Circulation

AHA SCIENTIFIC STATEMENT

Cardiopulmonary Impact of Electronic Cigarettes and Vaping Products: A Scientific Statement From the American Heart Association

Jason J. Rose, MD, MBA, Chair; Suchitra Krishnan-Sarin, PhD, Vice Chair; Vernat J. Exil, MD, MBA, FAHA; Naomi M. Hamburg, MD, FAHA; Jessica L. Fetterman, PhD; Fumito Ichinose, MD, PhD, FAHA; Miguel A. Perez-Pinzon, PhD, FAHA; Mary Rezk-Hanna, PhD, FAHA; Eric Williamson, MD; on behalf of the American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; Council on Epidemiology and Prevention; Council on Cardiovascular Radiology and Intervention; Council on Lifestyle and Cardiometabolic Health; Council on Peripheral Vascular Disease; Stroke Council; and Council on Arteriosclerosis, Thrombosis and Vascular Biology

ABSTRACT: Vaping and electronic cigarette (e-cigarette) use have grown exponentially in the past decade, particularly among youth and young adults. Cigarette smoking is a risk factor for both cardiovascular and pulmonary disease. Because of their more limited ingredients and the absence of combustion, e-cigarettes and vaping products are often touted as safer alternative and potential tobacco-cessation products. The outbreak of e-cigarette or vaping product use–associated lung injury in the United States in 2019, which led to >2800 hospitalizations, highlighted the risks of e-cigarettes and vaping products. Currently, all e-cigarettes are regulated as tobacco products and thus do not undergo the premarket animal and human safety studies required of a drug product or medical device. Because youth prevalence of e-cigarette and vaping product use was as high as 27.5% in high school students in 2019 in the United States, it is critical to assess the short-term and long-term health effects of these products, as well as the development of interventional and public health efforts to reduce youth use. The objectives of this scientific statement are (1) to describe and discuss e-cigarettes and vaping products use patterns among youth and adults; (2) to identify harmful and potentially harmful constituents in vaping aerosols; (3) to critically assess the molecular, animal, and clinical evidence on the acute and chronic cardiovascular and pulmonary risks of e-cigarette and vaping products use; (4) to describe the current evidence of e-cigarettes and vaping products as potential tobacco-cessation products; and (5) to summarize current public health and regulatory efforts of e-cigarettes and vaping products. It is timely, therefore, to review the short-term and especially the long-term implications of e-cigarettes and vaping products on cardiopulmonary health. Early molecular and clinical evidence suggests various acute physiological effects from electronic nicotine delivery systems, particularly those containing nicotine. Additional clinical and animal-exposure model research is critically needed as the use of these products continues to grow.

Key Words: AHA Scientific Statements ■ adolescent ■ electronic cigarettes ■ electronic nicotine delivery systems ■ heart ■ lung ■ tobacco products ■ vaping

Electronic (e-) cigarettes were created in the early 2000s in China by pharmacist Hon Lik as a device that generates nicotine vapor without smoke.[1] The basic mechanism behind the technology is the heating or atomization of a liquid solution, most commonly containing nicotine, stored in a reservoir (Supplemental Figure 1).[1,2] The aerosol generated from an e-cigarette or vaping product is inhaled. The solution, or e-liquid, generally contains a humectant, nicotine, and flavoring agents.[3] E-liquid formulations contain mostly nicotine but can also contain other drugs, most commonly tetrahydrocannabinol but also other substances such as methamphetamine, methadone, and vitamins.[4] In 2007, e-cigarette products began to be introduced into the United States. The US Food and Drug Administration (FDA) attempted to halt the importation of these products under the assumption these were drug-device combination products.[5] After years of litigation, a 2010 court ruling, Smoking Everywhere,

Supplemental material is available at https://www.ahajournals.org/doi/suppl/10.1161/CIR.0000000000001160.

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

Inc. vs US Food and Drug Administration, deemed e-cigarettes should be considered tobacco products, and thus, if the FDA were to regulate them, they should fall under the rubric of the recently enacted 2009 Family Smoking Prevention and Tobacco Control Act.[5–7] Thus began the adoption of e-cigarettes and vaping products into the US consumer market as tobacco products.[5] Since their introduction, different designs of electronic nicotine delivery system (ENDS) have been developed, with newer generations designed to withstand higher voltage levels without resulting in an unpleasant taste associated with overheating the flavored liquid that could result in higher reactive free radical concentrations.[1,8] The American Heart Association has published policy statements on e-cigarettes.[9] Accordingly, the objectives of this scientific statement are (1) to describe and discuss e-cigarettes and vaping products use patterns among youth and adults; (2) to identify harmful and potentially harmful constituents in vaping aerosols; (3) to critically assess the molecular, animal, and clinical evidence on the short- and long-term cardiovascular and pulmonary risks of e-cigarette and vaping products use; (4) to describe the existing evidence on the utility of e-cigarettes and vaping products as tobacco-cessation products; and (5) to summarize current public health and regulatory efforts of e-cigarettes and vaping products.

EPIDEMIOLOGY AND HISTORY OF INCREASING INCIDENCE OF VAPING AND ELECTRONIC CIGARETTE USE

ENDS Product Use in the Young

In the United States, ENDS products are the most commonly used tobacco product among youth, with a growing percentage of users who do not report ever smoking combustible cigarettes.[10–12] Data from the 2011 to 2018 NYTS (National Youth Tobacco Survey) showed an exponential increase in ENDS use among high school students; current (past 30-day) use increased from 1.5% in 2011 to 20.8% in 2018, an estimated 3.1 million students (Figure 1).[11,13] Among middle school students, current e-cigarette use increased from 0.6% in 2011 to 4.9% in 2018, an estimated 570 000 students.[11,13] Data from the 2019 NYTS showed that 27.5% of high school students (4.1 million) reported current e-cigarette use, whereas 5.8% reported using combustible cigarettes.[10] Data from Monitoring the Future Survey showed that current e-cigarette use more than doubled from 2017 to 2019 among middle and high school students.[14] In 2019, 25.5% of 12th graders reported current e-cigarette use compared with 11.0% in 2017. Current tetrahydrocannabinol vaping also dramatically increased from 2017 to 2019 in all grades, from 4.9% to 14.0% of 12th graders, 4.3% to 12.6% of 10th graders, and 1.6% to 3.9% of eighth graders. An estimated 72.2% of current exclusive e-cigarette

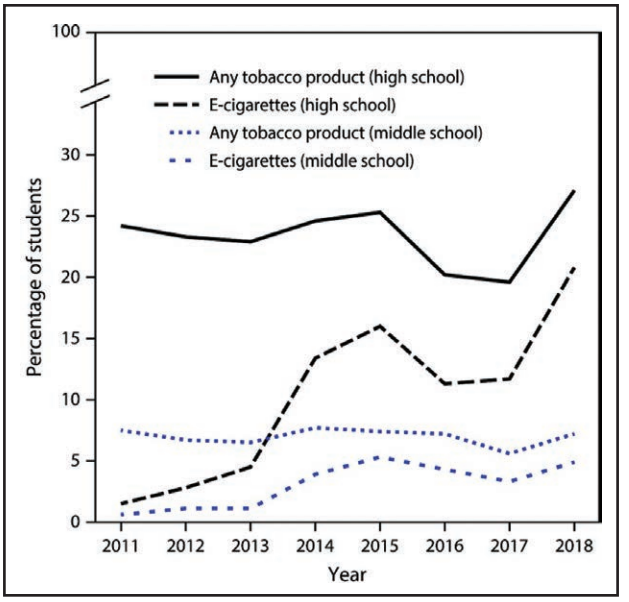

Figure 1. Percentage of middle and high school students who currently use electronic cigarettes and any tobacco product, National Youth Tobacco Survey, United States, 2011 to 2018.[11]

users reported use of flavored products.[10] Among middle school students, 10.5% (1.2 million) reported current e-cigarette use compared with 2.3% who reported combustible cigarette smoking. Among middle school students who reported exclusive ENDS use, 59.2% reported using flavors, with fruits, menthol or mint, and candy, desserts, or other sweets as the most commonly used flavors.[10] These data are consistent with findings from other studies indicating the rapid increase in prevalence of e-cigarette use among youth in other countries such as Canada and England.[15,16] The prevalence of ENDS use among youth remained stable despite the emergence of the coronavirus disease 2019 (COVID-19) pandemic and growing concern about the increased risks of COVID-19 from tobacco and ENDS products.[17,18] Data from the 2020 NYTS showed declines to 19.6% of high school students and 4.7% of middle school students with current ENDS use; whether this is an artifact of the great societal disruptions from the global pandemic or represents a decreased trend remains to be seen.[19]

Because of the rapid evolution of ENDS, it is important to examine prevalence rates with other vaping products besides e-cigarettes such as e-hookahs (e-waterpipes). E-hookahs are a new category of vaping devices, introduced in 2014 and recently patented by Philip Morris, that are marketed as healthier alternatives to traditional hookah fruit-flavored tobacco smoking.[20–22] Findings from the nationally represented PATH study (Population Assessment of Tobacco and Health; 2014–2015) in children 12 to 17 years of age indicated that 7.7% were identified as ever-users of e-hookahs compared with 14.26% who were ever-users of ENDS products.[23]

ENDS Product Use in Adults

In the United States, initial studies indicated a rapid increase in ever and current ENDS use among adults since 2010, with the vast majority of users being current or former cigarette smokers. Data from the NHIS (National Health Interview Survey) showed that although ever-use of ENDS among adults ≥18 years of age increased from 2014 to 2016 (12.6% to 15.3%), current use of ENDS decreased (3.7% to 3.2%).[24] Although the decrease in e-cigarette use was significant among current combustible cigarette smokers, the prevalence increased among former smokers and, it is important to note, never-smokers.[24] In 2016, data from the Behavioral Risk Factor Surveillance System showed that 1.2 million adults who never smoked combustible cigarettes were current ENDS users.[25] Dual use of ENDS and combustible cigarettes is common.[26,27] The 2016 Behavioral Risk Factor Surveillance System estimated that 54.6% of current ENDS users were current combustible cigarette smokers.[25] Recent analysis from the 2014 to 2018 NHIS data showed that young adults 18 to 24 years of age are using ENDS at high rates; current use increased from 5.1% to 7.6%, with large increases among never-smokers (1.5% to 4.6%) and former smokers (10.4% to 36.5%).[28]

ACUTE HEALTH EFFECTS AND TOXICITY OF E-CIGARETTES AND VAPING PRODUCTS

ENDS aerosol condensate generated from different device types and products results in differential effects on measures of endothelial and pulmonary epithelial cell toxicity. The toxicological differences are likely due to differences in product characteristics such as nicotine levels and flavoring additives, which is supported by studies directly treating vascular and pulmonary epithelial cells with individual ingredients.[29–31] Nicotine is commonly found in ENDS products; however, not all ENDS products contain nicotine. Regardless of the presence of nicotine, many ENDS product constituents, including flavoring additives, hygroscopic carriers such as propylene glycol and glycerol, and metals (from the heating coil), have been shown to induce cardiopulmonary toxicity in animal and in vitro studies.

Known Health Effects of Specific Components of Vaping Aerosols

Nicotine

Nicotine is an activator of the sympathetic nervous system, which has direct effects on the cardiovascular system.[32] In postganglionic sympathetic nerve terminals and the adrenal medulla, nicotine binds to α3β4 nicotinic acetylcholine receptors, triggering the release of catecholamines (norepinephrine, epinephrine).[33] Nicotine-stimulated catecholamine release by the sympathetic nervous system activates β-adrenergic receptors in the heart, resulting in increased heart rate, cardiac contractility, and workload (Figure 2).[2,32] Long-term overstimulation of the sympathetic nervous system results in cardiac remodeling, which promotes the development of heart failure and increases arrhythmogenesis.[32]

Nicotine also affects the vasculature by inducing vasoconstriction, resulting in elevated blood pressure and impaired wound healing in the microvasculature, which is mediated primarily through activation of the homomeric α7 nicotinic acetylcholine receptor expressed on endothelial

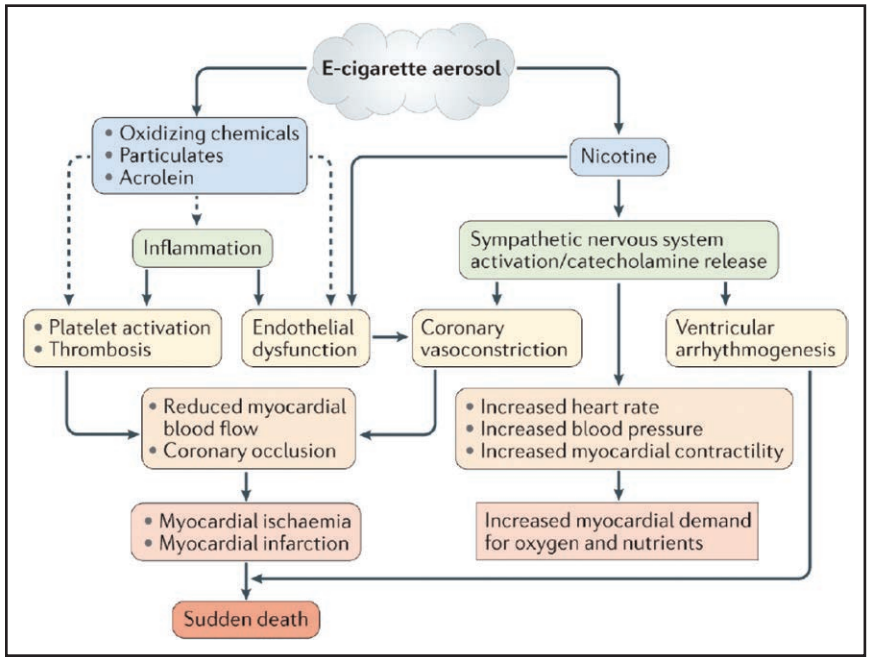

Figure 2. Overview of mechanisms by which electronic cigarette use might cause acute cardiovascular events. Solid lines indicate known pathways; dashed lines indicate pathways of concern but for which there are no empirical data for confirmation. Reprinted with permission from Nature/Springer, Benowitz and Fraiman,[2] Copyright © 2017.

cells and α1 receptors on vascular smooth muscle cells.[32,33] In vitro exposure of primary lung microvascular endothelial cells to nicotine increased primary lung microvascular endothelial cell permeability and impaired endothelial cell barrier function, which was likely mediated through oxidative stress–induced activation of p38 mitogen–activated protein kinase.[34] Nicotine has been shown to induce platelet-derived growth factor release, which induces cytoskeletal alteration in aortic smooth muscle cells.[35] In a randomized study of healthy younger smokers, acute use of a nicotine-containing ENDS had vascular hemodynamic effects suggestive of vascular remodeling and increased sympathetic activation of the cardiovascular system.[36] The findings of these studies may indicate cardiovascular changes consistent with the development of cardiovascular disease with nicotine inhalation from ENDS.[36]

Propylene Glycol and Glycerol

Emerging evidence suggests that the nicotine solvents propylene glycol and glycerol have cardiopulmonary effects. High levels of propylene glycol (greater than the recommended maximum dose of 25 $mg \cdot kg^{-1} \cdot d^{-1}$) systemically can lead to metabolic acidosis, acute kidney injury, and a sepsis-like syndrome.[37] Glycol mixtures are used to create theatrical fog and smoke, and long-term occupational exposure is associated with higher reports of wheezing and chest tightness.[38,39] Short-term exposure to glycol mixtures is associated with acute dry cough and throat irritation, as well as decreased lung function in individuals with higher exposures.[38,39] The upper airway irritation associated with short-term occupational exposure to propylene glycol appears to be mediated by the sensory receptors TRPV1 and TRPA1, receptors also known to promote asthmatic inflammation and airway hyperreactivity in animal models.[40–42]

Flavoring Additives and Sweeteners

Animal models and in vitro exposures of pulmonary and cardiovascular cells suggest that the flavoring additives have differing toxicities but are likely an important source of ENDS-induced cardiopulmonary toxicity. Sweeteners such as glucose and sucrose are commonly used in e-liquids and contribute to reactive aldehyde formation.[43–45] Reactive aldehydes are thought to be the primary contributors to combustible cigarette–induced cardiovascular disease and chronic obstructive pulmonary disease (COPD).[46]

Diacetyl and acetyl propionyl are flavoring additives that are associated with respiratory disease when inhaled during manufacturing.[47] Occupational exposure to diacetyl is associated with higher rates of chronic cough, shortness of breath, airway obstruction, and physician-diagnosed asthma and chronic bronchitis.[48–50] Cumulative diacetyl exposure positively correlates with spirometry abnormalities and decreased forced expiratory volume in the first second (FEV1) and has been shown to result in the development of bronchiolitis obliterans, or popcorn lung.[48–50] Inhalation of diacetyl or 2,3-pentanedione resulted in fibroproliferation and partial occlusion of the airways, as well as peribronchial and perivascular infiltrations of immune cells in the lungs of exposed rats, consistent with airway remodeling.[51] Diacetyl and related flavoring additives continue to be found in e-liquids.

Other flavoring additives used in ENDS have also been shown to have pulmonary toxicity. Air-liquid interface exposure of bronchial epithelial cells to menthol-, coffee-, and strawberry-flavored e-liquids resulted in reduced cellular viability and increased inflammatory cytokine production.[52] Strawberry-flavored e-liquid elicited the greatest inflammatory response, similar to the effects observed with combustible cigarette smoke exposure.[52] Treatment of human bronchial epithelial cells for 24 hours with the flavoring additives acetoin (imparting a butter flavor), diacetyl, ortho-vanillin, and maltol (malt flavor) increased interleukin-8 secretion, suggesting that the flavor additives independently induce toxicity.[53] In vitro exposure of pulmonary epithelial cells and monocytes to aerosol generated with each of 8 flavored JUUL pods increased inflammatory cytokine levels, induced mitochondrial oxidant generation, increased DNA damage, and impaired pulmonary epithelial barrier function.[54] In addition, 2,5-dimethylpyrazine (imparts a chocolate flavor) treatment of human or mouse pulmonary epithelial cell lines decreased salt and water apical cellular transport, which may have implications for airway surface liquid homeostasis.[55]

A number of flavored e-liquids and commonly used flavoring additives have been shown to impair endothelial cell function in vitro.[29,56] Exposure of induced pluripotent stem cell–derived endothelial cells to cinnamaldehyde- and menthol-containing e-liquid decreased cell viability through increased apoptosis and decreased tube formation and wound healing (eg, scratch test) and upregulated the expression in inflammatory cytokines.[29] Endothelial cells exposed to cinnamaldehyde-containing e-liquid or RY4 e-liquid (sweet tobacco, caramel, and vanilla flavoring) for 48 hours had greater activation of the macrophage-like cells to a proinflammatory phenotype, suggesting that the flavored e-liquids promote endothelial cell inflammatory cytokine and chemokine secretion.[29]

Vanillin, menthol, cinnamaldehyde, eugenol (clove flavoring), and acetylpyridine (burnt flavoring) increased interleukin-6 expression and impaired A23187-induced nitric oxide production in human aortic endothelial cells.[56] Exposure to menthol or eugenol resulted in impaired nitric oxide production in response to A23187 and to a degree similar to the impairment observed in endothelial cells from combustible cigarette smokers.[56] In standing e-liquid, the interaction of flavor aldehydes with propylene glycol or glycerin may form toxic acetals.[57,58] These have the potential to have more respiratory irritation than the parent aldehyde molecules.[57,58]

Metals

The heating elements of ENDS consist of metals that are released into the liquids and aerosols.[59,60] Rats exposed to aerosol generated with a nickel-chromium alloy atomizer that was free of nicotine, vitamin E acetate, or tetrahydrocannabinol developed labored mouth breathing, decreased activity, and wheezing.[61] Histological evaluation showed pneumonitis, pulmonary inflammation, and the accumulation of fibrin and inflammatory cells in the lumen of the trachea.[61] No such pulmonary alterations were noted for a similar device with a stainless steel atomizer, suggesting that the metal heating element may be a source of pulmonary toxicants.[61] A lifetime of chromium and nickel exposure as a result of daily inhalation of 2 mL e-liquid was used to estimate the risk of cancer and noncancer health effects, with chromium and nickel estimated to be the primary contributors.[62] Nickel is one of the few carcinogens found to be higher in ENDS than in combustible cigarettes.

Acute Cardiovascular Effects of ENDS Product Use

Limited clinical studies have assessed the impact of ENDS on acute cardiovascular events. Large survey studies have focused on younger adults, who have a low incidence of heart attack and stroke. Prospective, longer-term studies of ENDS users of all ages with regard to cardiovascular events and symptoms such as palpitations and chest pain are needed.

