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Position Statement

Smoking and diabetes interplay: A comprehensive review and joint statement

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ABSTRACT

Evidence shows that smoking increases the risk of pre-diabetes and diabetes in the general population. Among persons with diabetes, smoking has been found to increase the risk of all-cause mortality and aggravate chronic diabetic complications and glycemic control. The current paper, which is a joint position statement by the French-Speaking Society on Tobacco (*Société Francophone de Tabacologie*) and the French-Speaking Society of Diabetes (*Société Francophone du Diabète*), summarizes the data available on the association between smoking and diabetes and on the impact of smoking and smoking cessation among individuals with type 1, type 2, and gestational diabetes mellitus. It also provides evidence-based information about the pharmacological and behavioral strategies for smoking cessation in these patients.

Introduction

There were 537 million adults living with diabetes in 2021, and this number is projected to rise to 783 million by 2045, corresponding to a 46% increase [1]. Diabetes is also one of the most common metabolic disorders of pregnancy, with 1 in 6 pregnancies affected by diabetes. Of these, 80.3% are due to gestational diabetes mellitus (GDM), while 9.1% are due to type 1 or type 2 diabetes first detected during pregnancy, and 10.6% result from diabetes detected prior to pregnancy (i.e., pre-gestational diabetes) [1].

Abbreviations: ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron modified release Controlled Evaluation; CHD, coronary heart disease; CI, confidence interval; ESRD, end-stage renal disease; GDM, gestational diabetes mellitus; HbA_{1c}, hemoglobin A_{1c}; HOMA-β, homeostasis model assessment of β-cell function; HR, hazard ratio; IRS-1, insulin-receptor substrate-1; MI, motivational interviewing; NRT, nicotine replacement therapy; OR, odds ratio; PAD, peripheral arterial disease; RCT, randomized controlled trial; RR, relative risk; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; Th, T helper; VLDL, very-low-density lipoprotein

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Table 1
Evidence-grading system by the French National Authority for Health (*Haute Autorité de Santé*) [2].

Recommendation grade	Level of evidence
A	**Level 1**
High quality of evidence	Data derived from well-conducted, randomized controlled trials that are adequately powered and from meta-analyses of randomized controlled trials
B	**Level 2**
Moderate quality of evidence	Data derived from small and underpowered randomized controlled trials, from well-designed, controlled, non-randomized clinical trials, and from prospective cohort studies
C	**Level 3**
Low quality of evidence	Data derived from case-control studies
	Level 4
	Data derived from controlled studies with methodological flaws, retrospective studies, and case series

In the context of the growing global epidemic of diabetes, tobacco use among people with diabetes poses an incremental clinical and public health burden. It seemed, therefore, justified that the French-Speaking Society of Tobaccology (*Société Francophone de Tabacologie*) and the French-Speaking Society of Diabetes *(Société Francophone du Diabète*) collaborate to publish this joint position statement on the association between smoking and diabetes and on the impact of smoking and smoking cessation among individuals with type 1, type 2, and GDM following an in-depth review of the relevant literature. This paper also provides evidence-based information about the pharmacological and behavioral strategies for smoking cessation in these patients. The strength of different evidence statements is weighed according to scales for grading recommendations and levels of evidence predefined by the French National Authority for Health (*Haute Autorité de Santé*) [2], as outlined in Table 1.

Epidemiology of smoking in people with diabetes

The prevalence of tobacco use in type 2 diabetes mellitus (T2DM) has been extensively investigated (Fig. 1). Global patterns of tobacco use have been evaluated in a meta-analysis of 74 epidemiological studies, reporting data from 3.2 million individuals with T2DM across 33 countries [3]. The reported pooled prevalence of current smoking among individuals with T2DM was 20.8%, with individuals with T2DM 26% less likely to smoke compared to those without diabetes. In the same meta-analysis, there was a nearly 5 times higher prevalence of current smoking among men with T2DM (37.1%) than among women with T2DM (7.5%), which is in line with the general prevalence estimates of the gap between men's and women's smoking rates [3].

Although a higher prevalence of current smoking in men with diabetes compared to women with diabetes has been consistently reported, the smoking prevalence in women with diabetes has been steadily increasing, similarly to the non-diabetic population. For instance, in a large population-based study [4] from Austria, the prevalence of daily cigarette smoking increased from 19.1% in 2007 to 22.0% in 2014 ($P < 0.001$) in all women. In women with diabetes mellitus in particular, there was a 67% increase in the prevalence of daily cigarette smoking from 9.9% in 2007 to 16.4% in 2014 ($P = 0.005$) [4].

Compared to T2DM, smoking prevalence data for type 1 diabetes mellitus (T1DM) are more limited. According to data from the United States [5–7] and from Scotland [8], the prevalence of current smoking among persons with T1DM ranges from 10% to 30%, with a slightly higher prevalence among men than among women. For instance, in the Scottish registry linkage study conducted among 21,290 individuals with T1DM (12,014 men and 9,276 women), the prevalence of current smoking was 29.9% in men and 24.6% in women [8].

In France, smoking prevalence rates have been reported to be lower than the global average for T2DM, but higher for T1DM (Fig. 1). The 2007 ENTRED study, a French population-based, cross-sectional study conducted in a total of 8,926 adults with diabetes (92% of whom had T2DM and 6% T1DM), reported a 13% prevalence of current smoking among individuals with T2DM and a 39% prevalence among individuals with T1DM, with similar smoking rates among men (40%) and women (37%) with T1DM [9,10].

There is a notable paucity of data on the prevalence of smoking in pregnant women with diabetes. However, based on 1986–1988 data from France, the prevalence of smoking was 24% among pregnant women with GDM, 28% among pregnant women with T1DM, and 21% among pregnant women with T2DM [11].

