% for males and 91.1% for females; the 3-year survival rate was 85.2% for males and 85.3% for females. The 5-year survival rates based on 2008 to 2015 transplantations were 78.4% for males and 77.7% for females. The 1- and 5-year survival rates for White individuals undergoing cardiac transplantation were 90.7% and 79.1%, respectively. For Black people, they were 90.7% and 74.1%, respectively. For Hispanic people, they were 90.1% and 79.9%, respectively. For Asian individuals, they were 91.4% and 80.1%, respectively.
- Between 2011 and 2014, the median waiting time for individuals in United Network for Organ Sharing heart status 1A was 87 days (95% CI, 80–94). As a comparison, the median waiting time was 67 days (95% CI, 61–73) for patients with heart status 1A between 2007 and 2010.
- As of March 11, 2023, 3376 individuals were on the waiting list for a heart transplantation, and 35 people were on the list for a heart–lung transplantation.

**Table 27-1. Estimated Inpatient Cardiovascular Operations, Procedures, and Patient Data, by Sex and Age (in Thousands), United States, 2020**

| Operation/procedure | CCSR code | All | Sex | | Age, y | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Male | Female | 18–44 | 45–64 | 65–84 | ≥85 |
| Heart conduction mechanism procedures | CAR002 | 63 405 | 40 070 | 23 335 | 3350 | 19 535 | 36 700 | 3435 |
| CABG | CAR003 | 169 705 | 129 275 | 40 430 | 3885 | 63 825 | 99 395 | 2565 |
| PCI | CAR004 | 434 230 | 294 295 | 139 930 | 21 255 | 178 065 | 208 070 | 26 660 |
| Other coronary artery procedures (excluding CABG and PCI) | CAR005 | 6845 | 4795 | 2050 | 685 | 2450 | 2565 | 125 |
| CEA and stenting | CAR006 | 104 000 | 60 800 | 43 195 | 2500 | 25 135 | 69 070 | 6855 |
| Embolectomy, endarterectomy, and related vessel procedures (nonendovascular; excluding carotid) | CAR007 | 73 575 | 44 220 | 29 355 | 5380 | 25 380 | 37 595 | 4540 |
| Angioplasty and related vessel procedures (endovascular; excluding carotid) | CAR008 | 208 160 | 115 290 | 92 870 | 16 530 | 71 305 | 99 750 | 17 395 |
| Left atrial appendage procedures | CAR009 | 43 345 | 30 085 | 13 260 | 1140 | 13 650 | 27 710 | 800 |
| Ligation and embolization of vessels | CAR010 | 88 870 | 50 550 | 38 300 | 19 085 | 27 415 | 29 065 | 4370 |
| Aneurysm repair procedures | CAR011 | 77 855 | 48 330 | 29 525 | 6600 | 22 130 | 42 285 | 5375 |
| Vessel repair and replacement | CAR012 | 99 330 | 63 280 | 36 045 | 14 010 | 31 345 | 42 555 | 3800 |
| Heart and great vessel bypass procedures | CAR013 | 7700 | 4455 | 3245 | 400 | 615 | 660 | 80 |
| Peripheral arterial bypass procedures | CAR014 | 56 395 | 36 940 | 19 455 | 3215 | 21 415 | 29 435 | 2040 |
| Peripheral arteriovenous fistula and shunt procedures | CAR015 | 19 055 | 11 040 | 8015 | 2725 | 7920 | 7640 | 720 |
| Portal and other venous bypass procedures | CAR016 | 8155 | 5035 | 3115 | 1305 | 4030 | 2595 | 60 |
| Pericardial procedures | CAR017 | 24 355 | 14 035 | 10 315 | 3720 | 8480 | 9955 | 870 |
| Heart transplantation | CAR018 | 3540 | 2615 | 925 | 570 | 1915 | 660 | 0 |
| Septal repair and other therapeutic heart procedures | CAR019 | 35 150 | 19 100 | 16 035 | 4315 | 8835 | 10 245 | 570 |
| Saphenous vein harvest and other therapeutic vessel removal | CAR020 | 191 325 | 141 740 | 49 585 | 9795 | 70 155 | 105 765 | 3665 |
| Artery, vein, and great vessel procedures, NEC | CAR021 | 13 885 | 6750 | 7125 | 2015 | 4380 | 6165 | 660 |
| Heart valve replacement and other valve procedures (nonendovascular) | CAR022 | 89 625 | 56 670 | 32 955 | 9070 | 31 585 | 42 615 | 1085 |
| Heart valve replacement and other valve procedures (endovascular) | CAR023 | 97 830 | 56 055 | 41 760 | 1340 | 7970 | 64 770 | 22 740 |
| Pacemaker and defibrillator procedures | CAR026 | 90 375 | 58 835 | 31 525 | 5725 | 24 530 | 47 745 | 11 080 |
| Heart assist device procedures | CAR027 | 25 965 | 18 925 | 7040 | 1940 | 9610 | 12 660 | 1475 |

These data do not reflect any procedures performed on an outpatient basis. Over time, many more procedures are being performed on an outpatient basis. Weighted national estimates are from HCUP NIS AHRQ and based on data collected by individual states and provided AHRQ by the states. Total number of weighted discharges in the United States is based on HCUP NIS=32 355 827.

AHRQ indicates Agency for Healthcare Research and Quality; CABG, coronary artery bypass graft; CCSR, Clinical Classifications Software Refined; CEA, carotid endarterectomy HCUP, Healthcare Cost and Utilization Project; NEC, not elsewhere classified; NIS, National/Nationwide Inpatient Sample; and PCI, percutaneous coronary intervention.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using HCUP.[1]

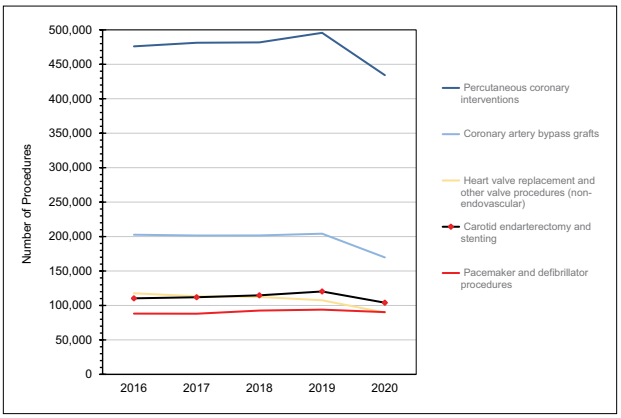



**Chart 27-1. Estimated inpatient cardiovascular operations and procedures, United States, 2016 to 2020.**
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Healthcare Cost and Utilization Project.[1]