Our current understanding of the deleterious cardiovascular effects is derived largely from short-term studies of ENDS users. Evidence indicates that there are acute changes in several hemodynamic measures, including increases in blood pressure and heart rate, with nicotine-containing ENDS use (Figure 2).[63,64] One systematic review estimates an increase of systolic and diastolic blood pressures of 2 mm Hg and heart rate of 2 bpm for nicotine-containing ENDS products, but the relative impact compared with combustible cigarettes may be lower.[65] In fact, in a cross-sectional analysis of 39 747 participants in the Health eHeart Study, ENDS use compared with no ENDS and no cigarette use was associated with lower general health scores and greater proportions of those who responded "yes" to having chest pain, palpitations, coronary heart disease, and arrythmia.[66] In addition, measures of heart rate variability show changes indicative of greater sympathetic tone after acute use, particularly in nicotine-containing ENDS versus non–nicotine-containing ENDS products.[67,68] Both acute nicotine-containing ENDS use and combustible cigarette use produce changes in ventricular repolarization, although the degree is more pronounced from the combustible product.[69]

ENDS products have been shown to impair endothelium-mediated dilation in the periphery, suggestive of reduced nitric oxide bioavailability.[70–72] Compared with sham vaping or vaping of vehicle alone (50:50 propylene glycol and glycerol), acute use of nicotine-containing liquid vaped through an e-cigarette device increased augmentation index, pulse-wave velocity, systolic blood pressure, diastolic blood pressure, and heart rate, suggesting vascular remodeling and sympathetic overactivation.[70] Although imaging studies have historically been limited in the evaluation of vascular dysfunction, a recent magnetic resonance imaging study showed reductions in blood velocity, vascular reactivity, and oxidation after ENDS use.[72] This study implies that the ENDS products may have a role in endothelial dysfunction and the development of cardiovascular disease.[72] E-hookah use has also been shown to have adverse effects on endothelial function, likely mediated by oxidative stress.[73] Higher arterial stiffness has been observed in ENDS users with an acute increase after use.[64,74] In a randomized study of healthy younger smokers, acute use of nicotine-containing ENDS products increased peripheral systolic blood pressure, heart rate, augmentation index, and pulse-wave velocity, but only when the e-liquid contained nicotine.[36] The effects of vaping a nicotine-containing e-cigarette or smoking a combustible cigarette resulted in similar elevations in pulse-wave velocity, suggesting increased arterial stiffness.[36]

In the coronary circulation, ENDS products lower the myocardial blood flow response to exercise without altering myocardial contraction or relaxation.[63,75] Long-term users of ENDS products had higher arterial stiffness but similar endothelial function compared with nonsmokers, suggesting that the endothelial effects may be largely present in the postuse state.[76] Studies have shown lower blood pressure, lower heart rate, and markers of improved vascular function in combustible cigarette users who switch to ENDS products.[77–79] Cigarette smoke has been shown to increase platelet activation, reactivity, adhesion aggregation, and inflammation, ultimately driving ischemic events such as myocardial infarction.[80] Platelet activation, reactivity, and aggregation have been shown to be increased after exposure to e-liquid aerosols in both nicotine-containing[81–84] and non–nicotine-containing substances.[85,86]

Studies comparing ENDS products that contain nicotine with nicotine-free products suggest that many of the acute vascular effects relate to nicotine exposure.[67,74] Nicotine-free aerosol has been shown to affect endothelial barrier function, postulated to be from the e-cigarette aerosol constituent acrolein.[34,86] The studies have included predominantly ENDS users who have a history of combustible cigarette use. A study of young healthy adults who never used combustible cigarettes did not observe any acute change in endothelial function.[87]

Studies of circulating biomarkers indicative of cardiovascular risk have also shown changes with acute ENDS use. Measures of oxidative stress increase after ENDS use, although less than with combustible cigarette use.[71] There appeared to be residual impact on inflammation and

oxidative stress in e-cigarette users even after a period of nonuse.[88] In a population-based study, inflammatory and oxidative stress biomarkers were elevated in both combustible cigarette users and dual combustible cigarette and ENDS users but not in exclusively ENDS users.[89]

There have been minimal studies on the acute impact of ENDS products in individuals with established cardiovascular disease who may be more at risk to negative health effects of ENDS. Whether the acute known cardiovascular effects of ENDS, particularly those containing nicotine, translate into heightened cardiovascular risk needs to be assessed fully. The presence of any acute cardiovascular effects of ENDS suggests that ENDS use is not benign and raises the possibility that adverse impact could accumulate over time.

General Cerebrovascular Effects of Smoking and E-Cigarettes

Combustible cigarette smoking increases risk of neurological disorders, including stroke[90] and vascular dementia[91] among others. Studies show that tobacco smoking can affect vascular endothelial function and the blood-brain barrier[92] with long-term consequences to the brain. More intrinsic mechanisms include increased oxidative stress and inflammation,[93] promotion of type 2 diabetes,[94] synaptic and electric activity alterations, and ultimately behavioral changes.[95–97] Tobacco smoking increases the risk of stroke, and nicotine exacerbates poststroke brain damage.[98] Studies in animal models have shown that nicotine can cause pathological effects similar to those observed with tobacco smoke such as oxidative damage and cerebrovascular impairments that lead to stroke and exacerbate ischemic injury.[99–101]

Similar to tobacco smoke, ENDS products increase vascular stiffness, increase endothelial microparticles, and promote reactive oxygen species through the NADPH oxidase pathway.[95] Another effect of nicotine and ENDS exposure is a decrease in brain glucose utilization.[102] Prolonged exposure to nicotine leads to an increase in GLUT1 expression in the brain, with a consequent decrease in glycolysis.[102] This glucose deprivation state may enhance ischemic brain injury or stroke risk.[102] Nicotine may lead to brain mitochondrial dysfunction because α7-nAChR is highly permeable to $Ca2^{+}$, a key player in both synaptic plasticity and ischemia-induced cell death.[103–105]

The systemic and metabolic effects of ENDS products are accompanied by changes in synaptic and electric activity in the brain. Beyond the addictive effects of nicotine (see later discussion), changes in glutamatergic receptors were observed after months of ENDS exposure: In the nucleus accumbens (shell), mGluR1 was upregulated, whereas mGluR5 and the glutamate transporter-1 were downregulated,[106] signaling potential addictive effects. The effect of ENDS on the hippocampus was an upregulation of mGluR5 and the glutamate transporter-1, which could elicit potential pathological consequences for cognitive performance or worsen the pathology of cerebral ischemia.[106] Furthermore, because the hippocampus is susceptible to ischemia, these effects could worsen the pathology of cerebral ischemia. The effects of nicotine on stroke patients are more prominent in women than men, thought to result partially from both nicotine and oral contraceptives being risk factors for peripheral thrombus formation.[107–110] The mechanisms for smoking and nicotine with oral contraceptive–induced thrombogenesis remain poorly understood. Nicotine exposure from ENDS products can inhibit aromatase enzyme activity, which catalyzes the conversion of androgens into estrogens.[111] In female rats, it was confirmed that long-term nicotine exposure reduced endogenous 17β-estradiol levels.[112] Endogenous and exogenous 17β-estradiol is known to protect the brain from ischemic injury in female rats.[113–116] Thus, worsening of cerebral ischemic outcomes by nicotine in women may involve decreases in estrogen levels.

Acute Pulmonary Effects of ENDS Product Use

The understanding of the acute pulmonary effects of ENDS is highlighted by several epidemiological studies on respiratory symptomology, physiological impact on pulmonary function, and animal or molecular studies. Large surveys of teens, adolescents, and adults have reported increased odds of chronic cough, phlegm, bronchitis, and dyspnea, especially with simultaneous cigarette use.[66,117–121] Large survey data in North America, Asia, and Europe demonstrated higher self-reported history of asthma, asthma exacerbations, and COPD.[122,123] Upper respiratory effects such as nose, mouth, throat, and airway irritation have been reported with ENDS use.[124,125] Prospective cohort studies are ultimately needed to assess the longer-term adverse consequences of ENDS products.

The acute effects of ENDS products on airway obstruction and lung volumes have been examined with pulmonary function testing. Some studies show evidence of airflow obstruction after an acute vaping session, with decreased FEV1, forced expiratory ratio (FEV1/forced vital capacity [FVC]), and forced expiratory flow 25% to 75% (FEV25%–75%).[126,127] Other studies did not demonstrate an acute change in airway obstruction, lung volumes, or diffusion capacity after ENDS use compared with control subjects.[128–131] Patients with preexisting airway disease may be at higher risk from acute worsening of airway obstruction with ENDS use.[132] Similar to cigarette smoking, some studies show a decreased fraction of exhaled nitric oxide with ENDS use.[133,134] Other measures of airway resistance such as impedance, respiratory resistance, and peripheral airway resistance were increased after ENDS product use for 5 minutes.[132,133]

In terms of evidence of direct lung injury from ENDS products, sporadic cases were reported before the outbreak of e-cigarette or vaping product use–associated lung injury (EVALI) in 2019 (see the section on EVALI).

Cases of eosinophilic pneumonitis,[135,136] hypersensitivity pneumonitis,[137] organizing pneumonia,[138] diffuse alveolar hemorrhage,[139] respiratory bronchiolitis–associated interstitial lung disease,[140] and acute lung injury were reported after ENDS use.[141] Many flavoring agents in e-liquids have known toxic effects on the lungs, particularly diacetyl (bronchiolitis obliterans, or popcorn lung),[142] 2,3 pentanedione,[143,144] vanillin, and cinnamaldehyde.[145] Whether these early cases of severe respiratory disease were individual susceptibility to ENDS use or reflected a particular agent remains unclear.

Several studies examined markers of airway injury and inflammation in otherwise healthy e-cigarette users. Healthy ENDS users were found to have erythematous and irritable airway mucosa.[146] Increased airway and bronchial epithelial MUC5AC (mucin-5AC) was found in ENDS users.[146–148] Increased mucin is a biomarker of chronic bronchitis in patients with declining lung function in COPD.[31,149] Sputum from ENDS users has shown increased neutrophil activation, myeloperoxidase, neutrophil elastase, and proteinase-3.[148,150] Increased proteases in the lung are thought to be a significant driver of lung damage in COPD from tobacco smoking and play a role in tumor progression.[151–153] Neutrophils collected from long-term ENDS users have greater neutrophil extracellular trap formation, a process that can injure the lung, compared with nonsmokers and cigarette smokers.[148,154] Studies with volunteers exposed to short sessions of vaping revealed both increased blood endothelial microparticles (marker of alveolar capillary injury) and lung-specific protein CC16 (secreted from club cells near terminal bronchioles suggestive of small airway injury), suggesting molecular changes.[129,155] Common molecular markers of lung injury and airway inflammation have been observed with exposure to ENDS.

ENDS use has been linked to an increased susceptibility to respiratory infection. A study with 30 healthy volunteers exposed to e-cigarette aerosol demonstrating decreased cough sensation, in combination with basic and animal studies showing ciliary dysfunction, suggested susceptibility to respiratory infections.[156,157] Nasal scrapings from vapers, smokers, and nonsmokers showed suppression of immune and inflammatory response genes in smokers and vapers.[158] In bronchoalveolar lavage of healthy nonsmokers, after brief ENDS aerosol exposure, altered gene expression was seen in alveolar macrophages, notably in inflammation-related genes.[129] With the COVID-19 pandemic, several epidemiological studies have assessed the effect of ENDS use on the development of or severity of COVID-19, but results have been conflicting.[159]

In most studies of the acute physiological effects of vaping, clinical changes are mild, similar to findings demonstrated in the early phase of cigarette adoption in younger healthy cigarette smokers in 1920s. The most detrimental long-term effects of cigarettes, borne out after years of smoking, were not identified more conclusively until decades later. Modern assessment at the molecular and cellular scale was not available in the early 20th century. Increasing evidence suggests that ENDS products have significant acute injurious effects on the airway epithelium, increased pulmonary inflammation, and respiratory immune suppression (Figure 3).[8]

Acute Effects of ENDS Product Use During Pregnancy

The use of ENDS products during pregnancy is prevalent among expectant mothers who smoke throughout pregnancy and who are using ENDS products to quit combustible cigarette smoking. For women who are trying to reduce the stigma or health concerns during pregnancy, ENDS use is often perceived as a safer alternative compared with combustible cigarette smoking.[160] Focus groups of pregnant smokers and smokers planning for pregnancy revealed that ENDS products were thought to have several advantages over cigarettes, including lower cost, the perception of being smoke-free, availability in appealing flavors, and fewer side effects despite the overall opinion that the use of any tobacco product was harmful during pregnancy.[160] It is important to note that many pregnant mothers become dual users, continuing to use both tobacco cigarettes and ENDS products throughout pregnancy.[161] There is a gap in knowledge in that studies on gestational health effects of ENDS products on the mother and on fetal development are lacking. Similarly, data on long-term health effects of ENDS exposure on the fetus after birth or on the mother are lacking.

Data in animal models reveal that ENDS products can be toxic to both the mother and the fetus. Reduced placental and cord blood flow has been reported with maternal ENDS use, along with growth restriction in the fetus and growth delay in the postnatal period.[162] In animal models, nicotine exposure during pregnancy leads to fetal growth deficits, systemic inflammation, fetal pulmonary and cardiac dysfunction, and cognitive issues in the newborn.[163,164] Perinatal exposure to nicotine results in angiotensin II–mediated vascular changes in offspring.[165] Furthermore, exposure in pregnancy to propylene glycol/vegetable glycerin, with or without nicotine, resulted in cognitive deficits in mice pups.[164] Lung development in newborns can be severely impaired from in utero exposure to nicotine.[163] The fetal cardiopulmonary health effects of in utero ENDS exposure, especially those containing nicotine, may be similar to those of combustible cigarettes and warrants further investigation.

Acute Addictive Effects of Inhaled Nicotine Products

Most ENDS products contain the constituent nicotine, which is the main mechanism for dependence. After brief, short-term inhalation of nicotine with an ENDS, brain nicotine concentrations have been shown to increase in adult humans.[166] Positron emission tomography imaging shows that e-cigarettes deliver both relatively high (ie, 36 mg/mL) and low (8 mg/mL) nicotine level occupancy of

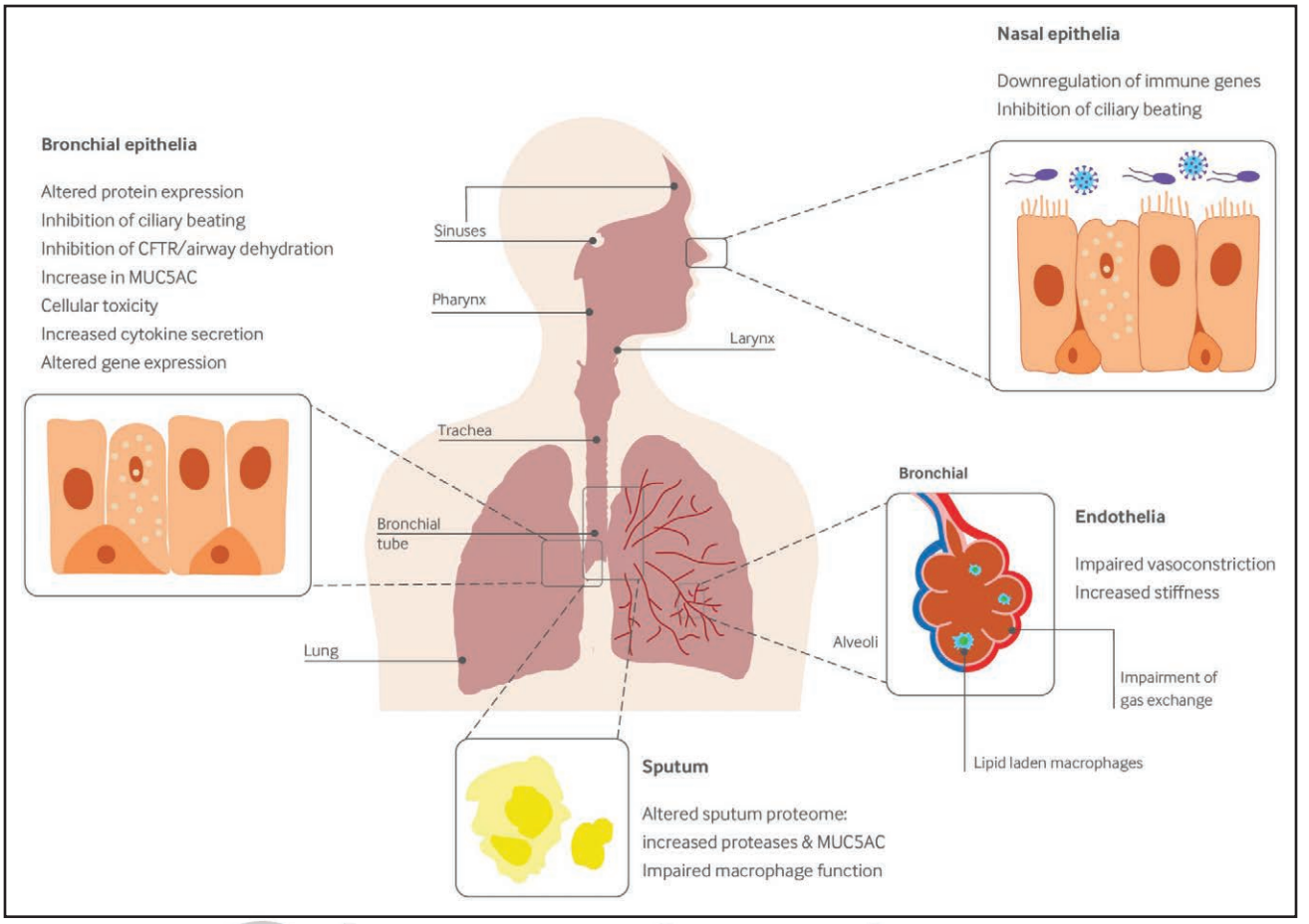

Figure 3. Reported effects of vaping on the human pulmonary system.
CFTR indicates cystic fibrosis transmembrane conductance regulator protein; and MUC5AC, mucin 5, subtypes A and C, tracheobronchial/gastric protein. Reprinted from Gotts et al.[8]

the β^2 nicotinic acetylcholine receptors in the brain, levels of occupancy similar to those achieved with smoking a combustible cigarette.[167]

The acute addictive effects of nicotine-containing ENDS products stem from the immediate reinforcing effects produced and from the relief from symptoms associated with nicotine abstinence in those with existing nicotine dependence.[168] In terms of reinforcing effects, compared with non–nicotine-containing ENDS products, ENDS products containing nicotine demonstrated increased acute satisfaction and pleasant sensations, as well as feelings of alertness.[169] In another study assessing the dependence-reinforcing effects of ENDS, after e-cigarette use in tobacco product users, feelings of pleasantness and satisfaction were increased.[170] Acute exposure to ENDS products in experimental studies decreases feelings of nicotine craving among nicotine users,[171] and compared with ENDS products with no nicotine, nicotine-containing ENDS products had superior reduction of craving.[172] Newer generations of ENDS products appear to have higher effects on craving reduction and positive associated subjective effects than older generations.[171] The product characteristics of newer ENDS products such as device power and voltage appear to increase nicotine delivery, affecting the effectiveness of nicotine delivery of these devices and thus the acute addictive effects.[173]

E-CIGARETTE OR VAPING PRODUCT USE–ASSOCIATED LUNG INJURY

Vaping can cause a wide array of severe adverse health effects that include nicotine poisoning, trauma from device battery explosions, and injury to the gastrointestinal, cardiovascular, and neurological systems.[174,175] Severe respiratory effects of vaping in case reports include status asthmaticus[176] and pneumothoraces.[177] Diffuse parenchymal lung disease had been reported for several years in case reports.[135–138,140,141] With the rapid adoption of vaping among the public, particularly youth, a new clinical entity, EVALI, was first recognized in August 2019.[178] When the US Centers for Disease Control and Prevention stopped reporting

EVALI cases on February 18, 2020, there were 2807 hospitalizations and 68 deaths resulting from EVALI in all 50 states within the United States.[179] Clinically, patients develop hypoxemia requiring supplemental oxygen and signs of systemic inflammation indicated by leukocytosis.[180,181]

Clinical Presentation

Three types of symptoms commonly present across EVALI cases: prominent gastrointestinal, general systemic (fever and fatigue), and respiratory symptoms.[182–187] Case series demonstrate that nearly all patients have presented with respiratory complaints.[182–187] Most patients required some form of respiratory support, ranging from supplemental oxygen, noninvasive ventilation, and mechanical ventilation to extracorporeal oxygenation.[182–187] Gastrointestinal symptoms also have been a common chief complaint, affecting >80% of patients.[183] Constitutional symptoms, including subjective fever, chills, and fatigue, have been common.[182–184] Definitions of confirmed and probable EVALI are shown in Supplemental Table 1.[188] The long-term effects of EVALI have been minimally studied, but 1 cohort of 41 patients with 1-year outcomes reported 24% of patients requiring inpatient readmission, 4.9% 1-year mortality, and 45% with continued symptoms on outpatient follow-up. Although most imaging findings were improved or resolved on follow-up, 75% of patients with pulmonary function testing had abnormalities after EVALI.[189]

Management

Management of EVALI is anecdotal and based on limited experience from treating similar disease processes. No clinical trials have tested therapies. In general, treatment is supportive. According to several reported case series, most patients described as having EVALI were initially managed in inpatient services.[182–185] In some series, more than half have presented with severe illness requiring intensive care unit admission.[182–185] Most patients (78%–100%) have required some degree of supplemental oxygen during hospital admission.[183–186] Severe respiratory failure has been common, with a maximal level of respiratory support that has included high-flow nasal cannula support (up to 47% in 1 study), noninvasive positive-pressure ventilation (up to 30%), and endotracheal intubation and invasive mechanical ventilation (up to 22%).[182–184] Severe cases of EVALI have required veno-venous extracorporeal membrane oxygenation, with 1 case proceeding to lung transplantation.[176,191,192] According to another review of 169 published articles on EVALI, most patients (95%) required hospitalization, and the majority (84%) received glucocorticoids.[193]