As in the general population, in addition to male sex, younger age groups, physical inactivity, and lower socioeconomic status have been found to be associated with smoking behavior among both individuals with T1DM and T2DM [5,12–15]. Interestingly, younger age

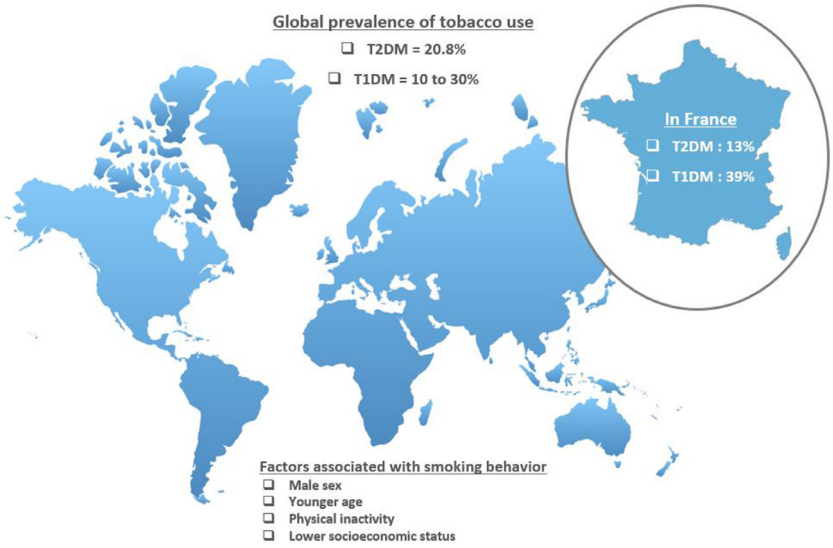

Fig. 1. Epidemiology of smoking in people with diabetes in the world and in France. Abbreviations: T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

at diagnosis has been associated with a lower likelihood of smoking in individuals with T1DM. This could be explained by the raised awareness in individuals diagnosed with T1DM earlier in life, who perceive smoking as a risk to disease management [13].

- The average smoking prevalence is 20% in people with T2DM and 30% in those with T1DM.
- In both individuals with T1DM and T2DM, smoking is more prevalent among men than women, lower socioeconomic groups, the physically inactive, and younger age groups.
- The smoking prevalence in women with diabetes has been steadily increasing.

Smoking and the risk of pre-diabetes and diabetes

Active smoking

There is accumulating evidence that active smoking increases the risk of both pre-diabetes and diabetes mellitus. The association between active smoking and pre-diabetes was highlighted in a large cross-sectional analysis of 2,142 healthy adults from Liechtenstein [16]. Compared with never-smokers, current smokers had an odds ratio (OR) for pre-diabetes of 1.82 (95% confidence interval [CI], 1.39−2.38), with a linear risk gradient across categories of cumulative smoking exposure. Individuals with a smoking exposure of < 5, 5−10, and > 10 pack-years had an OR for pre-diabetes of 1.34, 1.80, and 2.51, respectively. These data suggest that smoking can accelerate progression from normoglycemia to impaired glucose tolerance or impaired fasting glucose, thus increasing the risk of developing diabetes among smokers [16].

Indeed, a positive dose-dependent association between active smoking and T2DM risk has been consistently shown. In 2007, a first meta-analysis of 25 prospective cohort studies [17] showed that active smokers had a significantly increased risk of developing T2DM compared with non-smokers, with a pooled relative risk (RR) of 1.44 (95% CI, 1.31−1.58). In line with a dose-response phenomenon, the RR of T2DM was 1.61 in heavy smokers (≥ 20 cigarettes/day), 1.29 in light smokers (< 20 cigarettes/day), and 1.23 in former smokers [17]. In 2015, a second meta-analysis of 88 prospective cohort studies [18] found that both current smoking (pooled RR, 1.37; 95% CI, 1.33−1.42) and former smoking (pooled RR, 1.14; 95% CI, 1.10−1.18) were associated with an increased T2DM risk compared to never smoking, and estimated that 10.3% of global cases of T2DM in men and 2.2% in women could be attributable to active smoking [18].

Specific studies on the effect of active smoking on T2DM risk in women have been scarce. The Cancer Prevention Study I, a prospective cohort study conducted from 1959 through 1972 by the American Cancer Society, including 275,190 men and 434,637 women, found that women who smoke ≥ 40 cigarettes/day had a 74% increased risk of developing diabetes compared to non-smoking women, whereas the respective increase for men was 45% [19]. By contrast, in the aforementioned 2015 meta-analysis of 88 studies, the risk of T2DM was similar among male smokers (RR, 1.42; 95% CI, 1.34−1.50) and female smokers (RR, 1.33; 95% CI, 1.26−1.41) [18]. Similarly, in a 2019 meta-analysis of 17 prospective cohort studies [20] examining sex-specific effects of smoking on T2DM risk, compared with non-smoking, current smoking was associated with a 27% increased T2DM risk in women and a 35% increased risk in men, yielding a non-significant pooled female-to-male RR ratio (0.98; 95% CI, 0.96−1.01) [20].

Very limited research has been published on the effect of active smoking on T1DM risk. This may be related to the fact that T1DM is far less common than T2DM. However, a Scandinavian longitudinal cohort study [21] of over 600,000 children found that maternal sustained smoking during pregnancy was associated with a lower risk of T1DM in children (adjusted HR, 0.66; 95% CI, 0.51−0.85). According to the authors, sustained nicotine exposure *in utero* can reduce the incidence of T1DM by changing the profile of pancreatic cytokine expression from Th1 to Th2. Another possible biological mechanism for an *in utero* effect of maternal smoking is offspring differential DNA methylation [21]. Despite these results, it is important to keep in mind that any potential beneficial effect of maternal smoking on T1DM does not outweigh the several adverse pregnancy outcomes associated with maternal smoking (e.g., stillbirth, preterm birth, low birthweight, and congenital malformations). In addition, maternal smoking increased the risk of overweight/obesity, T2DM, and hypertension in the offspring [22,23].

Active smoking during pregnancy has also been associated with an increased risk for GDM. For instance, in a recent observational cohort study [24] from Finland including 4,111 primiparous women who delivered a singleton child between 2009 and 2015, the OR for GDM among smokers who continued smoking after the first trimester compared with non-smokers was 1.65 (95% CI, 1.09−2.57) after adjustments for age and pre-pregnancy body mass index. The OR for GDM in smokers who quit during the first trimester compared with non-smokers was 1.24 (95% CI, 0.90−1.72) after adjustments for the same confounders [24].

- Active smoking dose-dependently increases the risk of both pre-diabetes (level of evidence 2) and T2DM (level of evidence 1).
- Very limited research has been published on the effect of active smoking on T1DM risk.
- Active smoking during pregnancy has been associated with an increased risk for GDM (level of evidence 2).