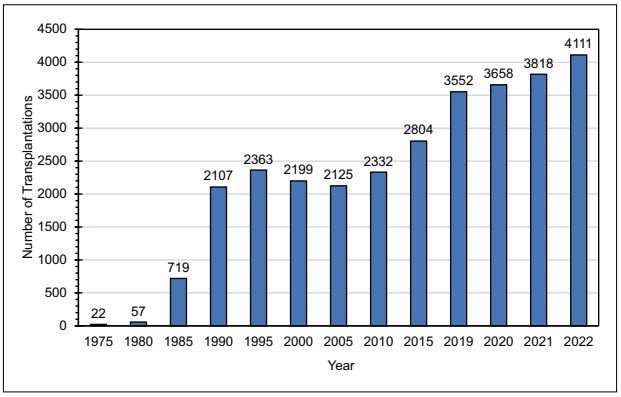



**Chart 27-2. Trends in heart transplantations, United States, 1975 to 2022.**
Source: Data derived from the Organ Procurement and Transplantation Network.[7]

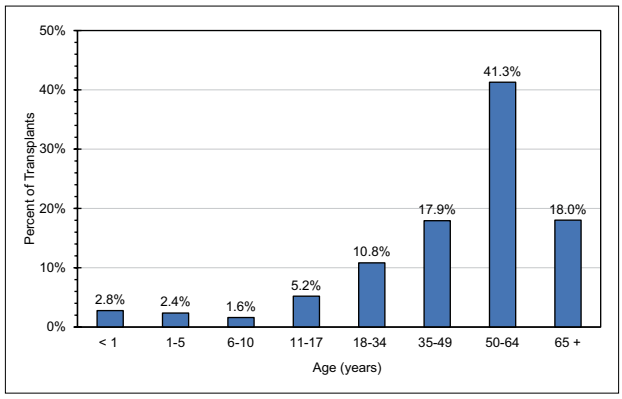



**Chart 27-3. Heart transplantations by recipient age, United States, 2022.**
Source: Data derived from the Organ Procurement and Transplantation Network.[7]

## REFERENCES


1. Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project (HCUP). Accessed April 1, 2023. http://hcupnet.ahrq.gov/
2. Bowdish ME, D'Agostino RS, Thourani VH, Schwann TA, Krohn C, Desai N, Shahian DM, Fernandez FG, Badhwar V. STS Adult Cardiac Surgery Database: 2021 update on outcomes, quality, and research. *Ann Thorac Surg*. 2021;111:1770–1780. doi: 10.1016/j.athoracsur.2021.03.043
3. Carroll JD, Mack MJ, Vemulapalli S, Herrmann HC, Gleason TG, Hanzel G, Deeb GM, Thourani VH, Cohen DJ, Desai N, et al. STS-ACC TVT Registry of transcatheter aortic valve replacement. *J Am Coll Cardiol*. 2020;76:2492–2516. doi: 10.1016/j.jacc.2020.09.595
4. Deleted in proof.
5. Freeman JV, Varosy P, Price MJ, Slotwiner D, Kusumoto FM, Rammohan C, Kavinsky CJ, Turi ZG, Akar J, Koutras C, et al. The NCDR Left Atrial Appendage Occlusion Registry. *J Am Coll Cardiol*. 2020;75:1503–1518. doi: 10.1016/j.jacc.2019.12.040
6. Freeman JV, Higgins AY, Wang Y, Du C, Friedman DJ, Daimee UA, Minges KE, Pereira L, Goldsweig AM, Price MJ, et al. Antithrombotic therapy after left atrial appendage occlusion in patients with atrial fibrillation. *J Am Coll Cardiol*. 2022;79:1785–1798. doi: 10.1016/j.jacc.2022.02.047
7. US Department of Health and Human Services. Organ Procurement and Transplantation Network website. Accessed April 18, 2023. https://optn.transplant.hrsa.gov/data/

# 28. ECONOMIC COST OF CARDIOVASCULAR DISEASE

*See Tables 28-1 and 28-2 and Charts 28-1 through 28-3*

Click here to return to the Table of Contents

Click here to return to the Abbreviations

According to data from MEPS (2019–2020),[1] the annual direct and indirect cost of CVD in the United States is an estimated $422.3 billion (Table 28-1 and Chart 28-1). This figure includes $254.3 billion in expenditures (direct costs, which include the costs of physicians and other professionals, hospital services, prescribed medications, and home health care but not the cost of nursing home care) and $168.0 billion in lost future productivity (indirect costs) attributed to premature CVD mortality in 2019 to 2020.

The direct costs for CVD for 2019 to 2020 (average annual) are available on the website of the nationally representative MEPS of the Agency for Healthcare Research and Quality.[1] Details on the advantages or disadvantages of using MEPS data are provided in the "Heart Disease and Stroke Statistics—2011 Update." Indirect mortality costs are estimated for 2019 to 2020 (average annual) by multiplying the number of deaths for those years attributable to CVD, in age and sex groups, by estimates of the present value of lifetime earnings for those age and sex groups as of 2019 to 2020.[2] Mortality data are from the NVSS of the NCHS.[3] The present values of lifetime earnings are unpublished estimates furnished by the Institute for Health and Aging, University of California, San Francisco, by Wendy Max, PhD, on April 4, 2018. Those estimates incorporate a 3% discount rate, which removes the effect of inflation in income over the lifetime of earnings.[4] The estimate is for 2014, inflated to 2020 to account for the 2014 to 2020 change in hourly worker compensation in the business sector reported by the US Bureau of Labor Statistics.[5] The indirect costs exclude lost productivity costs attributable to chronic, prevalent nonfatal CVD illness during 2019 to 2020 among workers, people keeping house, people in institutions, and people unable to work. Those morbidity costs were substantial in previous estimates, but because of the lack of contemporary data, an adequate comparable update could not be made.

## Costliest Diseases

### (See Tables 28-1 and 28-2 and Charts 28-2 and 28-3)

CVD accounted for 12% of total US health expenditures in 2019 to 2020, more than any major diagnostic group.[1] By way of comparison, CVD total direct costs shown in Table 28-1 were higher than the 2019 to 2020 Agency for Healthcare Research and Quality total direct expenditure for cancer, which was $156.4 billion (49% for outpatient or office-based events, 20% for inpatient stays, and 28% for prescription drugs).[1]

Table 28-2 shows direct and indirect costs for CVD by sex and by 2 broad age groups. During 2019 to 2020, 47% of the direct costs were in females and 43% of the direct costs were in individuals <65 years of age. Chart 28-2 shows total direct costs for the 23 leading chronic diseases on the MEPS list. HD was the fifth costliest condition.[1]

The estimated direct costs of CVD in the United States increased from $103.5 billion in 1996 to 1997 to $254.3 billion in 2019 to 2020 (Chart 28-3). In 2019 to 2020, stroke, HD, and hypertension represented 14%, 47% and 18%, respectively, of direct CVD costs.