Glucocorticoids were used in many case series and may be beneficial in the treatment of EVALI.[182,187,194,195] Dosing regimens varied widely.[185] Glucocorticoid administration may be warranted in severely ill patients when it is considered safe and feasible and concomitant infection has been ruled out; however, no definitive clinical trials have assessed their effectiveness. Patients have recovered without receiving glucocorticoids.[183–185] Most patients had a full microbiological and viral infection workup.[182–187] Between 78% and 100% of patients received empirical antibiotics therapy, at least initially, in case series.[182–187] Cases of recurrent EVALI with persistent ENDS use have been reported; therefore, cessation is paramount for these patients.[189]

Radiographic and Pathological Findings of EVALI

Because EVALI is often a diagnosis of exclusion, abnormal pulmonary imaging findings are typically required.[190] Pathological features associated with this pulmonary injury are consistent with a chemical-induced pneumonitis.[196] The pattern of acute lung injury is typical of organizing pneumonia, diffuse alveolar damage, or both. Acute eosinophilic pneumonia and diffuse alveolar hemorrhage are less common findings.[190] Typical computed tomography imaging features of EVALI-related organizing pneumonia consist of diffuse, symmetric, bilateral ground-glass opacities with subpleural sparing (Figure 4).[190] Thickening of the interlobular septum and centrilobular nodules is also frequently present.[190] Patients who develop diffuse alveolar damage demonstrate greater severity of pulmonary findings, consistent with more advanced disease. Imaging findings commonly include volume loss and consolidation or ground-glass opacities with a lower lobe predominance. As disease progresses, volume loss and architectural distortion increase.[190] Progression to chronic pulmonary disease is characterized by severe scarring. This progression can result in severe respiratory failure and even death.[176,179,191,192] Patients who survive can have chronic pulmonary dysfunction, and in rare cases, lung transplantation has been performed for EVALI.[176,182,191,192] Computed tomography imaging can be helpful in patients with chronic pulmonary injury to assess the degree of scarring and to diagnose complications associated with respiratory failure. These complications can include superimposed infection, formation of bullae, and development of pneumothorax.[190]

Proposed Mechanism of Action for EVALI

Vitamin E acetate has been implicated as the most likely causal factor for EVALI in the patients investigated in the 2019 US epidemic.[181] Vitamin E acetate is used as a thickening agent in some nicotine-containing e-cigarettes but mostly those containing tetrahydrocannabinol oil. Vitamin E acetate was found in the bronchial alveolar lavage of 49 of 51 patients (94%) with EVALI.[181] No other toxicant in the screening panel was identified, leading

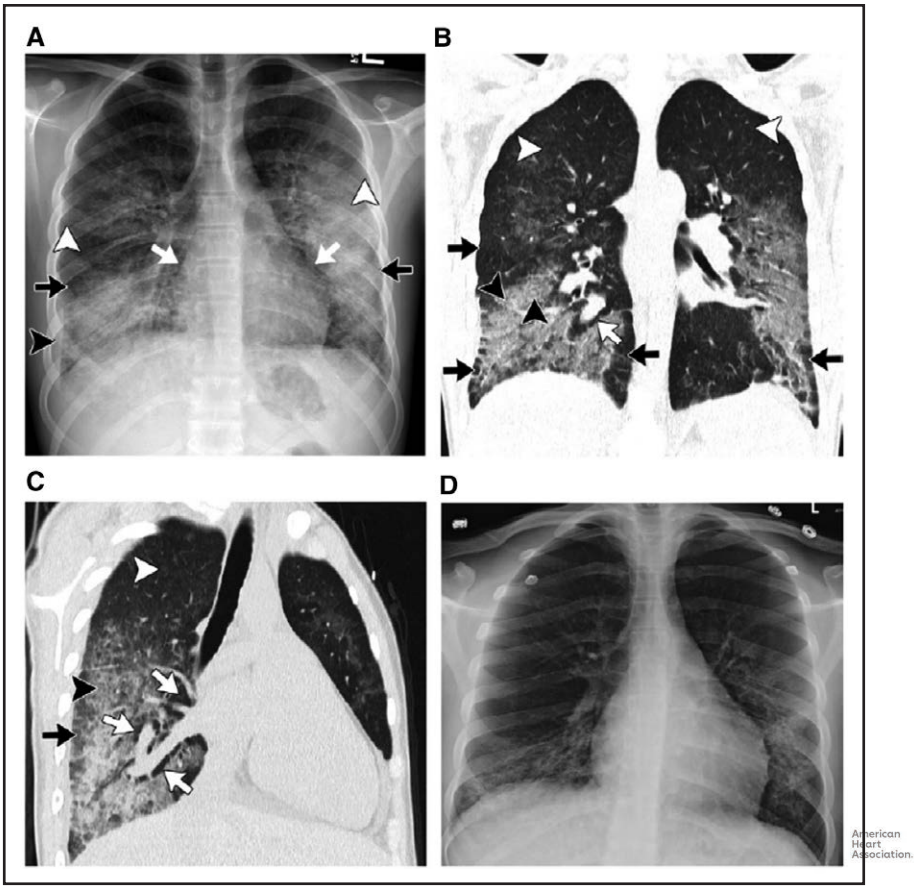

Figure 4. Images show electronic cigarette or vaping product use–associated lung injury with organizing pneumonia pattern secondary to vaping tetrahydrocannabinol in an 18-year-old man.
A, Posteroanterior radiograph shows midlung and lower lung consolidation and opacity bilaterally. Small right pleural effusion (black arrowhead) and septal thickening (white arrowhead) are seen. There is conspicuous sparing of cardiac borders (white arrows) as well as subpleural portions of lung (black arrows). **B**, Coronal and, **C**, sagittal oblique images from CT nicely illustrate radiographic findings with mild and lower lung–predominant ground-glass opacity with few areas of consolidation. Prominent subpleural and perilobular sparing is present (black arrows). In addition, there is conspicuous sparing of peribronchovascular interstitium, best illustrated around larger pulmonary arteries and veins (white arrows). Hazy upper lobe–predominant ground-glass centrilobular nodules are present bilaterally (white arrowheads). In addition to thickening of interlobular septa, there are few areas with thickening of intralobular septa creating "crazy paving" pattern (black arrowheads). **D**, Three days after initiation of steroids, patient showed dramatic clinical and radiographic improvement. Reprinted with permission from Kligerman et al.[190] Copyright ©2020 RSNA.

to the suggestion that vitamin E acetate may be linked to the development of the 2019 EVALI epidemic in the United States.[181] Both untargeted and targeted mass spectrometry evaluation of 38 e-liquid cartridges from patients who had developed EVALI revealed that 64% of the e-liquids contained vitamin E acetate.[198] The absence of vitamin E acetate in several cases and products suggests that additional product characteristics could contribute to the development of EVALI.

Elevated albumin, CD45$^+$ cells, and lipid-laden macrophages were found in the bronchial alveolar lavage fluid of mice exposed to 2 weeks of propylene glycol and glycerol with vitamin E acetate compared with filtered air–exposed animals.[199] Similar alterations were observed in animals exposed to only propylene glycol and glycerol, but not to the same extent as the animals that were exposed to vitamin E acetate.[199] Overall, evaluation of vitamin E acetate exposure in animal models shows a pulmonary pathology similar to that observed in patients with EVALI, suggesting that vitamin E acetate may be one of the contributors to the disease development.

The Future of EVALI

Emergency department visits related to EVALI declined sharply by early 2020, thought to be through a combination of increased public awareness about informal vaping products through rapid public health response (before the COVID-19 pandemic), removal of vitamin E acetate from some products, and law enforcement actions related to illicit products. The emergence of the COVID-19 pandemic and the overlap of many symptoms of EVALI and COVID-19 also likely contributed to less recognition of EVALI. The National Heart, Lung, and Blood Institute of the National Institutes of Health convened a working group on October 23, 2019, to identify the most relevant and urgent research priorities and challenges in EVALI.[200] One key goal was to lay out

 Circulation. 2023;148:e00–e00. DOI: 10.1161/CIR.0000000000001160

Table 1. National Institutes of Health Workshop on EVALI Conclusions From October 2019[200]

Key points of agreement
E-cigarette or vaping devices have been used to generate aerosols containing numerous active substances for inhalation, including nicotine, THC, and CBD.
The etiology of EVALI remains unknown. Available data from the CDC point to an association with oil-based ingredients, such as vitamin E acetate, added to THC liquids before vaping or dabbing (inhaling potent vapors from concentrated marijuana oil), but a specific cause for EVALI has not been proven mechanistically.
Vaping devices have not been shown to be safe for long-term use. The short- and long-term toxicities of inhaling aerosols generated from liquids containing vegetable glycerin, propylene glycol, nicotine, or flavors are unknown. Inhaling aerosols generated from THC- or CBD-containing liquids, which often contain additional chemical components, also have unknown health effects. Thus, elucidating their long-term respiratory, cardiac, and cancer health effects is a public health priority.
Physicians and other health care professionals need further guidance on how to take an accurate and detailed inhalant history. Acquisition of such data from across the country will help track EVALI cases and other vaping-related health effects.
Key priorities for future research
National and international registries of all patients with EVALI should be created that could be accessed by researchers and clinicians to track those affected and assess outcomes accurately.
We suggest that 3 cohorts of subjects be identified and followed up over time: (1) healthy vapers/dabbers, (2) patients with severe EVALI, and (3) patients with nonsevere (mild, moderate, subacute, and chronic) EVALI. Groups would be powered to identify causal agents, short- and long-term effects on lung function, overall health, and biomarkers of EVALI in both target organs (eg, the lung) and accessible biofluids (eg, blood, urine).
Acquisition and analysis of biospecimens from humans affected by EVALI (whole blood, tracheal aspirates or BAL, lung biopsy specimens, urine, autopsy specimens) will help profile inflammatory and fibrotic changes, determine whether a heretofore unknown viral or bacterial pathogen may be a causal agent, and gain an overall understanding of EVALI pathogenesis.
Research on vaping effects to date may not have identified EVALI because of multiple limitations, including but not limited to lack of access to and hence testing of THC liquids used in vaping and dabbing, rapid evolution of products on the market, inadequate dosing or exposure to e-cigarette aerosol in animal models. and an absence of studies in which multiple device types and liquids are applied to models to mimic use patterns in the affected demographic.
The occurrence of EVALI highlights the importance of broadening e-cigarette toxicity questions beyond comparators to smoking and smoking-related diseases because vaping has disease risks different from smoking.
Systematic and comprehensive laboratory-based studies should be conducted examining the toxicology and health effects of THC-containing vaping products to provide insights into potential causes of EVALI.

BAL indicates bronchoalveolar lavage; CBD, cannabidiol; CDC, Centers for Disease Control and Prevention; e-cigarette, electronic cigarette; EVALI, electronic cigarette or vaping product use–associated lung injury; and THC, tetrahydrocannabinol.

Adapted with permission from Crotty et al.[200] Copyright © 2020 American Thoracic Society.

future research priorities and to recommend strategies for the diagnosis, treatment, and prevention of the disease (Table 1).[200] There was consensus that long-term outcomes in EVALI are unknown[200]; in the ensuing years, reports emerged on long-term outcomes of EVALI,[189] but more data are needed.

CHRONIC HEALTH EFFECTS OF E-CIGARETTES AND VAPING PRODUCTS

E-cigarettes and vaping were introduced to the US market 15 years ago, with widespread adoption only in the past decade.[11,13] We do not yet know the long-term health effects of these products. Tobacco use is a major preventable cause of death; however, this was not appreciated until many years after cigarette smoking became widespread. Before the adoption of tobacco products, lung cancer was rare.[201] Increasing incidence of lung cancer in actuarial studies was not noted until 1930 (Figure 5).[201–206] Definitive scientific evidence associating cigarette smoking and lung cancer was not reported until the 1950s.[203–205] In 1964, the US Surgeon General report on tobacco and health attributed the increase in lung cancer to cigarette smoking.[206] Only then did cigarette smoking per capita begin to decline. With the delayed development of chronic disease from smoking, lung cancer deaths did not begin to fall accordingly until decades after the 1964 report (Figure 5).[201–206] Similarly, declines in mortality from myocardial infarction and stroke in recent decades have been attributed in part to the significant decline in cigarette smoking in the past 50 years.[207] Supposing similar time delays for the presentation of chronic disease from cigarettes (eg, lung cancer, COPD, or vascular disease) and for ENDS, epidemiological increases in disease prevalence would not be expected to be observed for years after ENDS products were introduced to the US market. It is critical to assess the limited amount of long-term clinical and animal data that emerge to better understand the long-term effects of ENDS use. The National Academies of Sciences, Engineering, and Medicine reviewed the health literature of ENDS products in 2018 and provided an evidence-based summary of health concerns.[208] The report found that there was no available evidence on whether ENDS use is associated with clinical cardiovascular outcomes such as coronary heart disease, stroke, and peripheral artery disease.[208] There was insufficient evidence that ENDS use was associated with long-term effects on heart rate, blood pressure, and cardiac function.[208] The report concluded that there was no available evidence on whether ENDS use causes respiratory diseases in humans, moderate evidence that ENDS use is associated with an increase in asthma exacerbations, and limited evidence of adverse effects of ENDS exposure on the respiratory system from animal and in vitro studies.

Few studies have evaluated the chronic cardiovascular effects of ENDS because the products have been available only for the past 10 to 15 years. In a murine model, 8 months of ENDS exposure increased arterial stiffness, reduced stimulated vascular relaxation, and enhanced sensitivity to vasoconstriction, similar to vascular alterations induced by cigarette smoking.[209] No effects were observed on more acute physiological markers such as heart rate, stroke volume, or cardiac output with e-cigarette

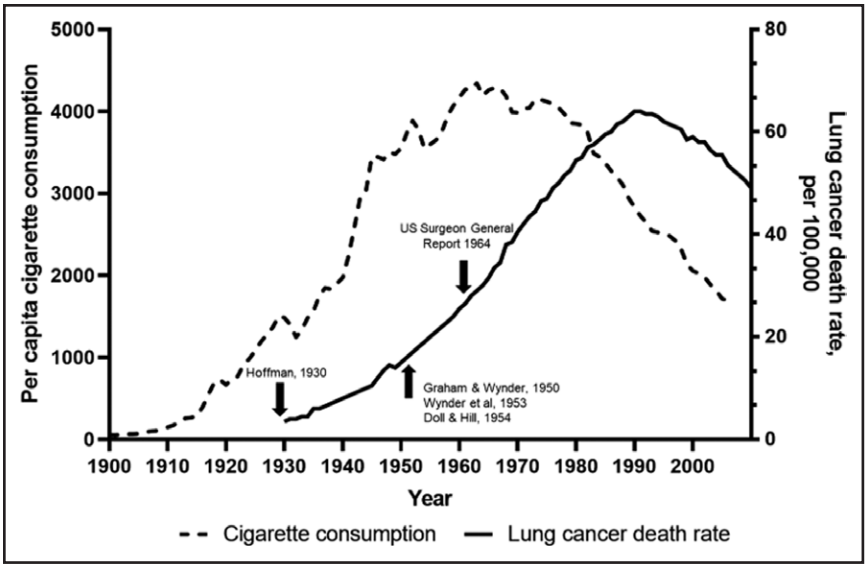

Figure 5. Tobacco use vs lung cancer death rates in the United States. Adapted from American Cancer Society. Cancer Facts & Figures 2013. Atlanta, GA: American Cancer Society; 2013.[202]

exposure.[209] Mice exposed to ENDS aerosol for 3 to 6 months have increased inflammation, organ fibrosis, and elevated systolic blood pressure compared with mice exposed to air[210]; another study showed that 3 months of ENDS exposure showed resulted in mutagenic DNA adducts in tissues, including the heart.[211] In the aforementioned studies, observed chronic toxicity of ENDS could be attributed, at least in part, to nicotine.[210,211]

Limited clinical data are available for chronic ENDS effects on the cardiovascular system. One cross-sectional case-control study showed that compared with nonvaping control subjects, regular ENDS users had a shift in autonomic balance toward sympathetic predominance, higher low-density lipoprotein oxidation, and elevated markers of inflammation, suggestive of an association with increased cardiovascular risk.[68] Activation of the splenocardiac axis after long-term exposure to cigarettes and ENDS products has been observed in healthy young adults.[212] Activation of the splenocardiac axis can be proinflammatory and is associated with the development of atherosclerosis and acute myocardial infarction.[212] The NHIS data of 2014 and 2016 were used to examine the cross-sectional association of ENDS use, cigarette smoking, and myocardial infarction.[213] With the use of a single logistic regression model that included demographics and medical history, daily ENDS use was independently associated with increased odds of having had a myocardial infarction (odds ratio, 1.79 [95% CI, 1.20–2.66]).[213] Although current evidence suggests possible cardiovascular risk from long-term exposure to ENDS, more long-term animal exposure model studies, population studies, and prospective clinical studies are needed.

A recent longitudinal analysis of the adult PATH study waves found a statistically significant association between former or current ENDS use at baseline and the development of incident respiratory disease (COPD, chronic bronchitis, emphysema, or asthma) at a follow-up of ≈2 years (adjusted OR, 1.31 and 1.29, respectively).[214] The majority of the investigations to study long-term respiratory effects associated with ENDS use were conducted in either current or previous cigarette smokers. A 1-year study found that FEV25%–75% improved in smokers who quit combustible cigarettes but other spirometry parameters (FEV1, FVC, or FEV1/FVC) were unchanged, regardless of complete cessation of ENDS use, suggesting that e-cigarette use in smokers may result in some improvement in small airway obstruction.[215] In observational cohorts of patients with COPD who were current or former smokers 45 to 80 years of age (COPDGene [Chronic Obstructive Pulmonary Disease Genetic Epidemiology], n=3536; SPIROMICS [Subpopulations and Intermediate Outcome Measures in COPD Study], n=1060), ENDS use was associated with a greater decline in lung function, higher nicotine exposure, and greater risk of COPD exacerbation.[216] No evidence of harm reduction was observed with ENDS use compared with combustible cigarettes.[216] Conversely, another study found improvements in COPD exacerbation and test scores during a 6-minute walk test with ENDS use compared with combustible cigarette use over 3 years.[217] This study was small (n=22 per group) and lacked a comparison with never-smoking patients, limiting the conclusions that can be drawn on the safety of ENDS use.[217]

A limited number of studies are available evaluating e-cigarette use and exposure among patients with chronic pulmonary conditions. A randomized controlled trial examined the effects of passive ENDS aerosol exposure in patients who had COPD who were nonsmokers.[218] Passive e-cigarette exposure resulted in alterations in exhaled surfactant protein A and increases in certain plasma proteins that could indicate inflammation.[218] In a large cross-sectional telephone survey of never-smokers, the odds of self-reported asthma were higher in current ENDS users compared with nonusers.[219] Similar survey

studies have shown higher self-reported asthma and COPD in ENDS users.[124,125] Acute ENDS exposure (5 minutes) does appear to worsen respiratory mechanics immediately after use in patients with asthma.[132] House dust or ovalbumin challenge in mice exposed to ENDS aerosol resulted in various alterations in airway hyperresponsiveness and airway inflammation that were at least partially dependent on flavoring and nicotine.[220–222]

No studies on ENDS product use have been performed in cohorts of patients with cystic fibrosis, interstitial lung disease, or pulmonary hypertension. A recent report found that vaporized ENDS liquids can induce CFTR (cystic fibrosis transmembrane conductance regulator) dysfunction.[223] Reduced CFTR function could worsen cystic fibrosis and may contribute to chronic bronchitis onset or progression.[224] ENDS vapor caused mucociliary dysfunction in sheep.[225]

In terms of the development of COPD or lung cancer, animal models will likely serve as the most reliable approach to examine the chronic health effects of ENDS until longer-term studies have been conducted in humans. In vitro studies and animal models suggest that ENDS use increases oxidative stress measures, proteases, inflammation, and DNA damage, all indicators that may increase the risk of COPD and lung cancer.[222] In a study of mice exposed to 12 weeks of ENDS aerosol, sustained extensive DNA damage in lungs, heart, and bladder mucosa was observed.[211] In a longer exposure (54 weeks), animals developed lung adenocarcinomas and bladder urothelial hyperplasia, with lesions being rare in controls.[226] Two studies have shown that long-term e-cigarette exposure in mice induces nicotine-dependent airway changes similar to COPD.[227,228] However, in another study examining long-term exposure to different flavors of nicotine-containing e-cigarette vapor, mice did not develop an emphysema-like syndrome.[209] This suggests that the different chemicals present across ENDS products (tetrahydrocannabinol, flavoring agents, metals) may well have different toxicity profiles. Last, few studies have investigated the effects of e-cigarettes on the pulmonary vasculature. Mice exposed to e-cigarettes had a significant reduction in pulmonary capillary numbers, similar to that seen from conventional tobacco smoke.[228] Ultimately, more studies, both clinical and in animal models, are required to better understand the long-term impact of ENDS product use and the development of cancer.