Secondhand smoke exposure

There is evidence that secondhand smoke exposure is independently associated with an increased risk of both T2DM [18] and GDM [25]. Based on data from 7 prospective cohort studies, it was estimated that compared with non-smokers with no secondhand smoke exposure, the pooled RR of T2DM was 1.22 (95% CI, 1.10−1.35) in those exposed to secondhand smoke [18]. Similarly, in a cohort study of 12,786 Chinese pregnant women, more women exposed to secondhand smoke developed GDM than non-exposed women (7.8% versus 6.3%; P = 0.002), with an adjusted OR of 1.29 (95% CI, 1.11−1.50) [25].

- Secondhand smoke exposure is associated with an increased risk of both T2DM (level of evidence 2) and GDM (level of evidence 3).

Smoking cessation

The effect of smoking cessation on diabetes mellitus risk is variable and may depend upon individual factors. In an analysis [26] of three large cohort studies from the United States (mean follow-up, 19.6 years), the risk of T2DM was higher among recent quitters (2 to 6 years since smoking cessation) than among current smokers (hazard ratio [HR], 1.22; 95% CI, 1.12−1.32). However, it has been found that T2DM risk in former smokers becomes equivalent to that of never-smokers at 10 years after quitting [18,27]. Although previous research has shown that the temporary increase in the risk of T2DM is attributed to weight gain commonly observed after smoking cessation [26], other studies have found that smoking cessation increases the short-term risk of T2DM irrespective of any weight gain [27−29].

Hence, weight gain is not the only factor contributing to the increased T2DM risk in recent quitters, which could also result from the overall cumulative exposure to smoking before quitting [18].

- Despite the short-term increased risk of T2DM associated with smoking cessation, the risk of T2DM decreases as time elapses after smokers quit (level of evidence 2).

The mechanisms behind the association between smoking and diabetes

The mechanisms by which tobacco may increase the risk of diabetes include reduced insulin secretion and enhanced insulin resistance (Fig. 2).

Although current evidence demonstrates that smoking increases insulin resistance in both healthy individuals and individuals with diabetes mellitus, the exact mechanisms behind smoking-induced insulin resistance remain to be elucidated. Insulin resistance may result, partially, from nicotine-induced increased secretion of hormones such as cortisol, catecholamines, and growth hormone that counteract the action of insulin, leading to an increased insulin requirement [30]. The nicotine-induced release of catecholamines stimulates beta-adrenergic receptors located on the fat cell, leading to lipolysis. Nicotine can also induce lipolysis directly, by binding to nicotinic cholinergic receptors located in the adipose tissue [31]. Nicotine's lipolytic action will promote the delivery of free fatty acids to the liver and skeletal muscle. These effects of nicotine are associated with increased hepatic secretion of very-low-density lipoprotein (VLDL) and increased intramyocellular lipid content as well as peripheral insulin resistance. Nicotine also increases serine-phosphorylation of the insulin-receptor substrate-1 (IRS-1) and consequently reduces insulin-stimulated glucose uptake in muscle cells, which further contributes to insulin resistance. Smoking also modifies the balance between male and female sex hormones via an anti-estrogenic effect mediated by the alkaloids contained in tobacco (including nicotine), favoring an android distribution of fat. Indeed, smokers are at increased risk of abdominal obesity and may have a greater waist-to-hip ratio, which is a known risk factor for insulin resistance [32]. Furthermore, by promoting chronic, low-grade inflammation, endothelial dysfunction, and oxidative stress, tobacco may decrease insulin signaling and lead to insulin resistance [33]. Although most mechanistic studies evaluating the impact of smoking on insulin resistance focused exclusively on nicotine, there are over 4,700 chemical components in tobacco smoke including heavy metals (i.e., lead, arsenic, mercury, cadmium), which may also induce insulin resistance [33].

In addition to the effects of smoking on insulin resistance, smoking may impair pancreatic β-cell function. In a cohort study [34] from Japan of 1,199 men, smoking was identified as a modifiable risk factor for impaired insulin secretion, as reflected by a multivariable-adjusted HR for impaired insulin secretion of 1.95 (95% CI, 1.44–2.63) in current smokers compared with never-smokers. Furthermore, the number of pack-years was found to dose-dependently impair β-cell function [34]. These findings from Japan are in accordance with a Swedish study [35], in which current male smokers had a lower β-cell function than never-smokers, as measured by the homeostatic model assessment method (HOMA-β) (mean of 58.1 in current smokers versus 90.1 in never-smokers; $P < 0.001$). Interestingly, results from this study suggested a differential effect of sex, as no significant relationships were found between smoking and β-cell function among female current and never-smokers [35]. There is hence a need to more thoroughly evaluate the association between smoking and impaired β-cell function according to sex. Although not fully understood, the impaired β-cell function among smokers might be attributed to a direct effect of nicotine, which can negatively affect pancreatic β-cell function (e.g., by increasing apoptosis of islet β-cells), through its interaction with neuronal nicotinic acetylcholine receptors present in pancreatic islets and β-cells [36].

- Smoking increases insulin resistance in patients with diabetes mellitus (level of evidence 2), and was identified as a modifiable risk factor for impaired insulin secretion, likely mediated by nicotine's effect on β-cell function (level of evidence 3).

Complications of smoking in people with diabetes

Smokers with diabetes have an increased risk of premature death, macrovascular (coronary heart disease [CHD], stroke, and peripheral arterial disease [PAD]) and microvascular (retinopathy, nephropathy, and neuropathy) complications, cancer, and poor glycemic control (Fig. 3).

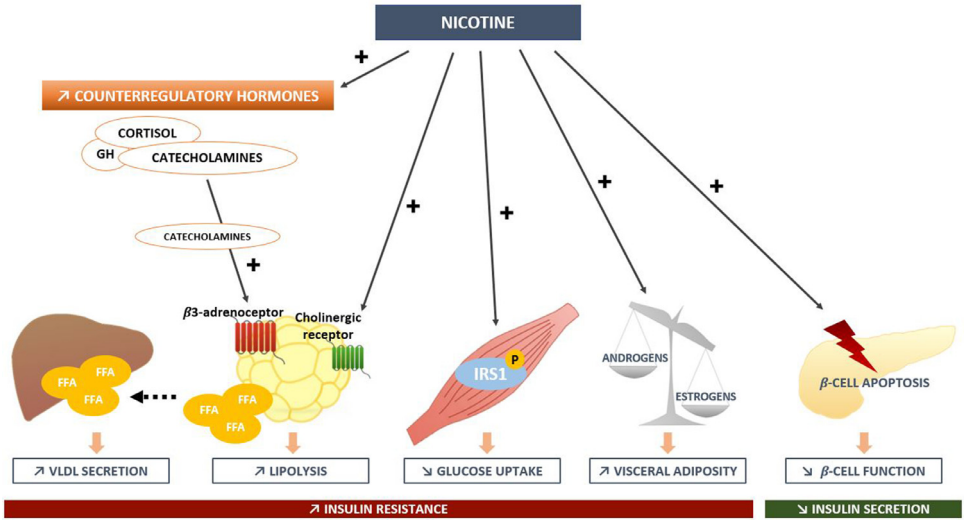

Fig. 2. .Mechanisms involved in the association between smoking and diabetes. Abbreviations: FFA, free fatty acids; GH, growth hormone; IRS1, insulin receptor substrate 1; P, phosphorylation; VLDL, very-low-density lipoprotein.