The 2024 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2024. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

**Table 28-1. Estimated Direct and Indirect Costs (in Billions of Dollars) of CVD, United States, Average Annual, 2019 to 2020**

| | HD* | Stroke | Hypertensive disease† | Other circulatory conditions‡ | Total CVD |
|---|---|---|---|---|---|
| Direct costs§ | | | | | |
| Hospital inpatient stays | 60.4 | 16.4 | 7.4 | 26.1 | 110.3 |
| Hospital ED visits | 4.3 | 1.2 | 1.5 | 2.2 | 9.1 |
| Hospital outpatient or office-based health care professional visits | 28.1 | 9.0 | 16.4 | 16.3 | 69.7 |
| Home health care | 10.1 | 6.4 | 7.2 | 3.2 | 27.0 |
| Prescribed medicines | 17.3 | 1.4 | 13.5 | 5.9 | 38.2 |
| Total expenditures | 120.2 | 34.5 | 46.0 | 53.6 | 254.3 |
| Indirect costs‖ | | | | | |
| Lost productivity/mortality | 132.0 | 21.8 | 6.5 | 7.8 | 168.0 |
| Grand totals | 252.2 | 56.2 | 52.4 | 61.4 | 422.3 |

Numbers do not add to total because of rounding.

CVD indicates cardiovascular disease; ED, emergency department; and HD, heart disease.

*This category includes coronary HD, heart failure, part of hypertensive disease, cardiac dysrhythmias, rheumatic HD, cardiomyopathy, pulmonary HD, and other or ill-defined HDs.

†Costs attributable to hypertensive disease are limited to hypertension without HD.

‡Other circulatory conditions include arteries, veins, and lymphatics.

§Medical Expenditure Panel Survey (MEPS) health care expenditures are estimates of direct payments for care of a patient with the given disease provided during the year, including out-of-pocket payments and payments by private insurance, Medicaid, Medicare, and other sources. Payments for over-the-counter drugs are not included. These estimates of direct costs do not include payments attributed to comorbidities. Total CVD costs are the sum of costs for the 4 diseases but with some duplication.

‖The Statistics Committee agreed to suspend presenting estimates of lost productivity attributable to morbidity until a better estimating method can be developed. Lost future earnings of people who died in 2019 to 2020, discounted at 3%.

Sources: Unpublished National Heart, Lung, and Blood Institute tabulation using the Household Component of the MEPS for direct costs (average annual 2019–2020).[1] Indirect mortality costs are based on 2019 to 2020 counts of deaths by the National Center for Health Statistics and an estimated present value of lifetime earnings furnished for 2014 by Wendy Max (Institute for Health and Aging, University of California, San Francisco, April 4, 2018) and inflated to 2020 from change in worker compensation reported by the US Bureau of Labor Statistics.[5]

**Table 28-2. Costs of CVD in Billions of Dollars, by Age and Sex, United States, Average Annual, 2019 to 2020**

| | Total | Males | Females | <65 y of age | ≥65 y of age |
|---|---|---|---|---|---|
| All direct | 254.3 | 135.0 | 119.4 | 109.4 | 144.9 |
| Indirect, mortality only | 168.0 | 125.7 | 42.3 | 138.1 | 30.0 |
| Total | 422.3 | 260.7 | 161.6 | 247.5 | 174.9 |

Numbers may not add to total because of rounding.

CVD indicates cardiovascular disease.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Medical Expenditure Panel Survey, average annual 2019 to 2020 (direct costs) and mortality data from the National Vital Statistics System, and present value of lifetime earnings from the Institute for Health and Aging, University of California, San Francisco (indirect costs).[1,3]

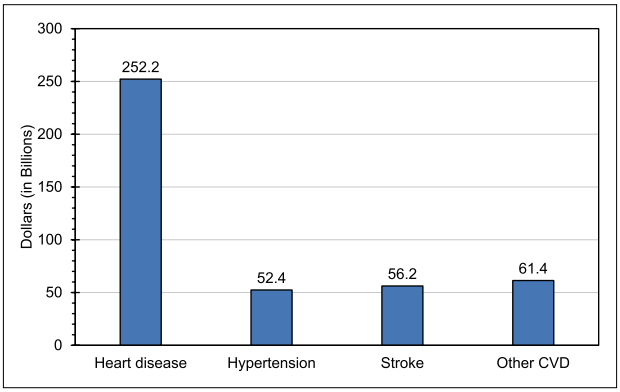



**Chart 28-1. Direct and indirect costs of CVD (in billions of dollars), United States, average annual 2019 to 2020.**
CVD indicates cardiovascular disease.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Medical Expenditure Panel Survey data and mortality data from the National Vital Statistics System.[1,3]

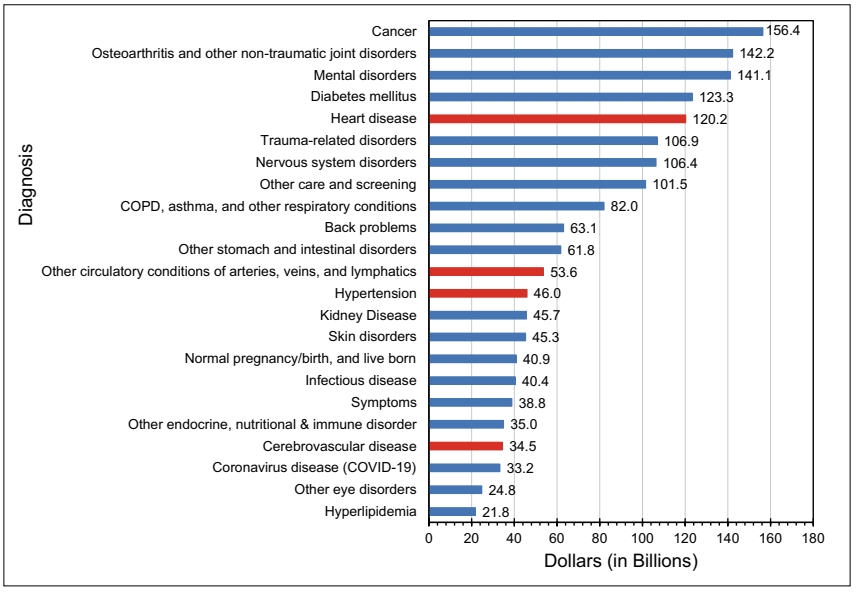



**Chart 28-2. The 23 leading diagnoses for direct health expenditures, United States, average annual 2019 to 2020 (in billions of dollars).**