EXAMINATION OF E-CIGARETTE AND VAPING PRODUCTS AS CIGARETTE-CESSATION PRODUCTS

Combustible cigarette smoking remains the leading cause of preventable death in the United States, with ≈480 000 deaths per year being directly attributable to smoking-related causes.[207] Given the established risks of cigarette smoking, ENDS products have been evaluated as cessation tools for cigarette use. A recent Cochrane Database of Systematic Reviews performed a meta-analysis on the efficacy of e-cigarettes for smoking cessation and frequency of adverse events related to e-cigarette use.[229] Compared with nicotine replacement therapy (NRT), the analysis found a moderate certainty of evidence that more people quit smoking with nicotine-containing ENDS products compared with NRT (4 studies, 1924 participants; relative effect, 1.53 [95% CI, 1.21–1.93]; Supplemental Figure 2).[125,229–231] Adverse events were similar.[229] In the Cochrane review, the analysis found that nicotine-containing ENDS products may help more people to stop smoking than no support or behavioral support only (6 studies, 2886 people; relative effect, 2.61 [95% CI, 1.44–4.74]) with low certainty.[232–236] Adverse events were higher at 12 weeks to 6 months in ENDS users compared with those with no support or behavioral support only.[229] One study compared e-cigarettes with varenicline, finding that e-cigarettes were less effective than varenicline (4 of 27 e-cigarette users versus 13 of 27 varenicline users stopped smoking; risk ratio, 0.31 [95% CI, 0.11–0.82]).[229,237] These main study results assessed smoking cessation not complete product cessation. This could mean that participants who quit smoking continued ENDS use.

A recent trial compared nicotine ENDS plus NRT (nicotine patch) with NRT alone and NRT plus nicotine-free ENDS.[238] There was a 7% abstinence rate in the nicotine patch and ENDS treatment groups, which was significantly higher than with the patch alone (2%) and a patch and nicotine-free ENDS (4%).[238] These findings are similar to an early clinical trial examining nicotine-containing ENDS products compared with the nicotine patch alone and nicotine patch plus nicotine-free ENDS condition.[230] Another trial showed that ENDS use may reduce smoking among those given a nicotine-containing ENDS product compared with a nicotine-free ENDS.[239]

Overall, more studies are needed to find the most effective method for cigarette smokers to stop. No current ENDS products have received FDA approval as a tobacco-cessation aid. There is only low to moderate confidence of improved cessation with nicotine-containing ENDS products compared with NRT or behavioral interventions.[229] It is important to note that there are many components of ENDS products, including flavors, device type, device features (eg, power, voltage), and nicotine strength, that, according to experimental work, may be expected to affect cessation efforts.[240] Future trials should make these variables a consideration.[240] Furthermore, because the dose-response relationship between combustible cigarettes and cardiovascular disease is nonlinear, it should be emphasized that complete cessation of the use of all tobacco products should be the ultimate goal.[241]

Although the effects of dual use remain incompletely understood, there are growing concerns that dual use

may make cessation more difficult to achieve, in part by sustaining the delivery of nicotine and supporting addiction. Compared with exclusive users, dual users have a higher prevalence of use of tobacco products and lower harm perceptions for tobacco products.[242] According to a systematic review and meta-analysis that examined the association between e-cigarette use and cigarette smoking cessation among adult cigarette smokers, the odds of quitting cigarettes were 28% lower among dual users compared with users who did not use e-cigarettes.[243] A recent prospective cohort study found that smokers who used ENDS products at baseline were less likely to quit smoking than those who did not use ENDS products at baseline (9.4% stopped smoking versus 18.9%).[244]

From a population health perspective, any potential benefits of ENDS products as effective cigarette-cessation products and the benefits to current smokers stopping cigarettes must be balanced with the risks that nonsmokers start using ENDS products exclusively or as a gateway to further tobacco product use.[245] The negative impact of initiation of ENDS products is a particularly important concern among youth.[246,247] Studies suggest that the rapid uptake of ENDS products among youth coincides with the rapid increases in their unregulated marketing.[248,249] Flavors have been found to be an important motivator for ENDS uptake.[10,250] Exposure to ENDS advertising is associated with lower ENDS harm perceptions and perceived addictiveness[249,251,252] and plays a role in a youth's decision to initiate ENDS use.[253] A recent systematic review suggested an association between exposure to ENDS advertisement and lower harm perceptions about ENDS products, higher intention to use ENDS products, and more ENDS experimentation in adolescents and young adults.[254] ENDS products are not only marketed in traditional media such as television and print advertisements[255] but also aggressively advertised in social media platforms that are highly accessible to youth.[256–261]

PUBLIC HEALTH EFFORTS, REGULATION, AND MARKETING OF E-CIGARETTES AND VAPING PRODUCTS

Summary of the Current Regulatory Environment for ENDS Products

The Family Smoking Prevention and Tobacco Control Act, signed by President Barack Obama in 2009, gave the US FDA the authority to regulate the manufacturing, marketing, distribution, and sale of tobacco products.[262–264] The authority, under the FDA Center for Tobacco Products, is different from drug and medical device regulation.[262–264] The FDA cannot ban the sale of certain categories of tobacco products or face-to-face sales at certain categories of retail outlets, cannot require prescriptions for the purchase of tobacco products, and cannot require the reduction of nicotine levels to zero.[262–264] Tobacco product manufacturers are required to submit to the FDA lists of the ingredients and constituents in their products and internal documents on their safety.[262–264] The Family Smoking Prevention and Tobacco Control Act formed the Tobacco Products Scientific Advisory Committee, which reviews data on the safety, dependence, and health issues related to tobacco products.[265] The committee then provides advice, information, and recommendations to the FDA such as whether a tobacco product should qualify as modified risk because it reduces harm or reduces exposure to an ingredient compared with another preexisting product.[266] Of note, the initial Family Smoking Prevention and Tobacco Control Act did not address ENDS products because there were few in the market at that time.

In 2016, the FDA finalized a rule that deemed ENDS and all other products that meet the definition of tobacco product to be subject to the agency's authority under the Federal Food, Drug and Cosmetic Act.[267] Besides prohibiting the sale of e-cigarettes to youth <18 years of age, this new rule prohibited false and misleading marketing claims and required premarket review. In January 2020, the FDA issued an enforcement policy to prohibit sales of certain flavored e-cigarettes. 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," and exempted all tobacco or menthol-flavored products.[268] The policy also exempted self-contained, disposable products and e-liquids for open-tank or refillable ENDS products. In response, many of these products such as the disposable e-cigarette Puff Bar with synthetic nicotine[269] gained dramatic market share after this FDA policy took effect.[270] Separately, the FDA proposed banning menthol cigarettes and all flavored cigars in April 2022.[271] To minimize adolescents and youth tobacco initiation, in December 2019, the president signed legislation to raise the federal minimum legal age of sale of tobacco products, including ENDS products, to 21 years, known as Tobacco 21, effective immediately.[272]

Despite all these regulatory approaches, there are continued gaps in regulation that allow the tobacco industry to continue to sell many tobacco products that are easily accessible to children and young adults.[273] The original Family Smoking Prevention and Tobacco Control Act was limited to 4 tobacco products (smokeless tobacco, roll-your-own tobacco, cigarettes, cigarette tobacco); cigars, e-cigarettes, pipe tobacco, and several other tobacco products were included later.[274] The FDA also has to contend with constant innovation in the tobacco product marketplace such as the emergence of pod-based vaping products in 2015, which led to huge increases in the rates of ENDS use among youth. Puff Bar and

some other e-cigarettes and oral nicotine products were also able to evade FDA flavor restrictions and premarket review requirements by claiming to be tobacco-free synthetic nicotine,[275] which the FDA did not have authority to regulate as a tobacco product until new legislation was enacted in March 2022; that legislation gave the FDA the authority to regulate all tobacco products regardless of the nicotine source.[276] Future innovations in the tobacco product marketplace continue to pose challenges to the FDA's regulatory authority.

Current Public Health Efforts to Reduce E-Cigarettes and Vaping Products in Youth and Young Adults

As indicated previously, the rates of ENDS use are high among adolescents and young adults.[14] This is particularly true of youths from underresourced populations: those with lower socioeconomic status,[277] those who identify as LGBTQ (lesbian, gay, bisexual, transgender, and queer), individuals from lower educational backgrounds, those from underserved communities, and those with mental health conditions.[278,279] Children are initially attracted to these products for their flavors,[280,281]; many then move on to regular use and nicotine addiction and then may transition to using other tobacco products such as combustible cigarettes.[282–285] Furthermore, ENDS use positively corelates with other substance use and abuse, including alcohol and marijuana.[286] The alarming prevalence of ENDS use among youth and the unknown potential for cardiovascular harm and toxicity emphasize the critical need for public health efforts to prevent and reduce the use of ENDS products among youth.

In response, several public health efforts aimed at preventing e-cigarette and vaping product use among youth and young adults have been developed. These include school-based interventions, community-based interventions, and public education intervention (as outlined in a review by the Ontario Tobacco Research Unit).[287] It is important to note that many of these interventions have not yet been empirically tested but have been implemented in various settings.

School-based prevention interventions include the CATCH my Breath Youth E-Cigarette Program,[288] the Tobacco Prevention Toolkit by Stanford University,[289] and "E-Cigarettes: What You Need to Know (Teacher's Guide)" by Scholastic.[290] The majority of these curriculums are aimed at middle and high school–aged students, and their main mode of delivery is teacher/educator-delivered educational materials. In a pilot in Texas middle schools, those receiving the CATCH my Breath program (compared with students in control schools) were observed to have lower prevalence of e-cigarette use after 16 months.[288] Other programs that are being developed and tested for use among students include smoke screen, an e-cigarette video game, and ASPIRE, a learning module aimed at middle and high school students, prior iterations of which demonstrated effectiveness at preventing cigarette use.[291,292] Several community-based text message programs have been created by Truth Initiative: This is Quitting, BecomeAnEX, and others are aimed at both cigarette and e-cigarette users.[293,294] This is Quitting was designed with youth and young adults in mind, whereas the other 2 programs are aimed at adult tobacco users.[293,294] Preliminary evidence on This is Quitting among young adults suggests that the intervention doubled the self-reported 30-day abstinence rates.[294]

Public education campaigns that use various approaches, including paid ads, social media, and materials such as fact sheets and posters, have also been developed. One example is the US FDA's Real Cost E-Cigarette Prevention Campaign, focused on debunking false information about e-cigarettes through advertisements, which has been shown to increase negative views of vaping among adolescents and to lower their intentions to use e-cigarettes.[295]

In summary, few empirically tested prevention and cessation programs for youth ENDS use exist. Some strategies that could deter minor ENDS use and improve adolescent ENDS cessation include the use of novel technology (ie, text messages, social media)[296] that has been used extensively to advertise ENDS products to youth,[259–261] educational efforts focused on parents and health educators, focused assessment and treatment by pediatricians and other health care professionals, and use of other behavioral methods such as incentives and cognitive behavior therapy that have been successfully shown to promote smoking cessation among youth.[297–299] Future work on developing and testing effective interventions is critically needed, and such work is being supported by the End Nicotine Addiction in Children and Teens initiative funded by the American Heart Association in 2020. This critical initiative funds scientific research at Boston University, The Ohio University, and Yale University to understand the health impact of ENDS use on youth and young adults and to develop interventions.[300] Furthermore, a recent presidential advisory from the American Heart Association delivered several positions on newer tobacco product regulation (Table 2).[301]

KNOWLEDGE GAPS AND RESEARCH PRIORITIES

ENDS products have undeniably been increasing in popularity, particularly among young adults and teens, in the past decade. The constituents of these products often include nicotine, which is well established to have negative health effects and strong addictive properties. Other ingredients, particularly in flavored products, have known health risks. Because ENDS products are not regulated as classic therapeutic drugs or devices, there are no

Table 2. AHA Positions on Newer Tobacco Product Regulation

Issue	
Tobacco endgame	The AHA supports ending the use of all combustible tobacco products while ensuring that other products do not addict the next generation of youth and adolescents and achieving a realistic goal of getting to ≤5% tobacco use prevalence.
Underresourced populations	Tobacco control and prevention efforts and regulation should be targeted and tailored to at-risk populations, including youth and adolescents, those who live in rural areas, racial and ethnic groups with high tobacco use, those with mental health conditions, individuals with less education and low income, and those who identify as LGBTQ.
Nicotine reduction strategy	The AHA favors lowering nicotine content in all combustible tobacco products. The AHA supports lowering nicotine concentrations in all combustible tobacco products to reduce tobacco-related mortality.
Flavorings	The removal of all characterizing flavors from all tobacco products is essential for reducing their appeal to youth.
Market review	The AHA supports restricting the marketing of JUUL and other similar e-cigarettes until their health risks to youth and adolescent users are clearly assessed and their potential benefits and harms in promoting tobacco cessation among adults are better understood. The agency should suspend internet sales of these products until adequate mechanisms and rules for age verification are established. In addition, the ban on underage sales by retailers should be effectively enforced, and the FDA should require that these products be submitted for review.
Marketing and advertising	The AHA supports robust FDA regulation restricting all tobacco marketing and advertising to youth and vulnerable populations, including the use of television, radio, and print ads and commercials; celebrity endorsement; movie placements; price promotions; free sampling; branded events; and nontobacco merchandise.
Public education	There is a significant need for robust public education about these newer tobacco products and the harms they pose, especially for youth and adolescents.
Tobacco 21	The AHA advocates for Tobacco 21 laws that incorporate all tobacco products to minimize youth and adolescent initiation.
Comprehensive smoke-free air	Smoke-free laws should explicitly include aerosolized, alternative nicotine delivery systems, and combustible products in comprehensive smoke-free air laws to ensure that there is no passive exposure to any harmful constituent byproducts or risk of renormalizing tobacco use.
Health care professional guidance	Health care professionals should screen for all tobacco product use and counsel cessation. Young patients should be screened for newer tobacco use and substance abuse and counseled on the dangers of these products. A previous AHA policy statement elucidated how clinicians should advise adult patients about cessation. Youth substance use prevention programs should target reduction of e-cigarette and cigar use. In the intersection between the health care system and public health, there is a need to develop public health messages that accurately convey the scientific data on the potential harm of newer tobacco products and differentiate the absolute from relative harm of these products compared with combustible tobacco.

AHA indicates American Heart Association; e-cigarette, electronic cigarette; FDA, US Food and Drug Administration; and LGBTQ, lesbian, gay, bisexual, transgender, and queer.

Adapted with permission from Bhatnagar et al.[301] Copyright © 2019 American Heart Association, Inc.

dedicated long-term safety studies. Critical questions remain unanswered about the short-term and, in particular, long-term health effects of ENDS products. Because the products have only recently gained widespread use, decades of prospective or retrospective data are not yet available to examine the long-term health effects of cigarettes. Early analysis suggests some utility of ENDS as a smoking cessation product; however, any benefit needs to be juxtaposed with a clear understanding of the health risks of the ENDS products themselves and the risks of product availability leading to nonsmokers initiating ENDS use. Regulatory bodies and governments worldwide will be required to examine these aspects critically as ENDS manufacturers market and distribute these products. The advent of EVALI emphasizes the pressing need to better understand the role of constituents used in these products. The large informal market, including online distribution, homemade vaping liquids, and locally manufactured vaping liquids, creates an ENDS user base that is difficult to regulate and study. Although more studies are desperately needed to understand the full health risk profile of different types of ENDS devices and ENDS liquids, claims that ENDS products present absolutely no health risks are false according to the limited, but growing, evidence available. Future research should focus on understanding the short- and long-term cardiopulmonary impact of ENDS product use and commonly used constituents such as flavoring agents in both human and animal exposure models. Studies on patients with preexisting cardiopulmonary disease (coronary artery disease, COPD) comparing ENDS products users with both smokers and nonsmokers will be important. Long-term effects of ENDS use will eventually be determined epidemiologically. However, to accurately balance the risks and benefits of ENDS on a population scale, long-term animal exposure models will be required in the interim before decades-long evidence emerges. Policies on the use of ENDS products as harm reduction tools need to be balanced with the fact that ENDS use is rising rapidly in young adults and youth who may have never started using combustible tobacco products.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on October 8, 2022, and the American Heart Association Executive Committee on February 25, 2023. A copy of the document is available at https://professional.heart.org/statements by using either "Search for Guidelines & Statements" or the "Browse by Topic" area. To purchase additional reprints, call 215-356-2721 or email Meredith.Edelman@wolterskluwer.com

The American Heart Association requests that this document be cited as follows: Rose JJ, Krishnan-Sarin S, Exil VJ, Hamburg NM, Fetterman JL, Ichinose F, Perez-Pinzon MA, Rezk-Hanna M, Williamson E; on behalf of the American

Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; Council on Epidemiology and Prevention; Council on Cardiovascular Radiology and Intervention; Council on Lifestyle and Cardiometabolic Health; Council on Peripheral Vascular Disease; Stroke Council; and Council on Arteriosclerosis, Thrombosis and Vascular Biology. Cardiopulmonary impact of electronic cigarettes and vaping products: a scientific statement from the American Heart Association. *Circulation*. 2023;148:e•••–e•••. doi: 10.1161/CIR.0000000000001160

The expert peer review of AHA-commissioned documents (eg, scientific statements, clinical practice guidelines, systematic reviews) is conducted by the AHA Office of Science Operations. For more on AHA statements and guidelines development, visit https://professional.heart.org/statements. Select the "Guidelines & Statements" drop-down menu, then click "Publication Development."

Disclosures

Writing Group Disclosures

Writing group member	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Expert witness	Ownership interest	Consultant/ advisory board	Other
Jason J. Rose	University of Maryland School of Medicine	Breathe Pennsylvania Foundation, a 501(c)(3) nonprofit organization (He was awarded a Lung Research grant to study the effects of flavored vaping products on young people in western Pennsylvania region.)*	None	None	None	Omnibus Medical Devices, LLC (no monetary income to report and no monetary value at this time)*	None	None
Suchitra Krishnan-Sarin	Yale University	NIH (PI of U54 from NIH on tobacco regulatory science)†; AHA (PI of ENACT)†; Novartis (free drug for alcohol treatment study unrelated to work presented in current article)*	None	None	None	None	AHA ATRAC (unpaid)*; USCF TCORS (unpaid)*; VCU TCORS*; CDC-ICSH (unpaid)*	None
Vernat J. Exil	Saint Louis University	None	None	None	None	None	None	None
Jessica L. Fetterman	Boston University School of Medicine	NHLBI (U54HL120163)†; NHLBI (K01 HL143142)†	None	None	None	None	MitoBridge*	None
Naomi M. Hamburg	Boston University School of Medicine	None	None	None	None	None	None	None
Fumito Ichinose	Massachusetts General Hospital Anesthesia Center for Critical Care Research	NIH (R01 and R21 grants)†; Kyowa Hakko Kirin (sponsored research agreement)*	None	Mallinckrodt*	Phelan, Phelan, and Danek, LLP†	None	Nihon Kohden Innovation Center*; ZOLL Foundation (unpaid)*; Wivil*	Nihon Kohden Innovation Center (immediate family members, office manager)†
Miguel A. Perez-Pinzon	University of Miami School of Medicine	None	None	None	None	None	None	None
Mary Rezk-Hanna	University of California, Los Angeles School of Nursing	None	None	None	None	None	None	None
Eric Williamson	Mayo Clinic	None	None	None	None	None	None	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.