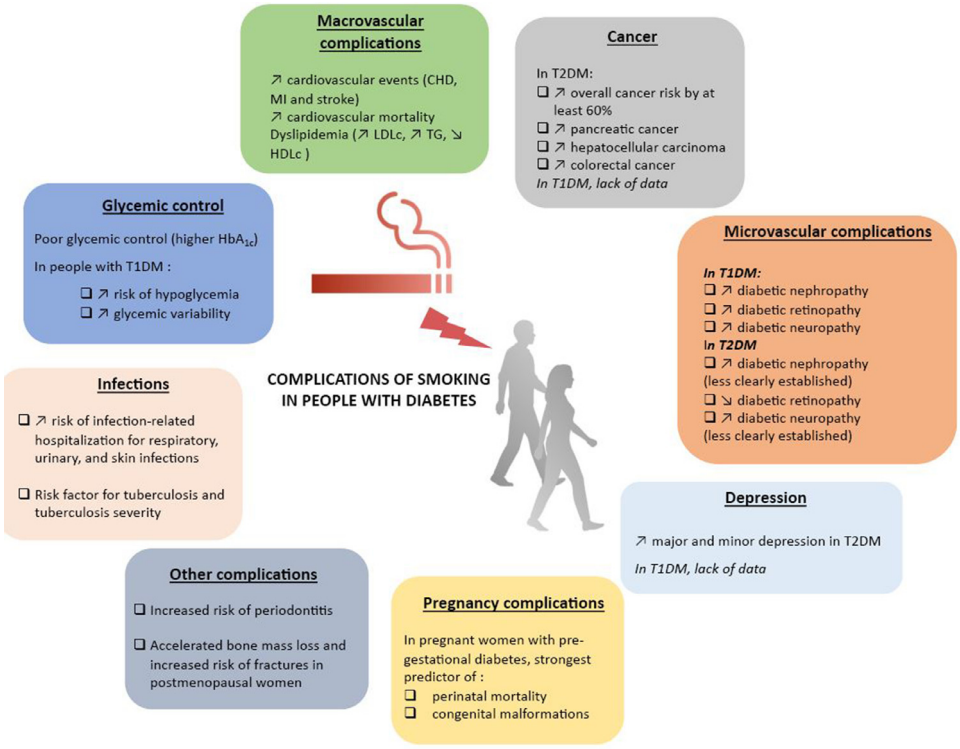

Fig. 3. Complications of smoking in people with diabetes. Abbreviations: CHD, coronary heart disease; HbA_{1c}, hemoglobin A_{1c}; HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol; MI, myocardial infarction; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TG, triglyceride.

Premature death and macrovascular disease

In both the general and diabetic populations, smoking has been consistently associated with an increased risk of all-cause mortality, cardiovascular events, and cardiovascular mortality. A 2013 meta-analysis [37] of observational prospective studies conducted in nearly 130,000 people with T1DM or T2DM reported that smoking increased the risk of all-cause death by 48%, cardiovascular mortality by 36%, CHD by 54%, myocardial infarction by 52%, and stroke by 44%. Subgroup analyses showed that these increased risks were consistent regardless of the type of diabetes. The hazards of smoking were also similar between men and women except for CHD, for which there was a non-significantly higher risk in women, as reflected by a pooled RR of 2.28 (95% CI, 0.71–7.37) among women versus 1.52 (95% CI, 0.49–4.71) among men [37]. Another large meta-analysis [38] of prospective cohort studies conducted in people with T1DM or T2DM similarly found that active smoking significantly increases the risk of total cardiovascular disease (16 studies) (pooled RR, 1.44; 95% CI, 1.34–1.54), stroke (15 studies) (pooled RR, 1.54; 95% CI, 1.41–1.69), and PAD (3 studies) (pooled RR, 2.15; 95% CI, 1.62–2.85).

There is also evidence that the risk of cardiovascular events and death increases with the number of cigarettes smoked per day, as highlighted in the Nurses' Health Study, a large prospective cohort study from the United States of female nurses with and without T2DM [39,40]. Among women with T2DM, compared with never-smokers, the multivariable-adjusted RRs for all-cause mortality were 1.31 for past smokers, 1.43 for current smokers of 1–14 cigarettes/-day, 1.64 for smokers of 15–34 cigarettes/day, and 2.19 for smokers of ≥ 35 cigarettes/day. Similarly, the RRs for cardiovascular mortality and CHD were 1.30 and 1.21 for past smokers, 1.58 and 1.66 for current smokers of 1–14 cigarettes/day, and 2.56 and 2.68 for smokers of ≥ 15 cigarettes/day, respectively [39,40].

Smoking has been shown to accentuate dyslipidemia, as reflected by higher low-density lipoprotein cholesterol and triglyceride levels as well as decreased high-density lipoprotein cholesterol in smokers with diabetes compared to non-smokers with diabetes [41]. This accentuated dyslipidemia may be one mechanism whereby smoking may increase cardiovascular disease risk in individuals with diabetes [41,42]. Smoking also has direct effects on the endothelium, prothrombotic factors, platelet activation, oxidative stress, and inflammation. These detrimental vascular effects facilitate the occurrence of atherosclerosis and cardiovascular disease [33].

- In people with diabetes, smoking is dose-dependently associated with an increased risk of all-cause mortality (level of evidence 1), cardiovascular events (level of evidence 2), and cardiovascular mortality (level of evidence 2).
- Compared with male smokers with diabetes, female smokers with diabetes appear to have a greater risk of CHD (level of evidence 2).
- The detrimental effects of smoking on blood lipids and on the vasculature predispose to atherosclerosis and to cardiovascular disease (level of evidence 2).