COPD indicates chronic obstructive pulmonary disease.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Medical Expenditure Panel Survey data and excluding nursing home costs.[1]

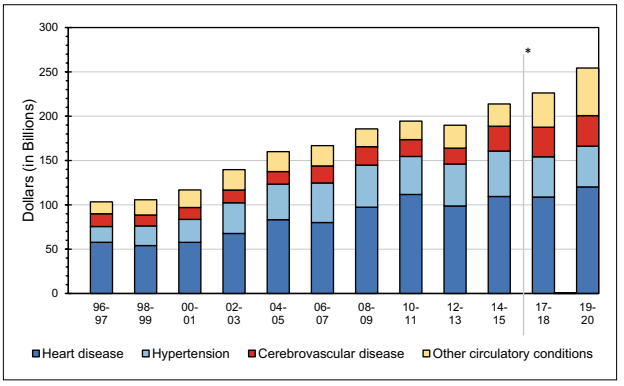



**Chart 28-3. Estimated direct cost (in billions of dollars) of CVD, United States, average annual (1996–1997 to 2019–2020).**

CVD indicates cardiovascular disease.

**International Classification of Diseases, 9th Revision* coding for 1996 to 2015; *International Classification of Diseases, 10th Revision* coding for 2017 to 2020. The 2016 data are omitted from this chart.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Medical Expenditure Panel Survey for direct costs (average annual 1996–1997 to 2019–2020).[1]

## REFERENCES


1. Agency for Healthcare Research and Quality. Medical Expenditure Panel Survey (MEPS): household component summary tables: medical conditions, United States. Accessed April 2, 2023. https://meps.ahrq.gov/mepsweb/
2. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, Carnethon MR, Dai S, de Simone G, Ford ES, et al; on behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics––2011 update: a report from the American Heart Association [published corrections appear in *Circulation*. 2011;123:e240 and *Circulation*. 2011;124:e426]. *Circulation*. 2011;123:e18–e209. doi: 10.1161/CIR.0b013e3182009701
3. Centers for Disease Control and Prevention and National Center for Health Statistics. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death micro-data files. Accessed April 8, 2023. https://cdc.gov/nchs/nvss/mortality_public_use_data.htm
4. Gold MR, Siegel JE, Russell LB, Weinstein MC. *Cost-Effectiveness in Health and Medicine*. New York, NY: Oxford University Press; 1996.
5. US Bureau of Labor Statistics and US Department of Labor. News release: Employment Cost Index–December 2020: Table 4, Employment Cost Index for total compensation, for civilian workers, by occupational group and industry. Accessed March 1, 2023. https://bls.gov/news.release/archives/eci_01292021.pdf

# 29. AT-A-GLANCE SUMMARY TABLES

*See Tables 29-1 through 29-3*

Click here to return to the Table of Contents

Click here to return to the Abbreviations

Sources: See the following summary tables for complete details:

- Overweight, Obesity, and Severe Obesity in Youth and Adults in the United States—Table 6-1
- High TC and LDL-C and Low HDL-C in the United States—Table 7-1
- HBP in the United States—Table 8-1
- Diabetes in the United States—Table 9-1
- CVDs in the United States—Table 14-1
- Stroke in the United States—Table 15-1
- CCDs in the United States—Table 17-2
- CHD in the United States—Table 21-1; AP in the United States—Table 21-2
- HF in the United States—Table 22-2

Note: In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.[1]

The 2024 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2024. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

**Table 29-1. Males and CVD: At-a-Glance Table**

| Diseases and risk factors | Both sexes | Total males | NH White males | NH Black males | Hispanic males | NH Asian males | NH American Indian/Alaska Native* (both sexes) | NH Native Hawaiian or Pacific Islander* (both sexes) |
|---|---|---|---|---|---|---|---|---|
| Overweight and obesity | | | | | | | | |
| Prevalence, 2017–2020 | | | | | | | | |
| Obesity, BMI ≥30.0 kg/m²† | 41.9% | 41.8% | 43.1% | 40.4% | 45.1% | 17.6% | … | … |
| Blood cholesterol | | | | | | | | |
| Prevalence, 2017–2020 | | | | | | | | |
| TC ≥200 mg/dL‡ | 86.4 M (34.7%) | 38.9 M (32.8%) | 32.5% | 27.5% | 32.8% | 40.7% | … | … |
| TC ≥240 mg/dL‡ | 24.7 M (10.0%) | 11.0 M (9.5%) | 9.6% | 6.9% | 9.3% | 13.0% | … | … |
| LDL-C ≥130 mg/dL‡ | 63.1 M (25.5%) | 30.3 M (25.6%) | 25.0% | 26.4% | 23.7% | 31.5% | … | … |
| HDL-C <40 mg/dL‡ | 41.3 M (16.9%) | 29.9 M (24.9%) | 25.0% | 15.3% | 29.5% | 25.4% | … | … |
| HBP | | | | | | | | |
| Prevalence, 2017–2020† | 122.4 M (46.7%) | 62.8 M (50.4%) | 48.9% | 57.5% | 50.3% | 50.2% | … | … |
| Mortality, 2021§,‖ | 124 508 | 61 079 (49.1%)¶ | 41 210 | 12 065 | 4909 | 1727# | 884 | 180 |
| Diabetes | | | | | | | | |
| Prevalence, 2017–2020 | | | | | | | | |
| Diagnosed diabetes† | 29.3 M (10.6%) | 16.4 M (12.2%) | 11.5% | 11.8% | 14.5% | 14.4% | … | … |
| Undiagnosed diabetes† | 9.7 M (3.5%) | 4.6 M (3.5%) | 2.6% | 5.6% | 5.3% | 5.4% | … | … |
| Prediabetes† | 115.9 M (46.4%) | 63.5 M (52.9%) | 57.2% | 35.3% | 50.7% | 51.6% | … | … |
| Incidence, diagnosed diabetes, 2019** | 1.4 M | 723 000 | … | … | … | … | … | … |
| Mortality, 2021§,‖ | 103 294 | 58 628 (56.8%)¶ | 38 428 | 9843 | 7029 | 1963# | 1269 | 314 |
| Total CVD | | | | | | | | |
| Prevalence, 2017–2020† | 127.9 M (48.6%) | 65.4 M (52.4%) | 51.2% | 58.9% | 51.9% | 51.5% | … | |
| Mortality, 2021§,‖ | 931 578 | 491 849 (52.8%)¶ | 368 383 | 66 044 | 36 680 | 13 468# | 4967 | 1355 |