Reviewer Disclosures

Reviewer	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Expert witness	Ownership interest	Consultant/ advisory board	Other
John W. Cole	Veterans Affairs Maryland Health Care System; University of Maryland School of Medicine	None	None	None	None	None	None	None
Kristian B. Fillon	McGill University (Canada)	Canadian Institutes of Health Research (I am a coinvestigator and Steering Committee Member of a Canadian Institutes of Health Research–funded trial that examined the use of e-cigarettes for smoking cessation in the general population [E3 Trial].)†; Canadian Institutes of Health Research (I am a coinvestigator and Steering Committee member of a Canadian Institutes of Health Research–funded trial that examines the use of e-cigarettes for smoking cessation among patients hospitalized with an acute coronary syndrome [ASAP trial].)†						
Edgar A. Jaimes	Memorial Sloan Kettering Cancer Center	None	None	None	None	None	None	None
Russell V. Luepker	University of Minnesota School of Public Health	None	None	None	None	None	None	None
Quinn R. Pack	Baystate Medical Center	NHLBI (just completed a K23 studying how to improve cardiac rehabilitation participation)*; NHLBI (pending grant to study smoking cessation in hospitalized patients)*	None	None	None	None	None	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 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 $10 000 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. 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
2. Benowitz NL, Fraiman JB. Cardiovascular effects of electronic cigarettes. *Nat Rev Cardiol*. 2017;14:447–456. doi: 10.1038/nrcardio.2017.36
3. US Department of Health and Human Services. E-cigarette use among youth and young adults: a report of the Surgeon General. 2016. Accessed November 1, 2021. https://e-cigarettes.surgeongeneral.gov/documents/2016_sgr_full_report_non-508.pdf
4. Mulder HA, Patterson JL, Halquist MS, Kosmider L, Turner JBM, Poklis JL, Poklis A, Peace MR. The Effect of Electronic Cigarette User Modifications and E-liquid Adulteration on the Particle Size Profile of an Aerosolized Product. *Sci Rep*. 2019;9:10221. doi: 10.1038/s41598-019-46387-2
5. Gottlieb MA. Regulation of e-cigarettes in the United States and its role in a youth epidemic. *Children (Basel)*. 2019;6:40. doi: 10.3390/children6030040d
6. Smoking Everywhere, Inc. v. U.S. Food and Drug Administration, 680 F. Supp. 2d 62: United States District Court, District of Columbia 2010. Accessed November 1, 2021. https://www.courtlistener.com/opinion/2485826/smoking-everywhere-inc-v-us-food-and-drug/
7. Family Smoking Prevention and Tobacco Control Act, Public Law 111–31, H.R. 1256 (2009).
8. Gotts JE, Jordt S-E, McConnell R, Tarran R. What are the respiratory effects of e-cigarettes? *BMJ*. 2019;366:l5275. doi: 10.1136/bmj.l5275
9. 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
10. Cullen KA, Gentzke AS, Sawdey MD, Chang JT, Anic GM, Wang TW, Creamer MR, Jamal A, Ambrose BK, King BA. E-cigarette use among youth in the United States, 2019. *JAMA*. 2019;322:2095–2103. doi: 10.1001/jama.2019.18387
11. Cullen KA, Ambrose BK, Gentzke AS, Apelberg BJ, Jamal A, King BA. Notes from the field: use of electronic cigarettes and any tobacco product among middle and high school students–United States, 2011-2018. *MMWR Morb Mortal Wkly Rep*. 2018;67:1276–1277. doi: 10.15585/mmwr.mm6745a5

12. 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
13. 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
14. Johnston LD, Miech RA, O'Malley PM, Bachman JG, Schulenberg JE, Patrick ME. Monitoring the future: national survey results on drug use 1975-2019: overview, key findings on adolescent drug use. ERIC. 2020. Accessed November 1, 2021. https://eric.ed.gov/?id=ED604018
15. McNeill A, Brose LS, Calder R, Bauld L, Robson D. Vaping in England: an evidence update February 2019: a report commissioned by Public Health England. Public Health England. Accessed September 20, 2020. https://www.gov.uk/government/publications/vaping-in-england-an-evidence-update-february-2019
16. Hammond D, Reid JL, Rynard VL, Fong GT, Cummings KM, McNeill A, Hitchman S, Thrasher JF, Goniewicz ML, Bansal-Travers M, et al. Prevalence of vaping and smoking among adolescents in Canada, England, and the United States: repeat national cross sectional surveys. *BMJ.* 2019;365:l2219. doi: 10.1136/bmj.l2219
17. Miech R, Leventhal A, Johnston L, O'Malley PM, Patrick ME, Barrington-Trimis J. Trends in use and perceptions of nicotine vaping among US youth from 2017 to 2020. *JAMA Pediatr.* 2021;175:185–190. doi: 10.1001/jamapediatrics.2020.5667
18. Yach D. Tobacco use patterns in five countries during the COVID-19 lockdown. *Nicotine Tob Res.* 2020;22:1671–1672. doi: 10.1093/ntr/ntaa097
19. Wang TW, Neff LJ, Park-Lee E, Ren C, Cullen KA, King BA. E-cigarette use among middle and high school students–United States, 2020. *MMWR Morb Mortal Wkly Rep.* 2020;69:1310–1312. doi: 10.15585/mmwr.mm6937e1
20. 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
21. National Institutes of Health. E-cigarettes and e-hookahs. Accessed March 30, 2018. http://medlineplus/ency/patientinstructions/000761.htm
22. Jawad M, Shihadeh A, Nakkash RT. Philip Morris patents "harm reduction" electronic waterpipe [published online June 25, 2020]. *Tob Control.* doi: 10.1136/tobaccocontrol-2020-055885
23. 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
24. Bao W, Xu G, Lu J, Snetselaar LG, Wallace RB. Changes in electronic cigarette use among adults in the United States, 2014-2016. *JAMA.* 2018;319:2039–2041. doi: 10.1001/jama.2018.4658
25. 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
26. Coleman BN, Rostron B, Johnson SE, Ambrose BK, Pearson J, Stanton CA, Wang B, Delnevo C, Bansal-Travers M, Kimmel HL, et al. Electronic cigarette use among US adults in the Population Assessment of Tobacco and Health (PATH) study, 2013-2014. *Tob Control.* 2017;26:e117–e126. doi: 10.1136/tobaccocontrol-2016-053462
27. Jaber RM, Mirbolouk M, DeFilippis AP, Maziak W, Keith R, Payne T, Stokes A, Benjamin E, Bhatnagar A, Blankstein R, et al. Electronic cigarette use prevalence, associated factors, and pattern by cigarette smoking status in the United States from NHANES (National Health and Nutrition Examination Survey) 2013-2014. *J Am Heart Assoc.* 2018;7:e008178. doi: 10.1161/jaha.117.008178
28. Dai H, Leventhal AM. Prevalence of e-cigarette use among adults in the United States, 2014-2018. *JAMA.* 2019;322:1824–1827. doi: 10.1001/jama.2019.15331
29. Lee WH, Ong SG, Zhou Y, Tian L, Bae HR, Baker N, Whitlatch A, Mohammadi L, Guo H, Nadeau KC, et al. Modeling cardiovascular risks of e-cigarettes with human-induced pluripotent stem cell-derived endothelial cells. *J Am Coll Cardiol.* 2019;73:2722–2737. doi: 10.1016/j.jacc.2019.03.476
30. Putzhammer R, Doppler C, Jakschitz T, Heinz K, Forste J, Danzl K, Messner B, Bernhard D. Vapours of US and EU market leader electronic cigarette brands and liquids are cytotoxic for human vascular endothelial cells. *PLoS One.* 2016;11:e0157337e0157337. doi: 10.1371/journal.pone.0157337
31. Anderson C, Majeste A, Hanus J, Wang S. E-cigarette aerosol exposure induces reactive oxygen species, DNA damage, and cell death in vascular endothelial cells. *Toxicol Sci.* 2016;154:332–340. doi: 10.1093/toxsci/kfw166
32. Benowitz NL, Gourlay SG. Cardiovascular toxicity of nicotine: implications for nicotine replacement therapy. *J Am Coll Cardiol.* 1997;29:1422–1431. doi: 10.1016/s0735-1097(97)00079-x
33. Benowitz NL, Burbank AD. Cardiovascular toxicity of nicotine: implications for electronic cigarette use. *Trends Cardiovasc Med.* 2016;26:515–523. doi: 10.1016/j.tcm.2016.03.001
34. Schweitzer KS, Chen SX, Law S, Van Demark M, Poirier C, Justice MJ, Hubbard WC, Kim ES, Lai X, Wang M, et al. Endothelial disruptive proinflammatory effects of nicotine and e-cigarette vapor exposures. *Am J Physiol Lung Cell Mol Physiol.* 2015;309:L175–L187. doi: 10.1152/ajplung.00411.2014
35. Cucina A, Sapienza P, Corvino V, Borrelli V, Randone B, Santoro-D'Angelo L, Cavallaro A. Nicotine induces platelet-derived growth factor release and cytoskeletal alteration in aortic smooth muscle cells. *Surgery.* 2000;127:72–78. doi: 10.1067/msy.2000.102422
36. Klaas FJW, Silja CT, Moritz M, Friedhelm S, Michael R, Klaus D, Kai M, Daniel D. E-cigarettes and cigarettes worsen peripheral and central hemodynamics as well as arterial stiffness: a randomized, double-blinded pilot study. *Vasc Med.* 2018;23:419–425. doi: 10.1177/1358863X18779694
37. Zar T, Graeber C, Perazella MA. Recognition, treatment, and prevention of propylene glycol toxicity. *Semin Dial.* 2007;20:217–219. doi: 10.1111/j.1525-139X.2007.00280.x
38. Varughese S, Teschke K, Brauer M, Chow Y, van Netten C, Kennedy SM. Effects of theatrical smokes and fogs on respiratory health in the entertainment industry. *Am J Ind Med.* 2005;47:411–418. doi: 10.1002/ajim.20151
39. Wieslander G, Norback D, Lindgren T. Experimental exposure to propylene glycol mist in aviation emergency training: acute ocular and respiratory effects. *Occup Environ Med.* 2001;58:649–655. doi: 10.1136/oem.58.10.649
40. Bessac BF, Jordt SE. Breathtaking TRP channels: TRPA1 and TRPV1 in airway chemosensation and reflex control. *Physiology (Bethesda).* 2008;23:360–370. doi: 10.1152/physiol.00026.2008
41. Niedermirtl F, Eberhardt M, Namer B, Leffler A, Nau C, Reeh PW, Kistner K. Etomidate and propylene glycol activate nociceptive TRP ion channels. *Mol Pain.* 2018;14:1744806918811699. doi: 10.1177/1744806918811699
42. Caceres AI, Brackmann M, Elia MD, Bessac BF, del Camino D, D'Amours M, Witek JS, Fanger CM, Chong JA, Hayward NJ, et al. A sensory neuronal ion channel essential for airway inflammation and hyperreactivity in asthma. *Proc Natl Acad Sci U S A.* 2009;106:9099–9104. doi: 10.1073/pnas.0900591106
43. Fagan P, Pokhrel P, Herzog TA, Moolchan ET, Cassel KD, Franke AA, Li X, Pagano I, Trinidad DR, Sakuma KK, et al. Sugar and aldehyde content in flavored electronic cigarette liquids. *Nicotine Tob Res.* 2018;20:985–992. doi: 10.1093/ntr/ntx234
44. Duell AK, McWhirter KJ, Korzun T, Strongin RM, Peyton DH. Sucralose-enhanced degradation of electronic cigarette liquids during vaping. *Chem Res Toxicol.* 2019;32:1241–1249. doi: 10.1021/acs.chemrestox.9b00047
45. Khlystov A, Samburova V. Flavoring compounds dominate toxic aldehyde production during e-cigarette vaping. *Environ Sci Technol.* 2016;50:13080–13085. doi: 10.1021/acs.est.6b05145
46. Haussmann HJ. Use of hazard indices for a theoretical evaluation of cigarette smoke composition. *Chem Res Toxicol.* 2012;25:794–810. doi: 10.1021/tx200536w
47. Farsalinos KE, Kistler KA, Gillman G, Voudris V. Evaluation of electronic cigarette liquids and aerosol for the presence of selected inhalation toxins. *Nicotine Tob Res.* 2015;17:168–174. doi: 10.1093/ntr/ntu176
48. Cummings KJ, Boylstein RJ, Stanton ML, Piacitelli CA, Edwards NT, LeBouf RF, Kreiss K. Respiratory symptoms and lung function abnormalities related to work at a flavouring manufacturing facility. *Occup Environ Med.* 2014;71:549–554. doi: 10.1136/oemed-2013-101927
49. Kreiss K, Gomaa A, Kullman G, Fedan K, Simoes EJ, Enright PL. Clinical bronchiolitis obliterans in workers at a microwave-popcorn plant. *N Engl J Med.* 2002;347:330–338. doi: 10.1056/NEJMoa020300
50. Akpinar-Elci M, Travis WD, Lynch DA, Kreiss K. Bronchiolitis obliterans syndrome in popcorn production plant workers. *Eur Respir J.* 2004;24:298–302. doi: 10.1183/09031936.04.00013903
51. Flake GP, Morgan DL. Pathology of diacetyl and 2,3-pentanedione airway lesions in a rat model of obliterative bronchiolitis. *Toxicology.* 2017;388:40–47. doi: 10.1016/j.tox.2016.10.013
52. Leigh NJ, Lawton RI, Hershberger PA, Goniewicz ML. Flavourings significantly affect inhalation toxicity of aerosol generated from electronic nicotine delivery systems (ENDS). *Tob Control.* 2016;25:ii81–ii87. doi: 10.1136/tobaccocontrol-2016-053205
53. Gerloff J, Sundar IK, Freter R, Sekera ER, Friedman AE, Robinson R, Pagano T, Rahman I. Inflammatory response and barrier dysfunction by different e-cigarette flavoring chemicals identified by gas chromatography-mass

spectrometry in e-liquids and e-vapors on human lung epithelial cells and fibroblasts. *Appl In Vitro Toxicol*. 2017;3:28–40. doi: 10.1089/aivt.2016.0030
54. Muthumalage T, Lamb T, Friedman MR, Rahman I. E-cigarette flavored pods induce inflammation, epithelial barrier dysfunction, and DNA damage in lung epithelial cells and monocytes. *Sci Rep*. 2019;9:19035. doi: 10.1038/s41598-019-51643-6
55. Sherwood CL, Boitano S. Airway epithelial cell exposure to distinct e-cigarette liquid flavorings reveals toxicity thresholds and activation of CFTR by the chocolate flavoring 2,5- dimethypyrazine. *Respir Res*. 2016;17:57. doi: 10.1186/s12931-016-0369-9
56. Fetterman JL, Weisbrod RM, Feng B, Bastin R, Tuttle ST, Holbrook M, Baker G, Robertson RM, Conklin DJ, Bhatnagar A, et al. Flavorings in tobacco products induce endothelial cell dysfunction. *Arterioscler Thromb Vasc Biol*. 2018;38:1607–1615. doi: 10.1161/ATVBAHA.118.311156
57. Erythropel HC, Jabba SV, DeWinter TM, Mendizabal M, Anastas PT, Jordt SE, Zimmerman JB. Formation of flavorant-propylene glycol adducts with novel toxicological properties in chemically unstable e-cigarette liquids. *Nicotine Tob Res*. 2019;21:1248–1258. doi: 10.1093/ntr/nty192
58. Jabba SV, Diaz AN, Erythropel HC, Zimmerman JB, Jordt SE. Chemical adducts of reactive flavor aldehydes formed in e-cigarette liquids are cytotoxic and inhibit mitochondrial function in respiratory epithelial cells. *Nicotine Tob Res*. 2020;22:S25–S34. doi: 10.1093/ntr/ntaa185
59. Olmedo P, Goessler W, Tanda S, Grau-Perez M, Jarmul S, Aherrera A, Chen R, Hilpert M, Cohen JE, Navas-Acien A, et al. Metal concentrations in e-cigarette liquid and aerosol samples: the contribution of metallic coils. *Environ Health Perspect*. 2018;126:027010. doi: 10.1289/EHP2175
60. Na CJ, Jo SH, Kim KH, Sohn JR, Son YS. The transfer characteristics of heavy metals in electronic cigarette liquid. *Environ Res*. 2019;174:152–159. doi: 10.1016/j.envres.2019.04.025
61. Kleinman MT, Arechavala RJ, Herman D, Shi J, Hasen I, Ting A, Dai W, Carreno J, Chavez J, Zhao L, et al. E-cigarette or vaping product use-associated lung injury produced in an animal model from electronic cigarette vapor exposure without tetrahydrocannabinol or vitamin E oil. *J Am Heart Assoc*. 2020;9:e017368. doi: 10.1161/JAHA.120.017368
62. Fowles J, Barreau T, Wu N. Cancer and non-cancer risk concerns from metals in electronic cigarette liquids and aerosols. *Int J Environ Res Public Health*. 2020;17:2146. doi: 10.3390/ijerph17062146
63. Farsalinos KE, Tsiapras D, Kyrzopoulos S, Savvopoulou M, Voudris V. Acute effects of using an electronic nicotine-delivery device (electronic cigarette) on myocardial function: comparison with the effects of regular cigarettes. *BMC Cardiovasc Disord*. 2014;14:78. doi: 10.1186/1471-2261-14-78
64. Vlachopoulos C, Ioakeimidis N, Abdelrasoul M, Terentes-Printzios D, Georgakopoulos C, Pietri P, Stefanadis C, Tousoulis D. Electronic cigarette smoking increases aortic stiffness and blood pressure in young smokers. *J Am Coll Cardiol*. 2016;67:2802–2803. doi: 10.1016/j.jacc.2016.03.569
65. Skotsimara G, Antonopoulos AS, Oikonomou E, Siasos G, Ioakeimidis N, Tsalamandris S, Charalambous G, Galiatsatos N, Vlachopoulos C, Tousoulis D. Cardiovascular effects of electronic cigarettes: a systematic review and meta-analysis. *Eur J Prev Cardiol*. 2019;26:1219–1228. doi: 10.1177/2047487319832975
66. Wang JB, Olgin JE, Nah G, Vittinghoff E, Cataldo JK, Pletcher MJ, Marcus GM. Cigarette and e-cigarette dual use and risk of cardiopulmonary symptoms in the Health eHeart Study. *PLoS One*. 2018;13:e0198681e0198681. doi: 10.1371/journal.pone.0198681
67. Moheimani RS, Bhetraratana M, Peters KM, Yang BK, Yin F, Gornbein J, Araujo JA, Middlekauff HR. Sympathomimetic effects of acute e-cigarette use: role of nicotine and non-nicotine constituents. *J Am Heart Assoc*. 2017;6:e006579. doi: 10.1161/JAHA.117.006579
68. Moheimani RS, Bhetraratana M, Yin F, Peters KM, Gornbein J, Araujo JA, Middlekauff HR. Increased cardiac sympathetic activity and oxidative stress in habitual electronic cigarette users: implications for cardiovascular risk. *JAMA Cardiol*. 2017;2:278–284. doi: 10.1001/jamacardio.2016.5303
69. Ip M, Diamantakos E, Haptonstall K, Choroomi Y, Moheimani RS, Nguyen KH, Tran E, Gornbein J, Middlekauff HR. Tobacco and electronic cigarettes adversely impact ECG indexes of ventricular repolarization: implication for sudden death risk. *Am J Physiol Heart Circ Physiol*. 2020;318:H1176–H1184. doi: 10.1152/ajpheart.00738.2019
70. Chaumont M, de Becker B, Zaher W, Culie A, Deprez G, Melot C, Reye F, Van Antwerpen P, Delporte C, Debbas N, et al. Differential effects of e-cigarette on microvascular endothelial function, arterial stiffness and oxidative stress: a randomized crossover trial. *Sci Rep*. 2018;8:10378. doi: 10.1038/s41598-018-28723-0
71. Carnevale R, Sciarretta S, Violi F, Nocella C, Loffredo L, Perri L, Peruzzi M, Marullo AG, De Falco E, Chimenti I, et al. Acute impact of tobacco vs electronic cigarette smoking on oxidative stress and vascular function. *Chest*. 2016;150:606–612. doi: 10.1016/j.chest.2016.04.012
72. Caporale A, Langham MC, Guo W, Johncola A, Chatterjee S, Wehrli FW. Acute effects of electronic cigarette aerosol inhalation on vascular function detected at quantitative MRI. *Radiology*. 2019;293:97–106. doi: 10.1148/radiol.2019190562
73. 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
74. Franzen KF, Willig J, Cayo Talavera S, Meusel M, Sayk F, Reppel M, Dalhoff K, Mortensen K, Droemann D. E-cigarettes and cigarettes worsen peripheral and central hemodynamics as well as arterial stiffness: a randomized, double-blinded pilot study. *Vasc Med*. 2018;23:419–425. doi: 10.1177/1358863X18779694
75. Rader F, Rashid M, Nguyen TT, Luong E, Kim A, Kim E, Elashoff R, Davoren K, Moy N, Nafeh F, et al. E-cigarette use and subclinical cardiac effects. *Circ Res*. 2020;127:1566–1567. doi: 10.1161/CIRCRESAHA.120.316683
76. Fetterman JL, Keith RJ, Palmisano JN, McGlasson KL, Weisbrod RM, Majid S, Bastin R, Stathos MM, Stokes AC, Robertson RM, et al. Alterations in vascular function associated with the use of combustible and electronic cigarettes. *J Am Heart Assoc*. 2020;9:e014570. doi: 10.1161/JAHA.119.014570
77. Farsalinos K, Cibella F, Caponnetto P, Campagna D, Morjaria JB, Battaglia E, Caruso M, Russo C, Polosa R. Effect of continuous smoking reduction and abstinence on blood pressure and heart rate in smokers switching to electronic cigarettes. *Intern Emerg Med*. 2016;11:85–94. doi: 10.1007/s11739-015-1361-y
78. Polosa R, Morjaria JB, Caponnetto P, Battaglia E, Russo C, Ciampi C, Adams G, Bruno CM. Blood pressure control in smokers with arterial hypertension who switched to electronic cigarettes. *Int J Environ Res Public Health*. 2016;13:1123. doi: 10.3390/ijerph13111123
79. George J, Hussain M, Vadiveloo T, Ireland S, Hopkinson P, Struthers AD, Donnan PT, Khan F, Lang CC. Cardiovascular effects of switching from tobacco cigarettes to electronic cigarettes. *J Am Coll Cardiol*. 2019;74:3112–3120. doi: 10.1016/j.jacc.2019.09.067
80. Csordas A, Bernhard D. The biology behind the atherothrombotic effects of cigarette smoke. *Nat Rev Cardiol*. 2013;10:219–230. doi: 10.1038/nrcardio.2013.8
81. Metzen D, M'Pembele R, Zako S, Mourikis P, Helten C, Zikeli D, Ahlbrecht S, Ignatov D, Ayhan A, Huhn R, et al. Platelet reactivity is higher in e-cigarette vaping as compared to traditional smoking. *Int J Cardiol*. 2021;343:146–148. doi: 10.1016/j.ijcard.2021.09.005
82. Ramirez JEM, Karim ZA, Alarabi AB, Hernandez KR, Taleb ZB, Rivera JO, Khasawneh FT, Alshbool FZ. The JUUL e-cigarette elevates the risk of thrombosis and potentiates platelet activation. *J Cardiovasc Pharmacol Ther*. 2020;25:578–586. doi: 10.1177/1074248420941681
83. Qasim H, Karim ZA, Silva-Espinoza JC, Khasawneh FT, Rivera JO, Ellis CC, Bauer SL, Almeida IC, Alshbool FZ. Short-term e-cigarette exposure increases the risk of thrombogenesis and enhances platelet function in mice. *J Am Heart Assoc*. 2018;7:e009264. doi: 10.1161/JAHA.118.009264
84. Loffredo L, Carnevale R, Battaglia S, Marti R, Pizzolo S, Bartimoccia S, Nocella C, Cammisotto V, Sciarretta S, Chimenti I, et al. Impact of chronic use of heat-not-burn cigarettes on oxidative stress, endothelial dysfunction and platelet activation: the SUR-VAPES Chronic Study. *Thorax*. 2021;76:618–620. doi: 10.1136/thoraxjnl-2020-215900
85. Hom S, Chen L, Wang T, Ghebrehiwet B, Yin W, Rubenstein DA. Platelet activation, adhesion, inflammation, and aggregation potential are altered in the presence of electronic cigarette extracts of variable nicotine concentrations. *Platelets*. 2016;27:694–702. doi: 10.3109/09537104.2016.1158403
86. Tarran R, Barr RG, Benowitz NL, Bhatnagar A, Chu HW, Dalton P, Doerschuk CM, Drummond MB, Gold DR, Goniewicz ML, et al. E-cigarettes and cardiopulmonary health. *Function (Oxf)*. 2021;2:zqab004. doi: 10.1093/function/zqab004
87. Haptonstall KP, Choroomi Y, Moheimani R, Nguyen K, Tran E, Lakhani K, Ruedisueli I, Gornbein J, Middlekauff HR. Differential effects of tobacco cigarettes and electronic cigarettes on endothelial function in healthy young people. *Am J Physiol Heart Circ Physiol*. 2020;319:H547–H556. doi: 10.1152/ajpheart.00307.2020
88. Kelesidis T, Tran E, Arastoo S, Lakhani K, Heymans R, Gornbein J, Middlekauff HR. Elevated cellular oxidative stress in circulating immune cells in otherwise healthy young people who use electronic cigarettes in a cross-sectional single-center study: implications for future cardiovascular risk. *J Am Heart Assoc*. 2020;9:e016983. doi: 10.1161/JAHA.120.016983