Microvascular complications

There is evidence that smoking increases the incidence and progression of nephropathy in people with diabetes, particularly in those with T1DM [43,44]. A meta-analysis of 19 observational studies (1 case-control, 8 cross-sectional, and 10 prospective cohort studies) found that smoking was an independent risk factor for the development of diabetic nephropathy in both individuals with T1DM and T2DM, with RRs of 1.31 (95% CI, 1.06–1.62; $P = 0.006$) and 1.44 (95% CI, 1.24–1.67; $P < 0.001$), respectively [45]. However, in a subsequent meta-analysis including only prospective cohort studies, smoking was associated with an increased risk of developing diabetic nephropathy in people with T1DM (HR, 1.05; 95% CI, 1.00–1.11; $P = 0.05$) but not in those with T2DM (HR, 1.15; 95% CI, 0.9–1.47;

$P = 0.25$) [43]. Smoking is also a risk factor for the progression of diabetic nephropathy, and the risk increases with higher tobacco consumption [44]. A population-based study [44] from Finland conducted in 3,613 individuals with T1DM found that the 12-year cumulative risks of microalbuminuria (18.9%), macroalbuminuria (14.4%), and end-stage renal disease (ESRD) (10.3%) were higher among current smokers compared with non-smokers (10.0%, 4.7%, and 5.6%, respectively). Moreover, each pack-year increased the risk of macroalbuminuria by 2.5% and of ESRD by 1.4% compared with non-smokers [44]. Smoking influences the development and progression of nephropathy in diabetes possibly through a combination of its negative effects on glycemic control, blood lipids, as well as oxidative stress, inflammation, and endothelial damage [44–46].

The role of smoking as a risk factor for diabetic retinopathy is well-established in individuals with T1DM, but disputed in T2DM. A meta-analysis of 73 studies found that compared with non-smokers, the risk of diabetic retinopathy significantly increased in smokers with T1DM (RR, 1.23; 95% CI, 1.14–1.33; $P < 0.001$), while the risk significantly decreased in smokers with T2DM (RR, 0.92; 95% CI, 0.86–0.98; $P = 0.01$) [47]. The underlying mechanisms for the associations between smoking and diabetic retinopathy are complex. On the one hand, experimental studies have shown that nicotine can accelerate diabetes-induced detrimental changes in the retina, manifested mainly by thinning of the outer nuclear layer [48]. Smoking has also been found to reduce retinal blood flow and the ability of the retinal vessels to autoregulate in response to hyperoxia [47,48]. On the other hand, it has been postulated that the lower blood pressure associated with smoking might contribute to the reduction of risk of diabetic retinopathy.

There are also conflicting results regarding the association of smoking with diabetic neuropathy. A 2015 meta-analysis [49] of 10 prospective cohort studies and 28 cross-sectional studies found that smoking increased the overall risk of diabetic peripheral neuropathy by 42%. However, subgroup analyses of the prospective studies revealed a significant association of smoking with diabetic neuropathy for individuals with T1DM (OR, 1.74; 95% CI, 1.48–2.04), but not for individuals with T2DM (OR, 0.65; 95% CI, 0.16–2.71) [49]. By contrast, in a nerve conduction study [50], smoking was identified as an independent risk factor for the development of neuropathy in people with T2DM, with heavy smokers exhibiting worse nerve conduction compared to light or moderate smokers and non-smokers [50]. Hence, smoking can increase the severity of diabetic peripheral neuropathy, which in turn can increase the risk of foot ulcers and other diabetic foot complications [50]. Indeed, a meta-analysis of 25 studies performed in people with T1DM or T2DM found that smoking was associated with a 1.38–fold increase in the risk of diabetic foot amputations [51]. Although smoking may increase the risk of nerve damage through oxidative stress, it also has direct toxic effects, and may induce diabetic peripheral neuropathy via hypoxemia and promote PAD, which in turn increases the risk of foot amputations by prolonging the healing process [49,51].

There is currently a paucity of data on the impact of sex on the risk of microvascular complications in smokers with diabetes. However, in a recent prospective cohort study [52] from the Netherlands of 1,884 individuals with T2DM with a mean follow-up of almost 7 years, there was no significant interaction between smoking and sex on the outcomes of diabetic retinopathy and neuropathy. However, smoking in men was associated with a lower risk of microalbuminuria than in women (HR, 0.60; 95% CI, 0.38–0.96), indicating a more detrimental effect of smoking on microalbuminuria in women [52].

- The role of smoking as a risk factor for diabetic retinopathy is well-established in individuals with T1DM (level of evidence 2), but disputed in T2DM, as the risk of diabetic retinopathy was significantly decreased in smokers with T2DM (level of evidence 2).
- The role of smoking as a risk factor for diabetic nephropathy and neuropathy is well-established in individuals with T1DM (level of evidence 2), but less clearly established in T2DM (level of evidence 2).

Cancer

Data from large cohort studies conducted in people with T2DM, namely the Fukuoka Diabetes Registry and the Fremantle Diabetes Study, as well as the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron modified release Controlled Evaluation) randomized controlled trial (RCT), have shown that compared with never-smokers, smoking increases overall cancer risk by at least 60% [53–55]. Regarding overall cancer mortality, a large cohort study of Taiwanese individuals with diabetes identified both current smoking (HR, 1.46; 95% CI, 1.36–1.56) and past smoking (HR, 1.22; 95% CI, 1.13–1.33) as risk factors for cancer death compared with never-smokers [56]. Similarly, in the Nurses' Health Study [39], among 7,401 women with T2DM diagnosed at baseline or during follow-up, compared with never-smokers, the multivariable-adjusted RRs for all-cancer mortality increased in a dose-response manner, and were 1.09 in current smokers of 1–14 cigarettes/day, 1.13 in smokers of 15–34 cigarettes/day, and 3.38 in smokers of ≥ 35 cigarettes/day [39].

In addition, the co-existence of diabetes and smoking has been associated with an increased risk of developing as well as dying from pancreatic cancer [57,58], from hepatocellular carcinoma [59,60], and from colorectal cancer [61,62]. Fortunately, the elevated risks of incident cancer and cancer death in people with diabetes diminish after smoking cessation [39,53]. Of note, most data are related to T2DM whereas for patients with T1DM, there is a notable lack of data evaluating the association between smoking and cancer.

- In people with T2DM, smoking has been associated with an increased risk of developing (level of evidence 2) and dying (level of evidence 3) from specific cancers such as pancreatic cancer, hepatocellular carcinoma, and colorectal cancer, as well as cancer overall.