(*Continued*)

**Table 29-1. Continued**

| Diseases and risk factors | Both sexes | Total males | NH White males | NH Black males | Hispanic males | NH Asian males | NH American Indian/Alaska Native* (both sexes) | NH Native Hawaiian or Pacific Islander* (both sexes) |
|---|---|---|---|---|---|---|---|---|
| Stroke | | | | | | | | |
| Prevalence, 2017–2020† | 9.4 M (3.3%) | 4.0 M (2.9%) | 2.7% | 4.8% | 2.5% | 1.8% | … | … |
| New and recurrent strokes§ | 795.0 K | 370.0 K (46.5%)¶ | 325.0 K†† | 45.0 K†† | … | … | … | … |
| Mortality, 2021§ | 162 890 | 70 852 (43.5%)¶ | 50 219 | 10 428 | 6433 | 2848# | 799‡‡ | 247 |
| CHD | | | | | | | | |
| Prevalence, CHD, 2017–2020† | 20.5 M (7.1%) | 11.7 M (8.7%) | 9.4% | 6.2% | 6.8% | 5.2% | … | … |
| Prevalence, MI, 2017–2020† | 9.3 M (3.2%) | 6.1 M (4.5%) | 4.8% | 4.0% | 3.1% | 2.8% | … | … |
| Prevalence, AP, 2017–2020† | 10.8 M (3.9%) | 5.6 M (4.3%) | 4.7% | 2.7% | 3.6% | 2.7% | … | … |
| New and recurrent MI and fatal CHD, 2005–2014§§ | 1.05 M | 610.0 K | 520.0 K†† | 90.0K†† | … | … | … | … |
| New and recurrent MI, 2005–2014§§ | 805.0 K | 470.0 K | … | … | … | … | … | … |
| Mortality, 2021, CHD§,‖ | 375 476 | 226 452 (60.3%)¶ | 174 148 | 25 543 | 17 095 | 6305 | 2012 | 543 |
| Mortality, 2021, MI§,‖ | 109 097 | 65 673 (60.2%)¶ | 50 529 | 7295 | 5051 | 1942# | 601 | 147 |
| HF | | | | | | | | |
| Prevalence, 2017–2020† | 6.7M (2.3%) | 3.7 M (2.7%) | 2.9% | 3.8% | 1.8% | 1.4% | … | … |
| Incidence, 2014‖‖ | 1.0 M | 495.0 K | 430.0 K†† | 65.0 K†† | … | … | … | … |
| Mortality, 2021§,‖ | 85 037 | 40 344 (47.4%)¶ | 31 993 | 4902 | 2249 | 734# | 363 | 82 |

AP indicates angina pectoris (chest pain); BMI, body mass index; CHD, coronary heart disease (includes MI, AP, or both); CVD, cardiovascular disease; ellipses (…), data not available; HBP, high blood pressure; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; K, thousands; LDL-C, low-density lipoprotein cholesterol; M, millions; MI, myocardial infarction (heart attack); NH, non-Hispanic; and TC, total cholesterol.

*Both sexes. Combined because of low numbers in these categories.

†Age ≥20 years.

‡Total data for TC are for Americans ≥20 years of age. Data for LDL-C, HDL-C, and all racial and ethnic groups are age adjusted for age ≥20 years.

§All ages.

‖Mortality for Hispanic, NH American Indian or Alaska Native, NH Asian, and NH Hawaiian or Other Pacific Islander people should be interpreted with caution because of inconsistencies in reporting.

¶These percentages represent the portion of total incidence or mortality that is for males vs females.

#Includes Chinese, Filipino, Japanese, and other Asian people.

**Age ≥18 years.

††Estimates include Hispanic and NH males. Estimates for White males include other non-Black races.

‡‡Estimate is considered unreliable or does not meet standards of reliability or precision.

§§Age ≥35 years.

‖‖Age ≥55 years.

**Table 29-2. Females and CVD: At-a-Glance Table**

| Diseases and risk factors | Both sexes | Total females | NH White females | NH Black females | Hispanic females | NH Asian females | NH American Indian/Alaska Native* (both sexes) | NH Native Hawaiian or Pacific Islander* (both sexes) |
|---|---|---|---|---|---|---|---|---|
| Overweight and obesity | | | | | | | | |
| Prevalence, 2017–2020 | | | | | | | | |
| Obesity, BMI ≥30.0 kg/m**2**† | 41.9% | 41.8% | 39.6% | 57.9% | 45.7% | 14.5% | … | … |
| Blood cholesterol | | | | | | | | |
| Prevalence, 2017–2020 | | | | | | | | |
| TC ≥200 mg/dL‡ | 86.4 M (34.7%) | 47.5 M (36.2%) | 37.2% | 29.6% | 33.6% | 37.7% | … | … |
| TC ≥240 mg/dL‡ | 24.7 M (10.0%) | 13.7 M (10.4%) | 10.7% | 9.3% | 10.0% | 8.7% | … | … |
| LDL-C ≥130 mg/dL‡ | 63.1 M (25.5%) | 32.8 M (25.4%) | 24.0% | 22.5% | 27.5% | 25.3% | … | … |
| HDL-C <40 mg/dL‡ | 41.3 M (16.9%) | 11.4 M (9.3%) | 8.8% | 7.9% | 11.8% | 6.9% | … | … |
| HBP | | | | | | | | |
| Prevalence, 2017–2020† | 122.4 M (46.7%) | 59.6 M (43.0%) | 42.6% | 58.4% | 35.3% | 37.6% | … | … |
| Mortality, 2021§,‖ | 124 508 | 63 429 (50.1%)¶ | 45 290 | 10 871 | 4484 | 1910# | 884 | 180 |
| Diabetes | | | | | | | | |
| Prevalence, 2017–2020 | | | | | | | | |
| Diagnosed diabetes† | 29.3 M (10.6%) | 12.9 M (9.1%) | 7.7% | 13.3% | 12.3% | 9.9% | … | … |
| Undiagnosed diabetes† | 9.7 M (3.5%) | 5.1 M (3.5%) | 2.8% | 3.2% | 4.5% | 5.2% | … | … |
| Prediabetes† | 115.9 M (46.4%) | 52.4 M (40.0%) | 38.8% | 35.7% | 41.3% | 40.2% | … | … |
| Incidence, diagnosed diabetes, 2019** | 1.4 M | 675 000 | … | … | … | … | … | … |
| Mortality, 2021§,‖ | 103 294 | 44 666 (43.2%)¶ | 27 361 | 9125 | 5460 | 1676# | 1269 | 314 |
| Total CVD | | | | | | | | |
| Prevalence, 2017–2020† | 127.9 M (48.6%) | 62.5 M (44.8%) | 44.6% | 59.0% | 37.3% | 38.5% | … | … |
| Mortality, 2021§,‖ | 931 578 | 439 729 (47.2%)¶ | 332 174 | 59 464 | 30 216 | 12 536# | 4967 | 1355 |
| Stroke | | | | | | | | |
| Prevalence, 2017–2020† | 9.4 M (3.3%) | 5.4 M (3.6%) | 3.6% | 5.4% | 2.5% | 1.5% | … | … |
| New and recurrent strokes§ | 795.0 K | 425.0 K (53.5%)¶ | 365.0 K†† | 60.0 K†† | … | … | … | … |
| Mortality, 2021§ | 162 890 | 92 038 (56.5%)¶ | 67 590 | 12 409 | 7343 | 3580# | 799‡‡ | 247 |
| CHD | | | | | | | | |
| Prevalence, CHD, 2017–2020† | 20.5 M (7.1%) | 8.8 M (5.8%) | 5.9% | 6.3% | 6.1% | 3.9% | … | … |
| Prevalence, MI, 2017–2020† | 9.3 M (3.2%) | 3.2 M (2.1%) | 2.2% | 2.3% | 1.9% | 0.5% | … | … |
| Prevalence, AP, 2017–2020† | 10.8 M (3.9%) | 5.2 M (3.6%) | 3.5% | 4.1% | 4.3% | 2.7% | … | … |
| New and recurrent MI and fatal CHD, 2005–2014§§ | 1.05 M | 445.0 K | 370.0 K†† | 75.0 K†† | … | … | … | … |
| New and recurrent MI, 2005–2014§§ | 805.0 K | 335.0 K | … | … | … | … | … | … |
| Mortality, 2021, CHD§,‖ | 375 476 | 149 024 (39.7%)¶ | 112 940 | 18 925 | 10 999 | 4242 | 2012 | 543 |
| Mortality, 2021, MI§,‖ | 109 097 | 43 424 (39.8%)¶ | 32 636 | 5638 | 3337 | 1296# | 601 | 147 |