89. Stokes AC, Xie W, Wilson AE, Yang H, Orimoloye OA, Harlow AF, Fetterman JL, DeFilippis AP, Benjamin EJ, Robertson RM, et al. Association of cigarette and electronic cigarette use patterns with levels of inflammatory and oxidative stress biomarkers among US adults: Population Assessment of Tobacco and Health Study. *Circulation*. 2021;143:869–871. doi: 10.1161/CIRCULATIONAHA.120.051551
90. Gill JS, Shipley MJ, Tsementzis SA, Hornby R, Gill SK, Hitchcock ER, Beevers DG. Cigarette smoking: a risk factor for hemorrhagic and nonhemorrhagic stroke. *Arch Intern Med*. 1989;149:2053–2057. doi: 10.1001/archinte.149.9.2053
91. Anstey KJ, von Sanden C, Salim A, O'Kearney R. Smoking as a risk factor for dementia and cognitive decline: a meta-analysis of prospective studies. *Am J Epidemiol*. 2007;166:367–378. doi: 10.1093/aje/kwm116
92. Hossain M, Sathe T, Fazio V, Mazzone P, Weksler B, Janigro D, Rapp E, Cucullo L. Tobacco smoke: a critical etiological factor for vascular impairment at the blood-brain barrier. *Brain Res*. 2009;1287:192–205. doi: 10.1016/j.brainres.2009.06.033
93. Naik P, Fofaria N, Prasad S, Sajja RK, Weksler B, Couraud PO, Romero IA, Cucullo L. Oxidative and pro-inflammatory impact of regular and denicotinized cigarettes on blood brain barrier endothelial cells: is smoking reduced or nicotine-free products really safe? *BMC Neurosci*. 2014;15:51. doi: 10.1186/1471-2202-15-51
94. Will JC, Galuska DA, Ford ES, Mokdad A, Calle EE. Cigarette smoking and diabetes mellitus: evidence of a positive association from a large prospective cohort study. *Int J Epidemiol*. 2001;30:540–546. doi: 10.1093/ije/30.3.540
95. Heldt NA, Reichenbach N, McGary HM, Persidsky Y. Effects of electronic nicotine delivery systems and cigarettes on systemic circulation and blood-brain barrier: implications for cognitive decline. *Am J Pathol*. 2021;191:243–255. doi: 10.1016/j.ajpath.2020.11.007
96. Arvin MC, Jin XT, Yan Y, Wang Y, Ramsey MD, Kim VJ, Beckley NA, Henry BA, Drenan RM. Chronic nicotine exposure alters the neurophysiology of habenulo-interpeduncular circuitry. *J Neurosci*. 2019;39:4268–4281. doi: 10.1523/JNEUROSCI.2816-18.2019
97. Alasmari F, Crotty Alexander LE, Hammad AM, Horton A, Alhaddad H, Schiefer IT, Shin J, Moshensky A, Sari Y. E-cigarette aerosols containing nicotine modulate nicotinic acetylcholine receptors and astroglial glutamate transporters in mesocorticolimbic brain regions of chronically exposed mice. *Chem Biol Interact*. 2021;333:109308. doi: 10.1016/j.cbi.2020.109308
98. Cojocaru IM, Cojocaru M, Sapira V, Ionescu A. Evaluation of oxidative stress in patients with acute ischemic stroke. *Rom J Intern Med*. 2013;51:97–106.
99. Kaisar MA, Villalba H, Prasad S, Liles T, Sifat AE, Sajja RK, Abbruscato TJ, Cucullo L. Offsetting the impact of smoking and e-cigarette vaping on the cerebrovascular system and stroke injury: is metformin a viable countermeasure? *Redox Biol*. 2017;13:353–362. doi: 10.1016/j.redox.2017.06.006
100. Li C, Sun H, Arrick DM, Mayhan WG. Chronic nicotine exposure exacerbates transient focal cerebral ischemia-induced brain injury. *J Appl Physiol (1985)*. 2016;120:328–333. doi: 10.1152/japplphysiol.00663.2015
101. Paulson JR, Yang T, Selvaraj PK, Mdzinarishvili A, Van der Schyf CJ, Klein J, Bickel U, Abbruscato TJ. Nicotine exacerbates brain edema during in vitro and in vivo focal ischemic conditions. *J Pharmacol Exp Ther*. 2010;332:371–379. doi: 10.1124/jpet.109.157776
102. Sifat AE, Vaidya B, Kaisar MA, Cucullo L, Abbruscato TJ. Nicotine and electronic cigarette (E-Cig) exposure decreases brain glucose utilization in ischemic stroke. *J Neurochem*. 2018;147:204–221. doi: 10.1111/jnc.14561
103. Dwyer JB, Broide RS, Leslie FM. Nicotine and brain development. *Birth Defects Res C Embryo Today*. 2008;84:30–44. doi: 10.1002/bdrc.20118
104. Broide RS, Leslie FM. The alpha7 nicotinic acetylcholine receptor in neuronal plasticity. *Mol Neurobiol*. 1999;20:1–16. doi: 10.1007/BF02741361
105. Dani JA, Bertrand D. Nicotinic acetylcholine receptors and nicotinic cholinergic mechanisms of the central nervous system. *Annu Rev Pharmacol Toxicol*. 2007;47:699–729. doi: 10.1146/annurev.pharmtox.47.120505.105214
106. Alhaddad H, Wong W, Sari AT, Alexander LEC, Sari Y. Effects of 3-month exposure to e-cigarette aerosols on glutamatergic receptors and transporters in mesolimbic brain regions of female C57BL/6 mice. *Toxics*. 2020;8:95. doi: 10.3390/toxics8040095 PMID - 33137879
107. Hawkins BT, Abbruscato TJ, Egleton RD, Brown RC, Huber JD, Campos CR, Davis TP. Nicotine increases in vivo blood-brain barrier permeability and alters cerebral microvascular tight junction protein distribution. *Brain Res*. 2004;1027:48–58. doi: 10.1016/j.brainres.2004.08.043
108. Lilienberg G, Venge P. Platelet adhesion in patients prone to arterial and venous thrombosis: the impact of gender, smoking and heredity. *Scand J Clin Lab Invest*. 1998;58:279–286. doi: 10.1080/00365519850186454
109. Lindenblatt N, Platz U, Hameister J, Klar E, Menger MD, Vollmar B. Distinct effects of acute and chronic nicotine application on microvascular thrombus formation and endothelial function in male and female mice. *Langenbecks Arch Surg*. 2007;392:285–295. doi: 10.1007/s00423-007-0173-6
110. Shufelt CL, Bairey Merz CN. Contraceptive hormone use and cardiovascular disease. *J Am Coll Cardiol*. 2009;53:221–231. doi: 10.1016/j.jacc.2008.09.042
111. Rune GM, Frotscher M. Neurosteroid synthesis in the hippocampus: role in synaptic plasticity. *Neuroscience*. 2005;136:833–842. doi: 10.1016/j.neuroscience.2005.03.056
112. Raval AP. Nicotine addiction causes unique detrimental effects on women's brains. *J Addict Dis*. 2011;30:149–158. doi: 10.1080/1055088 7.2011.554782
113. McCullough LD, Hurn PD. Estrogen and ischemic neuroprotection: an integrated view. *Trends Endocrinol Metab*. 2003;14:228–235. doi: 10.1016/s1043-2760(03)00076-6
114. Murphy S, McCullough L, Littleton-Kearney M, Hurn P. Estrogen and selective estrogen receptor modulators: neuroprotection in the Women's Health Initiative era. *Endocrine*. 2003;21:17–26. doi: 10.1385/endo:21:1:17
115. Wise PM. Estrogens and neuroprotection. *Trends Endocrinol Metab*. 2002;13:229–230. doi: 10.1016/s1043-2760(02)00611-2
116. Raval AP, Dave KR, Saul I, Gonzalez GJ, Diaz F. Synergistic inhibitory effect of nicotine plus oral contraceptive on mitochondrial complex-IV is mediated by estrogen receptor beta in female rats. *J Neurochem*. 2012;121:157–167. doi: 10.1111/j.1471-4159.2012.07661.x
117. Wang MP, Ho SY, Leung LT, Lam TH. Electronic cigarette use and respiratory symptoms in Chinese adolescents in Hong Kong. *JAMA Pediatr*. 2016;170:89–91. doi: 10.1001/jamapediatrics.2015.3024
118. McConnell R, Barrington-Trimis JL, Wang K, Urman R, Hong H, Unger J, Samet J, Leventhal A, Berhane K. Electronic cigarette use and respiratory symptoms in adolescents. *Am J Respir Crit Care Med*. 2017;195:1043–1049. doi: 10.1164/rccm.201604-0804OC
119. Hedman L, Backman H, Stridsman C, Bosson JA, Lundbäck M, Lindberg A, Rönmark E, Ekerljung L. Association of electronic cigarette use with smoking habits, demographic factors, and respiratory symptoms. *JAMA Netw Open*. 2018;1:e180789. doi: 10.1001/jamanetworkopen.2018.0789
120. Schneller LM, Quiñones Tavárez Z, Goniewicz ML, Xie Z, McIntosh S, Rahman I, O'Connor RJ, Ossip DJ, Li D. Cross-sectional association between exclusive and concurrent use of cigarettes, ENDS, and cigars, the three most popular tobacco products, and wheezing symptoms among U.S. adults. *Nicotine Tob Res*. 2020;22:S76–S84. doi: 10.1093/ntr/ntaa199
121. Cherian C, Buta E, Simon P, Gueorguieva R, Krishnan-Sarin S. Association of vaping and respiratory health among youth in the Population Assessment of Tobacco and Health (PATH) Study Wave 3. *Int J Environ Res Public Health*. 2021;18:8208. doi: 10.3390/ijerph18158208
122. Choi K, Bernat D. E-cigarette use among Florida youth with and without asthma. *Am J Prev Med*. 2016;51:446–453. doi: 10.1016/j.amepre.2016.03.010
123. Schweitzer RJ, Wills TA, Tam E, Pagano I, Choi K. E-cigarette use and asthma in a multiethnic sample of adolescents. *Prev Med*. 2017;105:226–231. doi: 10.1016/j.ypmed.2017.09.023
124. Hua M, Alfi M, Talbot P. Health-related effects reported by electronic cigarette users in online forums. *J Med Internet Res*. 2013;15:e59. doi: 10.2196/jmir.2324
125. 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
126. Ferrari M, Zanasi A, Nardi E, Morselli Labate AM, Ceriana P, Balestrino A, Pisani L, Corcione N, Nava S. Short-term effects of a nicotine-free e-cigarette compared to a traditional cigarette in smokers and non-smokers. *BMC Pulm Med*. 2015;15:120. doi: 10.1186/s12890-015-0106-z
127. Meo SA, Ansary MA, Barayan FR, Almusallam AS, Almehaid AM, Alarifi NS, Alsohaibani TA, Zia I. Electronic cigarettes: impact on lung function and fractional exhaled nitric oxide among healthy adults. *Am J Mens Health*. 2019;13:1557988318806073. doi: 10.1177/1557988318806073
128. Flouris AD, Chorti MS, Poulianiti KP, Jamurtas AZ, Kostikas K, Tzatzarakis MN, Wallace Hayes A, Tsatsakis AM, Koutedakis Y. Acute impact of active and passive electronic cigarette smoking on serum cotinine and lung function. *Inhal Toxicol*. 2013;25:91–101. doi: 10.3109/08958378.2012.758197
129. Staudt MR, Salit J, Kaner RJ, Hollmann C, Crystal RG. Altered lung biology of healthy never smokers following acute inhalation of E-cigarettes. *Respir Res*. 2018;19:78. doi: 10.1186/s12931-018-0778-z
130. Boulay M, Henry C, Bossé Y, Boulet LP, Morissette MC. Acute effects of nicotine-free and flavour-free electronic cigarette use on lung functions in healthy and asthmatic individuals. *Respir Res*. 2017;18:33. doi: 10.1186/s12931-017-0518-9
131. Veldheer S, Yingst J, Midya V, Hummer B, Lester C, Krebs N, Hrabovsky S, Wilhelm A, Liao J, Yen MS, et al. Pulmonary and other health effects of

electronic cigarette use among adult smokers participating in a randomized controlled smoking reduction trial. *Addict Behav*. 2019;91:95–101. doi: 10.1016/j.addbeh.2018.10.041
132. Lappas AS, Tzortzi AS, Konstantinidi EM, Teloniatis SI, Tzavara CK, Gennimata SA, Koulouris NG, Behrakis PK. Short-term respiratory effects of e-cigarettes in healthy individuals and smokers with asthma. *Respirology*. 2018;23:291–297. doi: 10.1111/resp.13180
133. Vardavas CI, Anagnostopoulos N, Kougias M, Evangelopoulou V, Connolly GN, Behrakis PK. Short-term pulmonary effects of using an electronic cigarette: impact on respiratory flow resistance, impedance, and exhaled nitric oxide. *Chest*. 2012;141:1400–1406. doi: 10.1378/chest.11-2443
134. Malinovschi A, Janson C, Holmkvist T, Norbäck D, Meriläinen P, Högman M. Effect of smoking on exhaled nitric oxide and flow-independent nitric oxide exchange parameters. *Eur Respir J*. 2006;28:339–345. doi: 10.1183/09031936.06.00113705
135. Thota D, Latham E. Case report of electronic cigarettes possibly associated with eosinophilic pneumonitis in a previously healthy active-duty sailor. *J Emerg Med*. 2014;47:15–17. doi: 10.1016/j.jemermed.2013.09.034
136. Arter ZL, Wiggins A, Hudspath C, Kisling A, Hostler DC, Hostler JM. Acute eosinophilic pneumonia following electronic cigarette use. *Respir Med Case Rep*. 2019;27:100825. doi: 10.1016/j.rmcr.2019.100825
137. Sommerfeld CG, Weiner DJ, Nowalk A, Larkin A. Hypersensitivity pneumonitis and acute respiratory distress syndrome from e-cigarette use. *Pediatrics*. 2018;141:e20163927. doi: 10.1542/peds.2016-3927
138. Khan MS, Khateeb F, Akhtar J, Khan Z, Lal A, Kholodovych V, Hammersley J. Organizing pneumonia related to electronic cigarette use: a case report and review of literature. *Clin Respir J*. 2018;12:1295–1299. doi: 10.1111/crj.12775
139. Agustin M, Yamamoto M, Cabrera F, Eusebio R. Diffuse alveolar hemorrhage induced by vaping. *Case Rep Pulmonol*. 2018;2018:9724530. doi: 10.1155/2018/9724530
140. Flower M, Nandakumar L, Singh M, Wyld D, Windsor M, Fielding D. Respiratory bronchiolitis-associated interstitial lung disease secondary to electronic nicotine delivery system use confirmed with open lung biopsy. *Respirol Case Rep*. 2017;5:e00230. doi: 10.1002/rcr2.230
141. He T, Oks M, Esposito M, Steinberg H, Makaryus M. "Tree-in-bloom": severe acute lung injury induced by vaping cannabis oil. *Ann Am Thorac Soc*. 2017;14:468–470. doi: 10.1513/AnnalsATS.201612-974LE
142. Klager S, Vallarino J, MacNaughton P, Christiani DC, Lu Q, Allen JG. Flavoring chemicals and aldehydes in e-cigarette emissions. *Environ Sci Technol*. 2017;51:10806–10813. doi: 10.1021/acs.est.7b02205
143. Hubbs AF, Cumpston AM, Goldsmith WT, Battelli LA, Kashon ML, Jackson MC, Frazer DG, Fedan JS, Goravanahally MP, Castranova V, et al. Respiratory and olfactory cytotoxicity of inhaled 2,3-pentanedione in Sprague-Dawley rats. *Am J Pathol*. 2012;181:829–844. doi: 10.1016/j.ajpath.2012.05.021
144. Allen JG, Flanigan SS, LeBlanc M, Vallarino J, MacNaughton P, Stewart JH, Christiani DC. Flavoring chemicals in e-cigarettes: diacetyl, 2,3-pentanedione, and acetoin in a sample of 51 products, including fruit-, candy-, and cocktail-flavored e-cigarettes. *Environ Health Perspect*. 2016;124:733–739. doi: 10.1289/ehp.1510185
145. Sassano MF, Davis ES, Keating JE, Zorn BT, Kochar TK, Wolfgang MC, Glish GL, Tarran R. Evaluation of e-liquid toxicity using an open-source high-throughput screening assay. *PLoS Biol*. 2018;16:e2003904. doi: 10.1371/journal.pbio.2003904
146. Carter T, Tucker D, Kilic A, Papadimos TJ, Barlow A, Berry E. Life-threatening vesicular bronchial injury requiring veno-venous extracorporeal membrane oxygenation rescue in an electronic nicotine delivery system user. *Clin Pract Cases Emerg Med*. 2017;1:212–217. doi: 10.5811/cpcem.2017.3.33171
147. Ghosh A, Coakley RC, Mascenik T, Rowell TR, Davis ES, Rogers K, Webster MJ, Dang H, Herring LE, Sassano MF, et al. Chronic e-cigarette exposure alters the human bronchial epithelial proteome. *Am J Respir Crit Care Med*. 2018;198:67–76. doi: 10.1164/rccm.201710-2033OC
148. Reidel B, Radicioni G, Clapp PW, Ford AA, Abdelwahab S, Rebuli ME, Haridass P, Alexis NE, Jaspers I, Kesimer M. E-cigarette use causes a unique innate immune response in the lung, involving increased neutrophilic activation and altered mucin secretion. *Am J Respir Crit Care Med*. 2018;197:492–501. doi: 10.1164/rccm.201708-1590OC
149. Kesimer M, Ford AA, Ceppe A, Radicioni G, Cao R, Davis CW, Doerschuk CM, Alexis NE, Anderson WH, Henderson AG, et al. Airway mucin concentration as a marker of chronic bronchitis. *N Engl J Med*. 2017;377:911–922. doi: 10.1056/NEJMoa1701632
150. Ghosh A, Coakley RD, Ghio AJ, Muhlebach MS, Esther CR Jr, Alexis NE, Tarran R. Chronic e-cigarette use increases neutrophil elastase and matrix metalloprotease levels in the lung. *Am J Respir Crit Care Med*. 2019;200:1392–1401. doi: 10.1164/rccm.201903-0615OC
151. Weitz JI, Crowley KA, Landman SL, Lipman BI, Yu J. Increased neutrophil elastase activity in cigarette smokers. *Ann Intern Med*. 1987;107:680–682. doi: 10.7326/0003-4819-107-5-680
152. Shapiro SD, Goldstein NM, Houghton AM, Kobayashi DK, Kelley D, Belaaouaj A. Neutrophil elastase contributes to cigarette smoke-induced emphysema in mice. *Am J Pathol*. 2003;163:2329–2335. doi: 10.1016/S0002-9440(10)63589-4
153. Mason SD, Joyce JA. Proteolytic networks in cancer. *Trends Cell Biol*. 2011;21:228–237. doi: 10.1016/j.tcb.2010.12.002
154. Law SM, Gray RD. Neutrophil extracellular traps and the dysfunctional innate immune response of cystic fibrosis lung disease: a review. *J Inflamm (Lond)*. 2017;14:29. doi: 10.1186/s12950-017-0176-1
155. Chaumont M, van de Borne P, Bernard A, Van Muylem A, Deprez G, Ullmo J, Starczewska E, Briki R, de Hemptinne Q, Zaher W, et al. Fourth generation e-cigarette vaping induces transient lung inflammation and gas exchange disturbances: results from two randomized clinical trials. *Am J Physiol Lung Cell Mol Physiol*. 2019;316:L705–L719. doi: 10.1152/ajplung.00492.2018
156. Carson JL, Zhou L, Brighton L, Mills KH, Zhou H, Jaspers I, Hazucha M. Temporal structure/function variation in cultured differentiated human nasal epithelium associated with acute single exposure to tobacco smoke or e-cigarette vapor. *Inhal Toxicol*. 2017;29:137–144. doi: 10.1080/08958378.2017.1318985
157. Dicpinigaitis PV, Lee Chang A, Dicpinigaitis AJ, Negassa A. Effect of e-cigarette use on cough reflex sensitivity. *Chest*. 2016;149:161–165. doi: 10.1378/chest.15-0817
158. Martin EM, Clapp PW, Rebuli ME, Pawlak EA, Glista-Baker E, Benowitz NL, Fry RC, Jaspers I. E-cigarette use results in suppression of immune and inflammatory-response genes in nasal epithelial cells similar to cigarette smoke. *Am J Physiol Lung Cell Mol Physiol*. 2016;311:L135–L144. doi: 10.1152/ajplung.00170.2016
159. Sharma P, Sheikh T, Williams C. Electronic vaping product use among adolescents in the era of the COVID-19 pandemic: an updated scientific review for clinicians. *WMJ*. 2021;120:205–208.
160. England LJ, Tong VT, Koblitz A, Kish-Doto J, Lynch MM, Southwell BG. Perceptions of emerging tobacco products and nicotine replacement therapy among pregnant women and women planning a pregnancy. *Prev Med Rep*. 2016;4:481–485. doi: 10.1016/j.pmedr.2016.09.002
161. Wagner NJ, Camerota M, Propper C. Prevalence and perceptions of electronic cigarette use during pregnancy. *Matern Child Health J*. 2017;21:1655–1661. doi: 10.1007/s10995-016-2257-9
162. Orzabal MR, Lunde-Young ER, Ramirez JI, Howe SYF, Naik VD, Lee J, Heaps CL, Threadgill DW, Ramadoss J. Chronic exposure to e-cig aerosols during early development causes vascular dysfunction and offspring growth deficits. *Transl Res*. 2019;207:70–82. doi: 10.1016/j.trsl.2019.01.001
163. England LJ, Aagaard K, Bloch M, Conway K, Cosgrove K, Grana R, Gould TJ, Hatsukami D, Jensen F, Kandel D, et al. Developmental toxicity of nicotine: a transdisciplinary synthesis and implications for emerging tobacco products. *Neurosci Biobehav Rev*. 2017;72:176–189. doi: 10.1016/j.neubiorev.2016.11.013
164. Church JS, Chace-Donahue F, Blum JL, Ratner JR, Zelikoff JT, Schwartzer JJ. Neuroinflammatory and behavioral outcomes measured in adult offspring of mice exposed prenatally to e-cigarette aerosols. *Environ Health Perspect*. 2020;128:47006. doi: 10.1289/EHP6067
165. Tao H, Rui C, Zheng J, Tang J, Wu L, Shi A, Chen N, He R, Wu C, Li J, et al. Angiotensin II-mediated vascular changes in aged offspring rats exposed to perinatal nicotine. *Peptides*. 2013;44:111–119. doi: 10.1016/j.peptides.2013.02.019
166. Solingapuram Sai KK, Zuo Y, Rose JE, Garg PK, Garg S, Nazih R, Mintz A, Mukhin AG. Rapid brain nicotine uptake from electronic cigarettes. *J Nucl Med*. 2020;61:928–930. doi: 10.2967/jnumed.119.230748
167. Baldassarri SR, Hillmer AT, Anderson JM, Jatlow P, Nabulsi N, Labaree D, Cosgrove KP, O'Malley SS, Eissenberg T, Krishnan-Sarin S, et al. Use of electronic cigarettes leads to significant beta2-nicotinic acetylcholine receptor occupancy: evidence from a PET imaging study. *Nicotine Tob Res*. 2018;20:425–433. doi: 10.1093/ntr/ntx091
168. Glasser AM, Collins L, Pearson JL, Abudayyeh H, Niaura RS, Abrams DB, Villanti AC. Overview of electronic nicotine delivery systems: a systematic review. *Am J Prev Med*. 2017;52:e33–e66. doi: 10.1016/j.amepre.2016.10.036
169. Hiler M, Breland A, Spindle T, Maloney S, Lipato T, Karaoghlanian N, Shihadeh A, Lopez A, Ramôa C, Eissenberg T. Electronic cigarette user