Infections

In people with diabetes, current smoking is associated with an elevated risk of infection-related hospitalization [63]. This was highlighted in the Hong Kong Diabetes Registry, a large prospective cohort study of Chinese adults with T2DM, in which current smoking was associated with an increased risk of hospitalization for all–site infections (HR, 1.32; 95% CI, 1.18–1.47), genitourinary tract infections (HR, 1.47; 95% CI, 1.14–1.88), skin infections (HR, 1.35; 95% CI, 1.09–1.67), and respiratory infections (HR, 1.69; 95% CI, 1.44–1.98). Compared to never-smokers, previous smokers also had a significantly higher risk of hospitalization for respiratory infections (HR, 1.45; 95% CI, 1.28–1.64), but the hospitalization risks for genitourinary tract and skin infections were comparable between never and previous smokers [63]. In people with T1DM, current smoking was likewise associated with an increased risk of infection–related hospitalization compared to never-smokers (multivariable-adjusted RR, 1.42; 95% CI, 1.18–1.70), whereas this risk was not increased in previous smokers [64]. Tobacco smoking has been further identified as a risk factor for tuberculosis and tuberculosis severity in people with diabetes [65].

- In people with diabetes, current smoking is associated with an increased risk for infection-related hospitalization, especially for respiratory, urinary, and skin infections (level of evidence 3).

Depression

A population-based study from the United States performed among 4,193 individuals with T1DM or T2DM revealed that smoking was associated with an increased risk of both major (OR, 2.15; 95% CI, 1.56–2.95) and minor (OR, 1.61; 95% CI, 1.08–2.38) depression [66]. McGihon and colleagues [67] sought to explore the direction of the association between the number of cigarettes smoked per day and depressive symptoms in a community-based sample of smokers with T2DM. They found that this association was best characterized by a "primary smoking" model, in which higher consumption of cigarettes predicted higher levels of depressive symptoms at subsequent time-points. These results highlight the importance of implementing early smoking cessation strategies in diabetes care [67]. The mechanisms by which smoking may potentially increase the risk of depression in the diabetic population remain unclear. It has been postulated that continual smoking, which is implicated in inflammation through its effect on immune-inflammatory cells, contributes to the chronic, low-grade inflammation that is associated with depression. This mechanism may be of particular relevance to T2DM, as smoking may exacerbate existing diabetes-related inflammation. In addition, smoking has been associated with cortisol hypersecretion and decreased activity of monoamine oxidase, which may also increase the risk of depression in patients with diabetes [67].

- In people with T2DM, smoking has been associated with an increased risk of depression, whereas more data are needed for people with T1DM (level of evidence 4).

Pregnancy complications

The association between maternal smoking and pregnancy complications in women with GDM is not well-established. A retrospective cohort study of 915 singleton pregnancies showed that smoking during pregnancy in patients with GDM reduces the risk of having a large for gestational age infant by 40% [68]. This finding is not surprising, given that the restricting effect of smoking on fetal growth (though vasoconstriction, nutritional deprivation, and direct toxic effects) might counteract the growth-stimulating effect of GDM (through maternal hyperglycemia stimulating fetal hyperinsulinemia which in turn results in accelerated fetal growth). However, maternal smoking in patients with GDM did not reduce other pregnancy complications such as preterm labor, preeclampsia, shoulder dystocia, and birth trauma. Moreover, postpartum hemorrhage was significantly more common among smokers with GDM than among non-smokers with GDM (OR, 2.30; 95% CI, 1.02–5.31) [68].

Regarding the association between maternal smoking and pregnancy complications in women with pre-gestational diabetes, a large cross-sectional study from Germany found that maternal smoking was the strongest predictor of both perinatal mortality (OR, 3.82; 95% CI, 1.95–7.51) and congenital malformations (OR, 2.90; 95% CI, 1.76–4.78) in pregnant women with pre-gestational diabetes [69]. These findings highlight the importance of giving extra attention to women with pre-gestational diabetes who smoke and vigorously encouraging them to stop smoking.

- There are insufficient research data assessing the impact of maternal smoking on obstetric and neonatal complications among women with GDM (level of evidence 4).

Other complications

Smoking increases the risk of other adverse health effects in patients with diabetes, such as periodontal disease. In a Korean population-based study, current smoking was associated with a nearly 2-fold increased risk of periodontitis in patients with diabetes mellitus [70]. Smoking also accelerates bone mass loss and increases the risk of fractures in postmenopausal women in the general population. A longitudinal study [71] from Norway of 4,160 postmenopausal women found that women with diabetes who were current smokers had a 3.5-fold higher risk of non-vertebral fractures than diabetic women who were never-smokers. This association was dose-dependent, as among heavy smokers (≥20 cigarettes/day), the multivariable-adjusted HR for non-vertebral fractures was 5.09, while it was 3.31 for smokers of < 10 cigarettes/day [71].

- Smoking increases the risk and progression of other adverse health effects in patients with diabetes, such as periodontal disease and non-vertebral fractures (level of evidence 4).

Poor glycemic control

In people with T1DM, T2DM, and GDM, smoking has been dose-dependently associated with poor glycemic control. A cross-sectional study [72] from China of 10,551 men and 15,297 women with T2DM found that current smokers have an increased risk for poor glycemic control (defined as hemoglobin A_{1c} [HbA_{1c}] ≥ 7.0%). The multivariable-adjusted OR for poor glycemic control in current smokers was 1.49 (95% CI, 1.35–1.66) in men and 1.56 (95% CI, 1.13–2.15) in women. Former smokers who quit smoking for less than 10 years remained at increased risk for poor glycemic control, with the risk declining after 10 years of smoking cessation to approximate that of non-smokers [72]. Consistently, in a meta-analysis [73] involving 87,593 patients with either T1DM or T2DM, non-smokers had significantly lower HbA_{1c} levels compared to smokers, with a pooled mean difference of HbA_{1c} between non-smokers and smokers of −0.61% (95% CI, −0.88 to −0.33; $P < 0.0001$). Meta-regression analysis did not show any statistically significant association between the type of diabetes and the mean difference of HbA_{1c} between non-smokers and smokers (p=0.08) [73].