(*Continued*)

**Table 29-2. Continued**

| Diseases and risk factors | Both sexes | Total females | NH White females | NH Black females | Hispanic females | NH Asian females | NH American Indian/Alaska Native* (both sexes) | NH Native Hawaiian or Pacific Islander* (both sexes) |
|---|---|---|---|---|---|---|---|---|
| HF | | | | | | | | |
| Prevalence, 2017–2020† | 6.7 M (2.3%) | 3.0 M (1.9%) | 1.6% | 3.3% | 1.6% | 0.5% | … | … |
| Incidence, 2014‖ | 1.0 M | 505.0K | 425.0 K‡‡ | 80.0 K‡‡ | … | … | … | … |
| Mortality, 2021§,‖ | 85 037 | 44 693 (52.6%)¶ | 35 873 | 5208 | 2398 | 869# | 363 | 82 |

AP indicates angina pectoris (chest pain); BMI, body mass index; CHD, coronary heart disease (includes MI, AP, or both); CVD, cardiovascular disease; ellipses (…), data not available; HBP, high blood pressure; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; K, thousands; LDL-C, low-density lipoprotein cholesterol; M, millions; MI, myocardial infarction (heart attack); NH, non-Hispanic; and TC, total cholesterol.

*Both sexes. Combined because of low numbers in these categories.

†Age ≥20 years.

‡Total data for TC are for Americans ≥20 years of age. Data for LDL-C, HDL-C, and all racial and ethnic groups are age adjusted for age ≥20 years.

§All ages.

‖Mortality for Hispanic, NH American Indian or Alaska Native, NH Asian, and NH Native Hawaiian or Other Pacific Islander people should be interpreted with caution because of inconsistencies in reporting.

¶These percentages represent the portion of total incidence or mortality that is for males vs females.

#Includes Chinese, Filipino, Japanese, and other Asian people.

**Age ≥18 years.

††Estimates include Hispanic and NH females. Estimates for White females include other non-Black races.

‡‡Estimate considered unreliable or does not meet standards of reliability or precision.

§§Age ≥35 years.

‖‖Age ≥55 years.

**Table 29-3. Children, Youth, and CVD: At-a-Glance Table**

| Diseases and risk factors | Both sexes | Total males | Total females | NH White | | NH Black | | Hispanic | | NH Asian | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Males | Females | Males | Females | Males | Females | Males | Females |
| Overweight and obesity | | | | | | | | | | | |
| Prevalence, 2017–2020 | | | | | | | | | | | |
| Obesity, 2–19 y of age* | 19.7% | 20.9% | 18.5% | 17.6% | 15.4% | 18.8% | 30.8% | 29.3% | 23.0% | 13.1% | 5.2% |
| Blood cholesterol, 2017–2020 | | | | | | | | | | | |
| Mean TC, mg/dL | | | | | | | | | | | |
| 6–11 y of age | 157.4 | 157.5 | 157.2 | 156.3 | 159.5 | 159.3 | 155.3 | 156.5 | 153.1 | 169.6 | 166.0 |
| 12–19 y of age | 154.8 | 150.1 | 159.7 | 148.8 | 162.4 | 153.1 | 156.8 | 149.8 | 154.9 | 156.3 | 161.0 |
| Mean HDL-C, mg/dL | | | | | | | | | | | |
| 6–11 y of age | 55.5 | 56.6 | 54.3 | 56.8 | 54.8 | 58.5 | 55.9 | 55.6 | 51.3 | 59.3 | 58.1 |
| 12–19 y of age | 51.7 | 49.0 | 54.6 | 48.2 | 55.2 | 53.8 | 55.9 | 48.2 | 52.2 | 51.1 | 55.3 |
| Mean LDL-C, mg/dL | | | | | | | | | | | |
| 12–19 y of age | 88.1 | 85.1 | 91.3 | 83.2 | 92.0 | 84.8 | 97.6 | 89.0 | 88.1 | 83.0 | 83.2 |
| CCDs (all age groups: children and adults) | | | | | | | | | | | |
| Mortality, 2020†,‡,§,‖ | 2931 | 1591 (54.3%)§ | 1340 (45.7%)§ | 986 | 829 | 211 | 227 | 279 | 195 | 50 | 32 |

CCD indicates congenital cardiovascular defect; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; M, millions; NH, non-Hispanic; and TC, total cholesterol.