plasma nicotine concentration, puff topography, heart rate, and subjective effects: influence of liquid nicotine concentration and user experience. *Exp Clin Psychopharmacol*. 2017;25:380–392. doi: 10.1037/pha0000140
170. Vansickel AR, Eissenberg T. Electronic cigarettes: effective nicotine delivery after acute administration. *Nicotine Tob Res*. 2013;15:267–270. doi: 10.1093/ntr/ntr316
171. Farsalinos KE, Spyrou A, Tsimopoulou K, Stefopoulos C, Romagna G, Voudris V. Nicotine absorption from electronic cigarette use: comparison between first and new-generation devices. *Sci Rep*. 2014;4:4133. doi: 10.1038/srep04133
172. Tucker MR, Laugesen M, Bullen C, Grace RC. Predicting short-term uptake of electronic cigarettes: effects of nicotine, subjective effects, and simulated demand. *Nicotine Tob Res*. 2018;20:1265–1271. doi: 10.1093/ntr/ntx269
173. Eversole A, Maloney S, Talih S, Salman R, Karaghlanian N, Lipato T, Eissenberg T, Breland A. Variable voltage, tank-style ENDS do not always deliver nicotine. *Tob Regul Sci*. 2020;6:416–422. doi: 10.18001/trs.6.6.5
174. Bartschat S, Mercer-Chalmers-Bender K, Beike J, Rothschild MA, Jübner M. Not only smoking is deadly: fatal ingestion of e-juice: a case report. *Int J Legal Med*. 2015;129:481–486. doi: 10.1007/s00414-014-1086-x
175. Hua M, Talbot P. Potential health effects of electronic cigarettes: a systematic review of case reports. *Prev Med Rep*. 2016;4:169–178. doi: 10.1016/j.pmedr.2016.06.002
176. Bradford LE, Rebuli ME, Ring BJ, Jaspers I, Clement KC, Loughlin CE. Danger in the vapor? ECMO for adolescents with status asthmaticus after vaping. *J Asthma*. 2020;57:1168–1172. doi: 10.1080/02770903.2019.1643361
177. Bonilla A, Blair AJ, Alamro SM, Ward RA, Feldman MB, Dutko RA, Karagounis TK, Johnson AL, Folch EE, Vyas JM. Recurrent spontaneous pneumothoraces and vaping in an 18-year-old man: a case report and review of the literature. *J Med Case Rep*. 2019;13:283. doi: 10.1186/s13256-019-2215-4
178. Werner AK, Koumans EH, Chatham-Stephens K, Salvatore PP, Armatas C, Byers P, Clark CR, Ghinai I, Holzbauer SM, Navarette KA, et al; Lung Injury Response Mortality Working Group. Hospitalizations and deaths associated with EVALI. *N Engl J Med*. 2020;382:1589–1598. doi: 10.1056/NEJMoa1915314
179. US Centers for Disease Control and Prevention. Outbreak of lung injury associated with the use of e-cigarette, or vaping, products. April 29 2021. Accessed November 1, 2021. https://cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html
180. Doukas SG, Kavali L, Menon RS, Izotov BN, Bukhari A. E-cigarette or vaping induced lung injury: a case series and literature review. *Toxicol Rep*. 2020;7:1381–1386. doi: 10.1016/j.toxrep.2020.09.010
181. Blount BC, Karwowski MP, Shields PG, Morel-Espinosa M, Valentin-Blasini L, Gardner M, Braselton M, Brosius CR, Caron KT, Chambers D, et al; Lung Injury Response Laboratory Working Group. Vitamin E acetate in bronchoalveolar-lavage fluid associated with EVALI. *N Engl J Med*. 2020;382:697–705. doi: 10.1056/NEJMoa1916433
182. Layden JE, Ghinai I, Pray I, Kimball A, Layer M, Tenforde MW, Navon L, Hoots B, Salvatore PP, Elderbrook M, et al. Pulmonary illness related to e-cigarette use in Illinois and Wisconsin: final report. *N Engl J Med*. 2020;382:903–916. doi: 10.1056/NEJMoa1911614
183. Blagev DP, Harris D, Dunn AC, Guidry DW, Grissom CK, Lanspa MJ. Clinical presentation, treatment, and short-term outcomes of lung injury associated with e-cigarettes or vaping: a prospective observational cohort study. *Lancet*. 2019;394:2073–2083. doi: 10.1016/S0140-6736(19)32679-0
184. Kalininskiy A, Bach CT, Nacca NE, Ginsberg G, Marraffa J, Navarette KA, McGraw MD, Croft DP. E-cigarette, or vaping, product use associated lung injury (EVALI): case series and diagnostic approach. *Lancet Respir Med*. 2019;7:1017–1026. doi: 10.1016/S2213-2600(19)30415-1
185. Zou RH, Tiberio PJ, Triantafyllou GA, Lamberty PE, Lynch MJ, Kreit JW, McVerry BJ, Gladwin MT, Morris A, Chiarchiaro J, et al. Clinical characterization of e-cigarette, or vaping, product use-associated lung injury in 36 patients in Pittsburgh, Pennsylvania. *Am J Respir Crit Care Med*. 2020;201:1303–1306. doi: 10.1164/rccm.202001-0079LE
186. Aberegg SK, Cirulis MM, Maddock SD, Freeman A, Keenan LM, Pirozzi CS, Raman SM, Schroeder J, Mann H, Callahan SJ. Clinical, bronchoscopic, and imaging findings of e-cigarette, or vaping, product use-associated lung injury among patients treated at an academic medical center. *JAMA Netw Open*. 2020;3:e2019176. doi: 10.1001/jamanetworkopen.2020.19176
187. Siegel DA, Jatlaoui TC, Koumans EH, Kiernan EA, Layer M, Cates JE, Kimball A, Weissman DN, Petersen EE, Reagan-Steiner S, et al. Interim guidance for health care providers evaluating and caring for patients with suspected e-cigarette, or vaping, product use associated lung injury: United States, October 2019. *MMWR Morb Mortal Wkly Rep*. 2019;68:919–927. doi: 10.15585/mmwr.mm6841e3
188. Schier JG, Meiman JG, Layden J, Mikosz CA, VanFrank B, King BA, Salvatore PP, Weissman DN, Thomas J, Melstrom PC, et al; CDC 2019 Lung Injury Response Group. Severe pulmonary disease associated with electronic-cigarette-product use: interim guidance. *MMWR Morb Mortal Wkly Rep*. 2019;68:787–790. doi: 10.15585/mmwr.mm6836e2
189. Triantafyllou GA, Tiberio PJ, Zou RH, Lynch MJ, Kreit JW, McVerry BJ, Morris A, Rose JJ. Long-term outcomes of EVALI: a 1-year retrospective study. *Lancet Respir Med*. 2021;9:e112–e113. doi: 10.1016/S2213-2600(21)00415-X
190. Kligerman S, Raptis C, Larsen B, Henry TS, Caporale A, Tazelaar H, Schiebler ML, Wehrli FW, Klein JS, Kanne J. Radiologic, pathologic, clinical, and physiologic findings of electronic cigarette or vaping product use-associated lung injury (EVALI): evolving knowledge and remaining questions. *Radiology*. 2020;294:491–505. doi: 10.1148/radiol.2020192585
191. Landman ST, Dhaliwal I, Mackenzie CA, Martinu T, Steele A, Bosma KJ. Life-threatening bronchiolitis related to electronic cigarette use in a Canadian youth. *CMAJ*. Dec 22019;191:E1321–E1331. doi: 10.1503/cmaj.191402
192. Grady D. Facing "certain death," teenager with vaping injury gets double lung transplant. *New York Times*. November 12, 2019. Accessed November 1, 2021. https://nytimes.com/2019/11/12/health/vaping-double-lung-transplant.html
193. Jonas AM, Raj R. Vaping-related acute parenchymal lung injury: a systematic review. *Chest*. 2020;158:1555–1565. doi: 10.1016/j.chest.2020.03.085
194. Evans ME, Twentyman E, Click ES, Goodman AB, Weissman DN, Kiernan E, Hocevar SA, Mikosz CA, Danielson M, Anderson KN, et al; Lung Injury Response Clinical Task Force. Update: interim guidance for health care professionals evaluating and caring for patients with suspected e-cigarette, or vaping, product use-associated lung injury and for reducing the risk for rehospitalization and death following hospital discharge–United States, December 2019. *MMWR Morb Mortal Wkly Rep*. 2020;68:1189–1194. doi: 10.15585/mmwr.mm685152e2
195. Jatlaoui TC, Wiltz JL, Kabbani S, Siegel DA, Koppaka R, Montandon M, Adkins SH, Weissman DN, Koumans EH, O'Hegarty M, et al; Lung Injury Response Clinical Working Group. Update: interim guidance for health care providers for managing patients with suspected e-cigarette, or vaping, product use-associated lung injury–United States, November 2019. *MMWR Morb Mortal Wkly Rep*. 2019;68:1081–1086. doi: 10.15585/mmwr.mm6846e2
196. Christiani DC. Vaping-induced acute lung injury. *N Engl J Med*. 2020;382:960–962. doi: 10.1056/NEJMe1912032
197. Deleted in proof
198. Duffy B, Li L, Lu S, Durocher L, Dittmar M, Delaney-Baldwin E, Panawennage D, LeMaster D, Navarette K, Spink D. Analysis of cannabinoid-containing fluids in illicit vaping cartridges recovered from pulmonary injury patients: identification of vitamin E acetate as a major diluent. *Toxics*. 2020;8:8. doi: 10.3390/toxics8010008
199. Bhat TA, Kalathil SG, Bogner PN, Blount BC, Goniewicz ML, Thanavala YM. An animal model of inhaled vitamin E acetate and EVALI-like lung injury. *N Engl J Med*. 2020;382:1175–1177. doi: 10.1056/NEJMc2000231
200. Crotty Alexander LE, Ware LB, Calfee CS, Callahan SJ, Eissenberg T, Farver C, Goniewicz ML, Jaspers I, Kheradmand F, King TE Jr, et al. E-cigarette or vaping product use-associated lung injury: developing a research agenda: an NIH workshop report. *Am J Respir Crit Care Med*. 2020;202:795–802. doi: 10.1164/rccm.201912-2332WS
201. Hoffman FL. Cancer and smoking habits. In: Adair FE, ed. *Cancer: International Contribution to the Study of Cancer in Honor of James Ewing*. JB Lippincott; 1931:50–67.
202. American Cancer Society. Cancer facts & figures 2013. Accessed January 9, 2021. https://cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2013.html
203. Wynder EL, Graham EA. Tobacco smoking as a possible etiologic factor in bronchiogenic carcinoma: a study of six hundred and eighty-four proved cases. *JAMA*. 1950;143:329–336. doi: 10.1001/jama.1950.02910390001001
204. Wynder EL, Graham EA, Croninger AB. Experimental production of carcinoma with cigarette tar. *Cancer Res*. 1953;13:855–864.
205. Doll R, Hill AB. The mortality of doctors in relation to their smoking habits; a preliminary report. *Br Med J*. 1954;1:1451–1455. doi: 10.1136/bmj.1.4877.1451
206. US Department of Health Education and Welfare. Smoking and health: report of the Advisory Committee to the Surgeon General of the Public

Health Service. 1964. Accessed November 1, 2021. https://govinfo.gov/app/details/GPO-SMOKINGANDHEALTH
207. US Department of Health and Human Services. The health consequences of smoking—50 years of progress: a report of the Surgeon General. 2014. Accessed November 1, 2021. https://cdc.gov/tobacco/sgr/50th-anniversary/index.htm
208. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Population Health and Public Health Practice; Committee on the Review of the Health Effects of Electronic Nicotine Delivery Systems. *Public Health Consequences of E-Cigarettes*. National Academies Press; 2018:774.
209. Olfert IM, DeVallance E, Hoskinson H, Branyan KW, Clayton S, Pitzer CR, Sullivan DP, Breit MJ, Wu Z, Klinkhachorn P, et al. Chronic exposure to electronic cigarettes results in impaired cardiovascular function in mice. *J Appl Physiol (1985)*. 2018;124:573–582. doi: 10.1152/japplphysiol.00713.2017
210. Crotty Alexander LE, Drummond CA, Hepokoski M, Mathew D, Moshensky A, Willeford A, Das S, Singh P, Yong Z, Lee JH, et al. Chronic inhalation of e-cigarette vapor containing nicotine disrupts airway barrier function and induces systemic inflammation and multiorgan fibrosis in mice. *Am J Physiol Regul Integr Comp Physiol*. 2018;314:R834–R847. doi: 10.1152/ajpregu.00270.2017
211. Lee HW, Park SH, Weng MW, Wang HT, Huang WC, Lepor H, Wu XR, Chen LC, Tang MS. E-cigarette smoke damages DNA and reduces repair activity in mouse lung, heart, and bladder as well as in human lung and bladder cells. *Proc Natl Acad Sci USA*. 2018;115:E1560–E1569. doi: 10.1073/pnas.1718185115
212. Boas Z, Gupta P, Moheimani RS, Bhetraratana M, Yin F, Peters KM, Gornbein J, Araujo JA, Czernin J, Middlekauff HR. Activation of the "splenocardiac axis" by electronic and tobacco cigarettes in otherwise healthy young adults. *Physiol Rep*. 2017;5:e13393. doi: 10.14814/phy2.13393
213. 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
214. Bhatta DN, Glantz SA. Association of e-cigarette use with respiratory disease among adults: a longitudinal analysis. *Am J Prev Med*. 2020;58:182–190. doi: 10.1016/j.amepre.2019.07.028
215. Cibella F, Campagna D, Caponnetto P, Amaradio MD, Caruso M, Russo C, Cockcroft DW, Polosa R. Lung function and respiratory symptoms in a randomized smoking cessation trial of electronic cigarettes. *Clin Sci (Lond)*. 2016;130:1929–1937. doi: 10.1042/CS20160268
216. Bowler RP, Hansel NN, Jacobson S, Graham Barr R, Make BJ, Han MK, O'Neal WK, Oelsner EC, Casaburi R, Barjaktarevic I, et al; for COPDGene and SPIROMICS Investigators. Electronic cigarette use in US adults at risk for or with COPD: analysis from two observational cohorts. *J Gen Intern Med*. 2017;32:1315–1322. doi: 10.1007/s11606-017-4150-7
217. Polosa R, Morjaria JB, Prosperini U, Russo C, Pennisi A, Puleo R, Caruso M, Caponnetto P. Health effects in COPD smokers who switch to electronic cigarettes: a retrospective-prospective 3-year follow-up. *Int J Chron Obstruct Pulmon Dis*. 2018;13:2533–2542. doi: 10.2147/COPD.S161138
218. Rosenkilde Laursen K, Bønløkke JH, Bendstrup E, Bilde M, Glasius M, Heitmann Gutzke V, Puthukkadan Moosakutty S, Olin AC, Ravn P, Østergaard K, et al. An RCT of acute health effects in COPD-patients after passive vape exposure from e-cigarettes. *Eur Clin Respir J*. 2020;8:1861580. doi: 10.1080/20018525.2020.1861580
219. 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
220. Chapman DG, Casey DT, Ather JL, Aliyeva M, Daphtary N, Lahue KG, van der Velden JL, Janssen-Heininger YMW, Irvin CG. The effect of flavored e-cigarettes on murine allergic airways disease. *Sci Rep*. 2019;9:13671. doi: 10.1038/s41598-019-50223-y
221. Lim HB, Kim SH. Inhalation of e-cigarette cartridge solution aggravates allergen-induced airway inflammation and hyper-responsiveness in mice. *Toxicol Res*. 2014;30:13–18. doi: 10.5487/TR.2014.30.1.013
222. Traboulsi H, Cherian M, Abou Rjeili M, Preteroti M, Bourbeau J, Smith BM, Eidelman DH, Baglole CJ. Inhalation toxicology of vaping products and implications for pulmonary health. *Int J Mol Sci* . 2020;21:3495. doi: 10.3390/ijms21103495
223. Lin VY, Fain MD, Jackson PL, Berryhill TF, Wilson LS, Mazur M, Barnes SJ, Blalock JE, Raju SV, Rowe SM. Vaporized e-cigarette liquids induce ion transport dysfunction in airway epithelia. *Am J Respir Cell Mol Biol*. 2019;61:162–173. doi: 10.1165/rcmb.2017-0432OC
224. Rab A, Rowe SM, Raju SV, Bebok Z, Matalon S, Collawn JF. Cigarette smoke and CFTR: implications in the pathogenesis of COPD. *Am J Physiol Lung Cell Mol Physiol*. 2013;305:L530–L541. doi: 10.1152/ajplung.00039.2013
225. Chung S, Baumlin N, Dennis JS, Moore R, Salathe SF, Whitney PL, Sabater J, Abraham WM, Kim MD, Salathe M. Electronic cigarette vapor with nicotine causes airway mucociliary dysfunction preferentially via TRPA1 receptors. *Am J Respir Crit Care Med*. 2019;200:1134–1145. doi: 10.1164/rccm.201811-2087OC
226. Tang MS, Wu XR, Lee HW, Xia Y, Deng FM, Moreira AL, Chen LC, Huang WC, Lepor H. Electronic-cigarette smoke induces lung adenocarcinoma and bladder urothelial hyperplasia in mice. *Proc Natl Acad Sci USA*. 2019;116:21727–21731. doi: 10.1073/pnas.1911321116
227. Garcia-Arcos I, Geraghty P, Baumlin N, Campos M, Dabo AJ, Jundi B, Cummins N, Eden E, Grosche A, Salathe M, et al. Chronic electronic cigarette exposure in mice induces features of COPD in a nicotine-dependent manner. *Thorax*. 2016;71:1119–1129. doi: 10.1136/thoraxjnl-2015-208039
228. Reinikovaite V, Rodriguez IE, Karoor V, Rau A, Trinh BB, Deleyiannis FW, Taraseviciene-Stewart L. The effects of electronic cigarette vapour on the lung: direct comparison to tobacco smoke. *Eur Respir J*. 2018;51:1701661. doi: 10.1183/13993003.01661-2017
229. Hartmann-Boyce J, McRobbie H, Butler AR, Lindson N, Bullen C, Begh R, Theodoulou A, Notley C, Rigotti NA, Turner T, et al. Electronic cigarettes for smoking cessation. *Cochrane Database Syst Rev*. 2021;9:CD010216. doi: 10.1002/14651858.CD010216.pub6
230. Bullen C, Howe C, Laugesen M, McRobbie H, Parag V, Williman J, Walker N. Electronic cigarettes for smoking cessation: a randomised controlled trial. *Lancet*. 2013;382:1629–1637. doi: 10.1016/S0140-6736(13)61842-5
231. Lee SM, Tenney R, Wallace AW, Arjomandi M. E-cigarettes versus nicotine patches for perioperative smoking cessation: a pilot randomized trial. *PeerJ*. 2018;6:e5609. doi: 10.7717/peerj.5609
232. Dawkins L, Bauld L, Ford A, Robson D, Hajek P, Parrott S, Best C, Li J, Tyler A, Uny I, et al. A cluster feasibility trial to explore the uptake and use of e-cigarettes versus usual care offered to smokers attending homeless centres in Great Britain. *PLoS One*. 2020;15:e0240968e0240968. doi: 10.1371/journal.pone.0240968
233. Eisenberg MJ, Hébert-Losier A, Windle SB, Greenspoon T, Brandys T, Fülöp T, Nguyen T, Elkouri S, Montigny M, Wilderman I, et al; E3 Investigators. Effect of e-cigarettes plus counseling vs counseling alone on smoking cessation: a randomized clinical trial. *JAMA*. 2020;324:1844–1854. doi: 10.1001/jama.2020.18889
234. Halpern SD, Harhay MO, Saulsgiver K, Brophy C, Troxel AB, Volpp KG. A pragmatic trial of e-cigarettes, incentives, and drugs for smoking cessation. *N Engl J Med*. 2018;378:2302–2310. doi: 10.1056/NEJMsa1715757
235. Holliday R, Preshaw PM, Ryan V, Sniehotta FF, McDonald S, Bauld L, McColl E. A feasibility study with embedded pilot randomised controlled trial and process evaluation of electronic cigarettes for smoking cessation in patients with periodontitis. *Pilot Feasibility Stud*. 2019;5:74. doi: 10.1186/s40814-019-0451-4
236. Lucchiari C, Masiero M, Mazzocco K, Veronesi G, Maisonneuve P, Jemos C, Omodeo Salè E, Spina S, Bertolotti R, Pravettoni G. Benefits of e-cigarettes in smoking reduction and in pulmonary health among chronic smokers undergoing a lung cancer screening program at 6 months. *Addict Behav*. 2020;103:106222. doi: 10.1016/j.addbeh.2019.106222
237. Ioakeimidis N, Vlachopoulos C, Georgakopoulos C, Abdelrasoul M, Skliros N, Katsi V, Vaina S, Tousoulis D. Smoking cessation rates with varenicline and electronic cigarettes in relapsed smokers with a history of acute coronary syndrome. *Eur Heart J*. 2018;39(suppl 1):ehy565.P1234. doi: 10.1093/eurheartj/ehy565.P1234
238. Walker N, Parag V, Verbiest M, Laking G, Laugesen M, Bullen C. Nicotine patches used in combination with e-cigarettes (with and without nicotine) for smoking cessation: a pragmatic, randomised trial. *Lancet Respir Med*. 2020;8:54–64. doi: 10.1016/S2213-2600(19)30269-3
239. Tseng TY, Ostroff JS, Campo A, Gerard M, Kirchner T, Rotrosen J, Shelley D. A randomized trial comparing the effect of nicotine versus placebo electronic cigarettes on smoking reduction among young adult smokers. *Nicotine Tob Res*. 2016;18:1937–1943. doi: 10.1093/ntr/ntw017
240. Harlow AF, Fetterman JL, Ross CS, Robertson RM, Bhatnagar A, Benjamin EJ, Stokes AC. Association of device type, flavours and vaping behaviour with tobacco product transitions among adult electronic cigarette users in the USA. *Tob Control*. 2021;31:e10–e17. doi: 10.1136/tobaccocontrol-2020-055999
241. Pope CA 3rd, Burnett RT, Krewski D, Jerrett M, Shi Y, Calle EE, Thun MJ. Cardiovascular mortality and exposure to airborne fine particulate matter and cigarette smoke: shape of the exposure-response relationship. *Circulation*. 2009;120:941–948. doi: 10.1161/CIRCULATIONAHA.109.857888