Studies focusing exclusively on patients with T1DM have similarly reported that smoking is independently associated with inadequate glycemic control [74,75]. For instance, in a cohort study of 763 patients with T1DM, mean HbA_{1c} during 5,047 patient-years of follow-up was 7.9% in smokers and 7.3% in non-smokers ($P < 0.001$), despite a higher mean insulin dosage in smokers (0.71 U/kg versus 0.65 U/kg in non-smokers; $P = 0.046$) [74]. In another cross-sectional study of 292 patients with T1DM, smoking was associated with inadequate glycemic control, defined as HbA_{1c} >8.6%, with an adjusted OR of 3.0 (95% CI, 1.2–7.2). However, sex-stratified analyses showed that the association between smoking and an HbA_{1c} > 8.6% was significant for men (OR, 4.2; 95% CI, 1.5–11.9; $P = 0.008$) but not for women (OR, 1.5; 95% CI, 0.2–9.5; $P = 0.66$) [75]. Alarmingly, smoking has been demonstrated to increase the risk of hypoglycemia in patients with T1DM, as shown in a population-based study of 537 patients with T1DM, in which current smokers were 2.6 times as likely to report ≥ 1 episode of severe hypoglycemia compared with non-smokers [76]. In a more recent retrospective study of 369 patients with T1DM, smoking was also associated with increased glycemic variability and increased time in hyperglycemia and in hypoglycemia compared to non-smokers [77]. However, these findings require additional validation in larger prospective studies.

Regarding the association between smoking and poor glycemic control in GDM, it was found that women with GDM who smoked at the beginning of their pregnancy had an oral glucose tolerance test consistent with accelerated glucose absorption and a higher HbA_{1c} than non-smokers [78]. Furthermore, in pregnant women with T1DM, Robertson and colleagues [79] reported that women who

smoked were 3 times more likely to have a severe hypoglycemia episode during their third trimester than non-smokers (P = 0.029). According to the authors, this observation could be because of smoking-induced impairment in trophoblastic development during the first trimester, resulting in a decrease in placental hormones influencing insulin resistance in the latter half of pregnancy [79].

- In people with T1DM, T2DM, and GDM, smoking has been dose-dependently associated with poor glycemic control (level of evidence 2).

Benefits and risks of smoking cessation in people with diabetes

In both the general population and in people with diabetes, smoking cessation is associated with substantial health benefits, including a reduced risk of premature death, cardiovascular morbidity and mortality, cancer development and mortality, pulmonary disease, infections, and fractures, as well as overall improved fetal and maternal outcomes in case of GDM. Moreover, despite not having data specific to people with diabetes, a recent meta-analysis of 102 studies representing over 169,500 participants from the general population revealed that compared with continuing to smoke, smoking cessation improved symptoms of anxiety, depression, and stress [80].

The Nurses' Health Study found that women with T2DM who had stopped smoking for ≥10 years had a similar mortality rate (RR, 1.11; 95% CI, 0.92−1.35) and a similar CHD risk (RR, 1.01; 95% CI, 0.73 −1.38) compared to never-smokers [39,40]. The cardiovascular benefits of smoking cessation have also been reported to occur independently of any potential weight gain in patients with diabetes [81,82]. Furthermore, smoking cessation has been consistently demonstrated to reduce the risk of progression of nephropathy in patients with both T1DM and T2DM [44,46,53,83]. Studies evaluating the impact of smoking cessation on other microvascular complications such as diabetic retinopathy and neuropathy are highly warranted. The benefits of quitting smoking seem to occur very quickly, as highlighted by a small controlled study, in which short-term smoking cessation of 1 −2 weeks was sufficient to reverse defects in insulin sensitivity and skeletal muscle insulin signaling, in a young population, without any changes in body weight or adiposity [84].

Although the potential adverse consequences of smoking cessation are far outweighed by the benefits, they are important to address in order to maximize the likelihood that a patient will successfully quit tobacco use. Smoking cessation is often associated with weight gain in people with or without diabetes. The mechanisms behind weight gain appear to be decreased metabolic rate, increased activity of lipoprotein lipase, and increased caloric intake. However, weight gain following smoking cessation decreases over time. In a community-based prospective cohort study from the United States performed in smokers with or without diabetes, the median 4-year weight gain was greater for recent quitters (≤ 4 years) without diabetes (2.7 kg) and with diabetes (3.6 kg) than for long-term quitters (> 4 years) (0.9 and 0.0 kg, respectively; P < 0.001 for both comparisons) [81]. Consistently, in a meta-analysis of 62 RCTs from the general population, smoking cessation was associated with a mean body weight increase of 4−5 kg after 12 months of quitting, with most weight gain occurring within the first 3 months of quitting [85]. Furthermore, a retrospective cohort study of 10,692 smokers with T2DM found that smoking cessation is associated with deterioration in glycemic control within the first year of quitting, as HbA_{1c} increased by 0.21% in that year. However, as cessation continued, glycemic control improved and became comparable to that of current smokers after 3 years. This increase in HbA_{1c} was unrelated to weight gain [86]. In light of this evidence, it is important that smoking cessation efforts are accompanied by a proactive review of glycemic control and lifestyle interventions, such as increasing physical activity and improving diet quality.

Qualitative research [87] conducted in smokers with T2DM found that satisfaction with current health status, inadequate knowledge about the relationship between T2DM and smoking, and misconceptions about smoking cessation resulted in negative attitudes towards quitting. In addition, the quitting process was reported to be challenging, with smoking peers, psychological addiction, and post-cessation weight gain hindering the quitting process [87]. Another qualitative study in men and women with T2DM further revealed that healthcare providers should take gender better into account when counseling for smoking cessation, as women's coping mechanisms and social contexts may be different from those of men with diabetes [88]. These findings underscore the need for multi-component, personalized interventions in order to increase the success rate of smoking cessation, including both behavioral counseling and pharmacotherapies.

- In people with diabetes, smoking cessation is associated with substantial health benefits, including reduced risks of premature death, cardiovascular morbidity and mortality, cancer development and mortality, infections and infection−related hospitalization, as well as improvement in symptoms of anxiety, depression, and stress, and overall improved fetal and maternal outcomes in case of GDM (level of evidence 2).

Behavioral approaches to smoking cessation in people with diabetes

Behavioral tobacco cessation interventions used in the diabetic population are similar to those used in the general population (Table 2), and include: brief provider-delivered interventions (e.g., advice from a physician or nurse), intensive counseling delivered on an individual basis or in a group including motivational interviewing, text messaging interventions, quitlines, self-help materials (e.g., written materials, videos, audiotapes, phone apps), psychotherapy, physical activity, and combinations of these approaches [89]. In addition, diabetes-specific education, focusing partly on the effects of smoking on the complications of diabetes and on glycemic control, has an important role in encouraging and supporting smokers with diabetes to quit and assume active responsibility for the day-to-day control of their condition [89,90].