*Note that obesity prevalence in children is a different source from the 2023 Statistics Update. In children, overweight and obesity are based on body mass index (BMI)–for–age values at or above the 85th percentile of the 2000 Centers for Disease Control and Prevention (CDC) growth charts. Obesity is based on BMI-for-age values at or above the 95th percentile of the CDC growth charts.

†All ages.

‡Mortality for Hispanic, American Indian or Alaska Native, NH Asian, and NH Native Hawaiian or Other Pacific Islander people should be interpreted with caution because of inconsistencies in reporting.

§These percentages represent the portion of total congenital cardiovascular mortality that is for males vs females.

‖NH American Indian or Alaska Native, mortality: 35; NH Native Hawaiian or Other Pacific Islander, mortality: suppressed because of confidentiality constraints because there were <10 deaths.

## REFERENCE

1. Stierman B, Afful J, Carroll M, Chen T, Davy O, Fink S, Fryar C, Gu Q, Hales C, Hughes J, et al. National Health and Nutrition Examination Survey 2017-March 2020 prepandemic data files: development of files and prevalence estimates for selected health outcomes. 2021. Accessed March 17, 2022. https://stacks.cdc.gov/view/cdc/106273

## 30. GLOSSARY

Click here to return to the Table of Contents

Click here to return to the Abbreviations

- *Age-adjusted rates*—Used mainly to compare the rates of ≥2 communities or population groups or the nation as a whole over time. The American Heart Association (AHA) uses a standard population (2000), so these rates are not affected by changes or differences in the age composition of the population. Unless otherwise noted, all death rates in this publication are age adjusted per 100 000 population and are based on underlying cause of death.
- *Agency for Healthcare Research and Quality (AHRQ)*—A part of the US Department of Health and Human Services, this is the lead agency charged with supporting research designed to improve the quality of health care, to reduce the cost of health care, to improve patient safety, to decrease the number of medical errors, and to broaden access to essential services. The AHRQ sponsors and conducts research that provides evidence-based information on health care outcomes, quality, cost, use, and access. The information helps health care decision makers (patients, clinicians, health system leaders, and policymakers) make more informed decisions and improve the quality of health care services. The AHRQ conducts the Medical Expenditure Panel Survey (MEPS; ongoing) and sponsors the Healthcare Cost and Utilization Project (HCUP; ongoing).
- *Body mass index (BMI)*—A mathematical formula to assess body weight relative to height. The measure correlates highly with body fat. It is calculated as weight in kilograms divided by the square of height in meters (kg/m$^2$).
- *Centers for Disease Control and Prevention/National Center for Health Statistics (CDC/NCHS)*—The CDC is an agency within the US Department of Health and Human Services. The CDC conducts the Behavioral Risk Factor Surveillance System (BRFSS), an ongoing survey. The CDC/NCHS conducts or has conducted these surveys (among others):
  - National Health Examination Survey (NHES I, 1960–1962; NHES II, 1963–1965; NHES III, 1966–1970)
  - National Health and Nutrition Examination Survey I (NHANES I; 1971–1975)
  - National Health and Nutrition Examination Survey II (NHANES II; 1976–1980)
  - National Health and Nutrition Examination Survey III (NHANES III; 1988–1994)
  - National Health and Nutrition Examination Survey (NHANES; 1999–…) (ongoing)
  - National Health Interview Survey (NHIS; ongoing)
  - National Hospital Discharge Survey (NHDS; 1965–2010)
  - National Ambulatory Medical Care Survey (NAMCS; ongoing)
  - National Hospital Ambulatory Medical Care Survey (NHAMCS;1992–2022)
  - National Nursing Home Survey (periodic)
  - National Home and Hospice Care Survey (periodic)
  - National Vital Statistics System (ongoing)
- *Centers for Medicare & Medicaid Services*—The federal agency that administers the Medicare, Medicaid, and Child Health Insurance programs.
- *Comparability ratio*—Provided by the NCHS to allow time-trend analysis from one *International Classification of Diseases* (*ICD*) revision to another. It compensates for the "shifting" of deaths from one causal code number to another. Its application to mortality based on one *ICD* revision means that mortality is "comparability modified" to be more comparable to mortality coded to the other *ICD* revision.
- *Coronary heart disease (CHD) (ICD-10 codes I20–I25)*—This category includes acute myocardial infarction (AMI; I21–I22); certain current complications after AMI (I23); other acute ischemic (coronary) heart disease (I24); angina pectoris (I20); atherosclerotic cardiovascular disease (I25.0); and all other forms of chronic ischemic (coronary) heart disease (I25.1–I25.9).
- *Death rate*—The relative frequency with which death occurs within some specified interval of time in a population. National death rates are computed per 100 000 population. Dividing the total number of deaths by the total population gives a crude death rate for the total population. Rates calculated within specific subgroups such as age-specific or sex-specific rates are often more meaningful and informative. They allow well-defined subgroups of the total population to be examined. Unless otherwise stated, all death rates in this publication are age adjusted and are per 100 000 population.
- *Diseases of the circulatory system (ICD-10 codes I00–I99)*—Included as part of what the AHA calls

The 2024 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2024. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

"cardiovascular disease" ("total cardiovascular disease" in this Glossary).