242. Cooper M, Case KR, Loukas A, Creamer MR, Perry CL. E-cigarette dual users, exclusive users and perceptions of tobacco products. *Am J Health Behav*. 2016;40:108–116. doi: 10.5993/AJHB.40.1.12
243. Kalkhoran S, Glantz SA. E-cigarettes and smoking cessation in real-world and clinical settings: a systematic review and meta-analysis. *Lancet Respir Med*. 2016;4:116–128. doi: 10.1016/S2213-2600(15)00521-4
244. Weaver SR, Huang J, Pechacek TF, Heath JW, Ashley DL, Eriksen MP. Are electronic nicotine delivery systems helping cigarette smokers quit? Evidence from a prospective cohort study of U.S. adult smokers, 2015-2016. *PLoS One*. 2018;13:e0198047e0198047. doi: 10.1371/journal.pone.0198047
245. Samet JM, Barrington-Trimis J. E-cigarettes and harm reduction: an artificial controversy instead of evidence and a well-framed decision context. *Am J Public Health*. 2021;111:1572–1574. doi: 10.2105/AJPH.2021.306457
246. Balfour DJK, Benowitz NL, Colby SM, Hatsukami DK, Lando HA, Leischow SJ, Lerman C, Mermelstein RJ, Niaura R, Perkins KA, et al. Balancing consideration of the risks and benefits of e-cigarettes. *Am J Public Health*. 2021;111:1661–1672. doi: 10.2105/AJPH.2021.306416
247. Cohen JE, Krishnan-Sarin S, Eissenberg T, Gould TJ, Berman ML, Bhatnagar A, Barnett TE, Soule E, Popova L, Tan ASL, et al. Balancing risks and benefits of e-cigarettes in the real world. *Am J Public Health*. 2022;112:e1–e2. doi: 10.2105/AJPH.2021.306607
248. Bunnell RE, Agaku IT, Arrazola RA, Apelberg BJ, Caraballo RS, Corey CG, Coleman BN, Dube SR, King BA. Intentions to smoke cigarettes among never-smoking US middle and high school electronic cigarette users: National Youth Tobacco Survey, 2011-2013. *Nicotine Tob Res*. 2015;17:228–235. doi: 10.1093/ntr/ntu166
249. Duke JC, Lee YO, Kim AE, Watson KA, Arnold KY, Nonnemaker JM, Porter L. Exposure to electronic cigarette television advertisements among youth and young adults. *Pediatrics*. 2014;134:e29–e36. doi: 10.1542/peds.2014-0269
250. Notley C, Gentry S, Cox S, Dockrell M, Havill M, Attwood AS, Smith M, Munafò MR. Youth use of e-liquid flavours: a systematic review exploring patterns of use of e-liquid flavours and associations with continued vaping, tobacco smoking uptake or cessation. *Addiction*. 2022;117:1258–1272. doi: 10.1111/add.15723
251. Farrelly MC, Duke JC, Crankshaw EC, Eggers ME, Lee YO, Nonnemaker JM, Kim AE, Porter L. A randomized trial of the effect of e-cigarette TV advertisements on intentions to use e-cigarettes. *Am J Prev Med*. 2015;49:686–693. doi: 10.1016/j.amepre.2015.05.010
252. Pu J, Zhang X. Exposure to advertising and perception, interest, and use of e-cigarettes among adolescents: findings from the US National Youth Tobacco Survey. *Perspect Public Health*. 2017;137:322–325. doi: 10.1177/1757913917703151
253. Padon AA, Lochbuehler K, Maloney EK, Cappella JN. A randomized trial of the effect of youth appealing e-cigarette advertising on susceptibility to use e-cigarettes among youth. *Nicotine Tob Res*. 2018;20:954–961. doi: 10.1093/ntr/ntx155
254. 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
255. Kim AE, Arnold KY, Makarenko O. E-cigarette advertising expenditures in the U.S., 2011-2012. *Am J Prev Med*. 2014;46:409–412. doi: 10.1016/j.amepre.2013.11.003
256. Chu KH, Allem JP, Cruz TB, Unger JB. Vaping on Instagram: cloud chasing, hand checks and product placement. *Tob Control*. 2016;26:575–578. doi: 10.1136/tobaccocontrol-2016-053052
257. Laestadius LI, Wahl MM, Pokhrel P, Cho YI. From Apple to Werewolf: a content analysis of marketing for e-liquids on Instagram. *Addict Behav*. 2019;91:119–127. doi: 10.1016/j.addbeh.2018.09.008
258. McCausland K, Maycock B, Leaver T, Jancey J. The messages presented in electronic cigarette-related social media promotions and discussion: scoping review. *J Med Internet Res*. 2019;21:e11953. doi: 10.2196/11953
259. Huang J, Kornfield R, Szczypka G, Emery SL. A cross-sectional examination of marketing of electronic cigarettes on Twitter. *Tob Control*. 2014;23(suppl 3):iii26–iii30. doi: 10.1136/tobaccocontrol-2014-051551
260. Basch CH, Mongiovi J, Hillyer GC, MacDonald Z, Basch CE. YouTube (TM) videos related to e-cigarette safety and related health risks: implications for preventing and emerging epidemic. *Public Health*. 2016;132:57–59. doi: 10.1016/j.puhe.2015.12.003
261. Lee AS, Hart JL, Sears CG, Walker KL, Siu A, Smith C. A picture is worth a thousand words: electronic cigarette content on Instagram and Pinterest. *Tob Prev Cessat*. 2017;3:119. doi: 10.18332/tpc/74709
262. Deyton L, Sharfstein J, Hamburg M. Tobacco product regulation: a public health approach. *N Engl J Med*. 2010;362:1753–1756. doi: 10.1056/NEJMp1004152
263. Public Law 111-31 HR. Accessed October 1, 2020. http://gpo.gov/fdsys/pkg/PLAW-111publ31/pdf/PLAW-111publ31.pdf
264. Ashley DL, Backinger CL. The Food and Drug Administration's regulation of tobacco: the Center for Tobacco Products' Office of Science. *Am J Prev Med*. 2012;43(suppl 3):S255–S263. doi: 10.1016/j.amepre.2012.08.004
265. US Department of Health and Human Services. Food and Drug Administration, Advisory Committee; Tobacco Products Scientific Advisory Committee; establishment: 74 FR 43042. 43042–43043. 2009. https://www.federalregister.gov/documents/2009/08/26/E9-20485/advisory-committee-tobacco-products-scientific-advisory-committee-establishment
266. LeSage MG, Smethells JR, Harris AC. Status and future directions of preclinical behavioral pharmacology in tobacco regulatory science. *Behav Anal (Wash DC)*. 2018;18:252–274. doi: 10.1037/bar0000113
267. US Department of Health and Human Services, 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. *Fed Registr*. 2016;81:28973–29106. https://www.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
268. 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 October 1, 2020. https://fda.gov/media/133880/download
269. Majmundar A, Xue Z, Asare S, Nargis N. Trends in public interest in shopping and point-of-sales of JUUL and Puff Bar 2019-2021 [published online May 11, 2022]. *Tob Control*. doi: 10.1136/tobaccocontrol-2021-056953. https://fda.gov/media/133880/download
270. Jordt SE. Synthetic nicotine has arrived. *Tob Control*. 2023;32:e113–e117. doi: 10.1136/tobaccocontrol-2021-056626
271. US Department of Health and Human Services, Food and Drug Administration. FDA commits to evidence-based actions aimed at saving lives and preventing future generations of smokers. 2021. Accessed April 29, 2021. https://fda.gov/news-events/press-announcements/fda-commits-evidence-based-actions-aimed-saving-lives-and-preventing-future-generations-smokers
272. Dobbs PD, Chadwick G, Dunlap CM, White KA, Cheney MK. Tobacco 21 policies in the U.S.: the importance of local control with federal policy. *Am J Prev Med*. 2021;60:639–647. doi: 10.1016/j.amepre.2020.12.009
273. Krishnan-Sarin S, Jackson A, Morean M, Kong G, Bold KW, Camenga DR, Cavallo DA, Simon P, Wu R. E-cigarette devices used by high-school youth. *Drug Alcohol Depend*. 2019;194:395–400. doi: 10.1016/j.drugalcdep.2018.10.022
274. Freiberg MJ. Federal approaches to the regulation of noncigarette tobacco products. *Am J Prev Med*. 2012;43(suppl 3):S249–S254. doi: 10.1016/j.amepre.2012.07.036
275. Duell AK, Kerber PJ, Luo W, Peyton DH. Determination of (R)-(+)- and (S)-(-)-nicotine chirality in Puff Bar e-liquids by (1)H NMR spectroscopy, polarimetry, and gas chromatography-mass spectrometry. *Chem Res Toxicol*. 2021;34:1718–1720. doi: 10.1021/acs.chemrestox.1c00192
276. Chowdhury A, Gill N, Hsu J. FDA receives authorization to regulate synthetic nicotine. *National Law Review*. Volume XII, Number 75. Accessed March 16, 2022. https://www.natlawreview.com/article/fda-receives-authorization-to-regulate-synthetic-nicotine
277. Simon P, Camenga DR, Morean ME, Kong G, Bold KW, Cavallo DA, Krishnan-Sarin S. Socioeconomic status and adolescent e-cigarette use: the mediating role of e-cigarette advertisement exposure. *Prev Med*. 2018;112:193–198. doi: 10.1016/j.ypmed.2018.04.019
278. US Public Health Service, Office of the Surgeon General. *The Health Consequences of Smoking–50 Years Of Progress: A Report of the Surgeon General*. US Department of Health and Human Services, Public Health Service, Office of the Surgeon General; 2014.
279. Lee JG, Griffin GK, Melvin CL. Tobacco use among sexual minorities in the USA, 1987 to May 2007: a systematic review. *Tob Control*. 2009;18:275–282. doi: 10.1136/tc.2008.028241
280. Morean ME, Butler ER, Bold KW, Kong G, Camenga DR, Cavallo DA, Simon P, O'Malley SS, Krishnan-Sarin S. Preferring more e-cigarette flavors is associated with e-cigarette use frequency among

adolescents but not adults. *PLoS One*. 2018;13:e0204349e0189015. doi: 10.1371/journal.pone.0204349
281. Camenga DR, Morean M, Kong G, Krishnan-Sarin S, Simon P, Bold K. Appeal and use of customizable e-cigarette product features in adolescents. *Tob Regul Sci*. 2018;4:51–60. doi: 10.18001/trs.4.2.5
282. Barrington-Trimis JL, Kong G, Leventhal AM, Liu F, Mayer M, Cruz TB, Krishnan-Sarin S, McConnell R. E-cigarette use and subsequent smoking frequency among adolescents. *Pediatrics*. 2018;142:e20180486. doi: 10.1542/peds.2018-0486
283. Bold KW, Kong G, Camenga DR, Simon P, Cavallo DA, Morean ME, Krishnan-Sarin S. Trajectories of e-cigarette and conventional cigarette use among youth. *Pediatrics*. 2018;141:e20171832. doi: 10.1542/peds.2017-1832
284. Primack BA, Shensa A, Sidani JE, Hoffman BL, Soneji S, Sargent JD, Hoffman RM, Fine MJ. Initiation of traditional cigarette smoking after electronic cigarette use among tobacco-naive US young adults. *Am J Med*. 2018;131:443.e1–443.e9. doi: 10.1016/j.amjmed.2017.11.005
285. Soneji S, Barrington-Trimis JL, Wills TA, Leventhal AM, Unger JB, Gibson LA, Yang J, Primack BA, Andrews JA, Miech RA, et al. Association between initial use of e-cigarettes and subsequent cigarette smoking among adolescents and young adults: a systematic review and meta-analysis. *JAMA Pediatr*. 2017;171:788–797. doi: 10.1001/jamapediatrics.2017.1488
286. Temple JR, Shorey RC, Lu Y, Torres E, Stuart GL, Le VD. E-cigarette use of young adults motivations and associations with combustible cigarette alcohol, marijuana, and other illicit drugs. *Am J Addict*. 2017;26:343–348. doi: 10.1111/ajad.12530
287. O'Conner S, Pelletier H, Bayoumy D, Schwartz RP. Interventions to prevent harms from vaping. May 2019. Accessed November 1, 2021. https://otru.org/wp-content/uploads/2019/05/special_vape_interventions.pdf
288. Kelder SH, Mantey DS, Van Dusen D, Case K, Haas A, Springer AE. A middle school program to prevent e-cigarette use: a pilot study of "CATCH My Breath." *Public Health Rep*. 2020;135:220–229. doi: 10.1177/0033354919900887
289. Stanford University School of Medicine. Tobacco Prevention Toolkit. Accessed January 20, 2021. https://med.stanford.edu/tobaccopreventiontoolkit.html
290. Scholastic and National Institute on Drug Abuse. NIDA and Scholastic - heads up resources. Accessed January 20, 2021. https://archives.nida.nih.gov/about-nida/initiatives/nida-scholastic-heads-up-resources
291. Prokhorov AV, Kelder SH, Shegog R, Murray N, Peters R Jr, Agurcia-Parker C, Cinciripini PM, de Moor C, Conroy JL, Hudmon KS, et al. Impact of A Smoking Prevention Interactive Experience (ASPIRE), an interactive, multimedia smoking prevention and cessation curriculum for culturally diverse high-school students. *Nicotine Tob Res*. 2008;10:1477–1485. doi: 10.1080/14622200802323183
292. Duncan LR, Hieftje KD, Pendergrass TM, Sawyer BG, Fiellin LE. Preliminary investigation of a videogame prototype for cigarette and marijuana prevention in adolescents. *Subst Abus*. 2018;39:275–279. doi: 10.1080/08897077.2018.1437862
293. Graham AL, Zhao K, Papandonatos GD, Erar B, Wang X, Amato MS, Cha S, Cohn AM, Pearson JL. A prospective examination of online social network dynamics and smoking cessation. *PLoS One*. 2017;12:e0183655e0183655. doi: 10.1371/journal.pone.0183655
294. Graham AL, Jacobs MA, Amato MS, Cha S, Bottcher MM, Papandonatos GD. Effectiveness of a quit vaping text message program in promoting abstinence among young adult e-cigarette users: protocol for a randomized controlled trial. *JMIR Res Protoc*. 2020;9:e18327. doi: 10.2196/18327
295. Noar SM, Rohde JA, Prentice-Dunn H, Kresovich A, Hall MG, Brewer NT. Evaluating the actual and perceived effectiveness of e-cigarette prevention advertisements among adolescents. *Addict Behav*. 2020;109:106473. doi: 10.1016/j.addbeh.2020.106473
296. Kong G, Ells DM, Camenga DR, Krishnan-Sarin S. Text messaging-based smoking cessation intervention: a narrative review. *Addict Behav*. 2014;39:907–917. doi: 10.1016/j.addbeh.2013.11.024
297. Krishnan-Sarin S, Cavallo DA, Cooney JL, Schepis TS, Kong G, Liss TB, Liss AK, McMahon TJ, Nich C, Babuscio T, et al. An exploratory randomized controlled trial of a novel high-school-based smoking cessation intervention for adolescent smokers using abstinence-contingent incentives and cognitive behavioral therapy. *Drug Alcohol Depend*. 2013;132:346–351. doi: 10.1016/j.drugalcdep.2013.03.002
298. Morean ME, Kong G, Camenga DR, Cavallo DA, Carroll KM, Pittman B, Krishnan-Sarin S. Contingency management improves smoking cessation treatment outcomes among highly impulsive adolescent smokers relative to cognitive behavioral therapy. *Addict Behav*. 2015;42:86–90. doi: 10.1016/j.addbeh.2014.11.009
299. American Academy of Pediatrics. Youth tobacco cessation. Accessed March 5 2022. https://aap.org/en/patient-care/tobacco-control-and-prevention/youth-tobacco-cessation/
300. American Heart Association. Nearly $17 million invested in research to fast-track studies on health impacts of e-cigarettes and nicotine on youth. Accessed March 5, 2022. https://newsroom.heart.org/news/nearly-17-million-invested-in-research-to-fast-track-studies-on-health-impacts-of-e-cigarettes-and-nicotine-on-youth
301. 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