- *Diseases of the heart (ICD-10 codes I00–I09, 111, 113, 120–151)*—Classification that the NCHS uses in compiling the leading causes of death. Includes acute rheumatic fever/chronic rheumatic heart diseases (I00–I09); hypertensive heart disease (I11); hypertensive heart and renal disease (I13); CHD (I20–I25); pulmonary heart disease and diseases of pulmonary circulation (I26–I28); heart failure (I50); and other forms of heart disease (I30–I49, I51). "Diseases of the heart" are not equivalent to "total cardiovascular disease," which the AHA prefers to use to describe the leading causes of death.
- *Hispanic origin*—In US government statistics, "Hispanic" includes people who trace their ancestry to Mexico, Puerto Rico, Cuba, Spain, the Spanish-speaking countries of Central or South America, the Dominican Republic, or other Spanish cultures, regardless of race. It does not include people from Brazil, Guyana, Suriname, Trinidad, Belize, or Portugal because Spanish is not the first language in those countries. Most of the data in this update are for all Hispanic people, as reported by government agencies or specific studies. In certain time-trend charts and tables, data for Mexican American people are shown because data are not available for all Hispanic people.
- *Hospital discharges*—The number of inpatients (including newborn infants) discharged from short-stay hospitals for whom some type of disease was the principal diagnosis. Discharges include those discharged alive, dead, or "status unknown."
- *International Classification of Diseases (ICD) codes*—A classification system in standard use in the United States. The *ICD* is published by the World Health Organization. This system is reviewed and revised approximately every 10 to 20 years to ensure its continued flexibility and feasibility. The 10th revision (*ICD-10*) began with the release of 1999 final mortality data. The *ICD* revisions can cause considerable change in the number of deaths reported for a given disease. The NCHS provides "comparability ratios" to compensate for the "shifting" of deaths from one *ICD* code to another. To compare the number or rate of deaths with that of an earlier year, the "comparability-modified" number or rate is used.
- *Incidence*—An estimate of the number of new cases of a disease that develop in a population, usually in a 1-year period. For some statistics, new and recurrent attacks, or cases, are combined. The incidence of a specific disease is estimated by multiplying the incidence rates reported in community- or hospital-based studies by the US population. The rates in this report change only when new data are available; they are not computed annually.
- *Infective endocarditis*—An infection of the inner lining (endocardium) of the heart or of the heart valves. The bacteria that most often cause endocarditis are streptococci, staphylococci, and enterococci.
- *Major cardiovascular diseases*—Disease classification commonly reported by the NCHS; represents *ICD-10* codes I00 to I78. The AHA does not use "major cardiovascular disease" for any calculations. See "total cardiovascular disease" in this Glossary.
- *Metabolic syndrome*—Metabolic syndrome is defined as the presence of any 3 of the following 5 diagnostic measures: elevated waist circumference (>102 cm in males or >88 cm in females), elevated triglycerides (≥150 mg/dL [1.7 mmol/L] or drug treatment for elevated triglycerides), reduced high-density lipoprotein cholesterol (<40 mg/dL [0.9 mmol/L] in males, <50 mg/dL [1.1 mmol/L] in females, or drug treatment for reduced high-density lipoprotein cholesterol), elevated blood pressure (≥130 mm Hg systolic blood pressure, ≥85 mm Hg diastolic blood pressure, or drug treatment for hypertension), and elevated fasting glucose (≥100 mg/dL or drug treatment for elevated glucose).
- *Morbidity*—Both incidence and prevalence rates are measures of morbidity (ie, measures of various effects of disease on a population).
- *Mortality*—Mortality data for states can be obtained from the NCHS website (http://cdc.gov/nchs/), by direct communication with the CDC/NCHS, or from the AHA on request. The total number of deaths attributable to a given disease in a population during a specific interval of time, usually 1 year, is reported. These data are compiled from death certificates and sent by state health agencies to the NCHS. The process of verifying and tabulating the data takes ≈2 years.
- *National Heart, Lung, and Blood Institute (NHLBI)*—An institute in the National Institutes of Health in the US Department of Health and Human Services. The NHLBI conducts such studies as the following:
  - Framingham Heart Study (FHS; 1948–…) (ongoing)
  - Honolulu Heart Program (HHP; 1965–2002)
  - Cardiovascular Health Study (CHS; 1989–…) (ongoing)
  - Atherosclerosis Risk in Communities (ARIC) study (1987–…) (ongoing)
  - Strong Heart Study (SHS; 1989–…) (ongoing)
  - Multi-Ethnic Study of Atherosclerosis (MESA; 2000–…) (ongoing)
- *National Institute of Neurological Disorders and Stroke (NINDS)*—An institute in the National Institutes of Health of the US Department of Health and Human Services. The NINDS sponsors and conducts research studies such as these:
  - Greater Cincinnati/Northern Kentucky Stroke Study (GCNKSS)

  - Rochester (Minnesota) Stroke Epidemiology Project
  - Northern Manhattan Study (NOMAS)
  - Brain Attack Surveillance in Corpus Christi (BASIC) Project
- *Physical activity*—Any bodily movement produced by the contraction of skeletal muscle that increases energy expenditure above a basal level.
- *Physical fitness*—The ability to perform daily tasks with vigor and alertness, without undue fatigue, and with ample energy to enjoy leisure-time pursuits and to respond to emergencies. Physical fitness includes a number of components consisting of cardiorespiratory endurance (aerobic power), skeletal muscle endurance, skeletal muscle strength, skeletal muscle power, flexibility, balance, speed of movement, reaction time, and body composition.
- *Prevalence*—An estimate of the total number of cases of a disease existing in a population during a specified period. Prevalence is sometimes expressed as a percentage of population. Rates for specific diseases are calculated from periodic health examination surveys that government agencies conduct. Annual changes in prevalence as reported in this Statistical Update reflect changes in the population size. Changes in rates can be evaluated only by comparing prevalence rates estimated from surveys conducted in different years. Note: In the data tables, which are located in the different disease and risk factor chapters, if the percentages shown are age adjusted, they will not add to the total.
- *Race and Hispanic origin*—Race and Hispanic origin are reported separately on death certificates. In this publication, unless otherwise specified, deaths of people of Hispanic origin are included in the totals for White, Black, American Indian or Alaska Native, and Asian or Pacific Islander people according to the race listed on the decedent's death certificate. Data for Hispanic people include all people of Hispanic origin of any race. See "Hispanic origin" in this Glossary.
- *Stroke (ICD-10 codes I60–I69)*—This category includes subarachnoid hemorrhage (I60); intracerebral hemorrhage (I61); other nontraumatic intracranial hemorrhage (I62); cerebral infarction (I63); stroke, not specified as hemorrhage or infarction (I64); occlusion and stenosis of precerebral arteries not resulting in cerebral infarction (I65); occlusion and stenosis of cerebral arteries not resulting in cerebral infarction (I66); other cerebrovascular diseases (I67); cerebrovascular disorders in diseases classified elsewhere (I68); and sequelae of cerebrovascular disease (I69).
- *Total cardiovascular disease (ICD-10 codes I00–I99)*—This category includes rheumatic fever/rheumatic heart disease (I00–I09); hypertensive diseases (I10–I15); ischemic (coronary) heart disease (I20–I25); pulmonary heart disease and diseases of pulmonary circulation (I26–I28); other forms of heart disease (I30–I52); cerebrovascular disease (stroke) (I60–I69); atherosclerosis (I70); other diseases of arteries, arterioles, and capillaries (I71–I79); diseases of veins, lymphatics, and lymph nodes not classified elsewhere (I80–I89); and other and unspecified disorders of the circulatory system (I95–I99).
- *Underlying cause of death or any-mention cause of death*—These terms are used by the NCHS when defining mortality. Underlying cause of death is defined by the World Health Organization as "the disease or injury which initiated the chain of events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury." Any-mention cause of death includes the underlying cause of death and up to 20 additional multiple causes listed on the death certificate.