All smokers with or without diabetes who are ready to quit should receive brief counseling from their healthcare professionals, known as the "5 A's". The "5 A's" model encourages clinicians to (1) Ask patients about their smoking status; (2) Advise all smokers to quit; (3) Assess their readiness to quit; (4) Assist them with their smoking cessation efforts; and (5) Arrange for follow-up contact to prevent relapse [91]. However, longer behavioral interventions (e.g., multiple counseling sessions of ≥ 10 minutes conducted over several weeks) are more effective than brief clinician counseling in producing long-term abstinence from tobacco, and are thus recommended for diabetic smokers [92]. Behavioral interventions are particularly appropriate for pregnant smokers with or without GDM, given the lack of safety information on pharmacotherapies during pregnancy.

Regarding the efficacy of behavioral interventions specifically in people with diabetes attempting to quit smoking, there is limited evidence so far, with mixed findings (Table 2). Nevertheless, in a RCT from Spain involving 280 smokers with T1DM or T2DM, one-on-one support in the form of counseling, education, telephone calls, letters, and visits by a nurse (n = 147) was associated with a 6-month smoking cessation rate of 17.0% compared with 2.3% in smokers assigned to usual care (n = 133), resulting in a cessation incidence ratio of 7.5 (95% CI, 2.3−24.4) [93]. In another cluster RCT from the United Kingdom performed in 824 smokers with newly diagnosed T2DM, those

Table 2
Behavioral approaches to smoking cessation in people with diabetes.

Approach	Description	Assessment in people with diabetes
Brief intervention	• 5-15 minutes of brief intervention to stop smoking • Motivating, vigorous, and empathetic advice • Unique or systematic (i.e., repeated at all patient visits) • Examples of brief intervention: « Quitting smoking is the most important decision you can make to protect your health. I can help you if you want. »« It's important that you stop smoking, and I can help you to do that. »« Continuing to smoke will worsen your diabetes [. . .] but quitting will improve your glycemic control. »	In one randomized controlled trial (RCT) of people with T2DM, a brief tailored intervention was not effective in promoting quitting or reducing smoking compared to usual care [106].
Structured behavioral intervention	• 10 weekly 90-minute sessions • Objective: self-monitoring reduction of nicotine intake • Patients are encouraged to gradually decrease their cigarette consumption and quit smoking after the fifth session • Non-smoking contract to be signed by each patient • Relaxation techniques may be associated	In one RCT of people with T1DM and T2DM, structured behavioral therapy for smoking cessation was no more successful than an unstructured physician's advice [107].
Motivational interviewing (MI)	• Patient-centered relational approach • To strengthen an individual's motivation to develop the behavioral changes necessary to manage their diabetes • Cooperative and collaborative partnership promoting patient empowerment • To assess the patient's wishes, beliefs, and expectations regarding smoking and smoking cessation assistance. For example: « What does smoking do for you? »« Why would you want to quit smoking? »« Are you afraid to quit smoking? If so, why? »« If you decide to quit smoking, how confident would you be in your ability to do so? »	• 11 studies evaluating MI in people with diabetes (mainly T2DM) [93,94,106-114] • Heterogeneity between studies (MI types and comparative groups) • Benefits of MI in the majority of studies compared to usual care • Of note, 45% of these studies combined drug aids
Quitlines/Text messages	• Structured conversation series • Support for anyone who wants to quit or has recently quit	Ongoing RCTs in people with diabetes [115,116].
Self-help materials	• Tobacco Stop websites (for example: tabac-info-service.fr) • Personalized support in one's quitting process or that of relatives	Not specifically assessed in people with diabetes.
Physical activity		Benefit not established in people with diabetes, specifically for smoking cessation.
Therapeutic education	• Improved knowledge and life skills for healthy individuals • In diabetes-specific education, need to focus on effects of smoking on diabetes complications and on glycemic control	In two RCTs in people with T2DM [90,117], diabetes education resulted in significantly higher abstinence at 6 and 12 months versus usual care.

who attended a 6-hour structured group education program on biomedical, psychosocial, and lifestyle measures (n = 437) were ≥ 3 times more likely to succeed in giving up smoking after 12 months than those allocated to usual care (n = 387) [90]. A third RCT from India including 224 male smokers with diabetes also revealed that a brief intervention by doctors can result in a quit rate of up to 13%. However, if this brief intervention was further supported by counseling sessions by a trained healthcare professional, patients were able to reach a 52% quit rate at a 6-month follow-up [94].

Despite the benefits of behavioral interventions, it is important to underscore that wherever possible, behavioral support should be used in conjunction with pharmacotherapy, as in the general population, the combination of behavioral support and pharmacotherapy increased the chance of smoking cessation success by 70%–100% compared to behavioral support alone [95].

- Behavioral tobacco cessation interventions used in the diabetic population are similar to those used in the general population, and include: brief intervention, motivational interviewing, physical activity, and diabetes-specific education (level of evidence 2).

Pharmacotherapy for smoking cessation in people with diabetes

First-line pharmacologic therapies for smoking cessation in the general population (Table 3) include nicotine replacement therapy (NRT), varenicline, and bupropion, which all aim to reduce nicotine withdrawal symptoms (e.g., restlessness, anxiety, increased appetite, insomnia), thereby making it easier to stop smoking. In order to reduce the risk of smoking relapse, pharmacotherapy for smoking cessation is recommended for at least 3 months [96].

So far, there are very limited data on smoking cessation pharmacotherapies in people with diabetes, particularly in patients with T1DM. However, in the general population, the benefit-risk profile of each first-line therapy for smoking cessation has been proven. For instance, the EAGLES trial, which directly compared varenicline, bupropion, NRT, and placebo in over 8,000 smokers (6% of whom had diabetes), found comparative efficacy between the three pharmacological treatments, with similar neuropsychiatric and cardiovascular safety profiles [97,98].

NRT is available in different formulations, such as transdermal patches, chewing gum, lozenges, sublingual tablets, inhalers, and nasal or mouth sprays. When using NRT, combination NRT is considered the standard of care, and usually consists of the use of the long-acting nicotine transdermal patch and a short-acting form of the patient's choice (e.g., gum or lozenges). The combination could be sequential or concurrent. The rationale for the sequential NRT is that the patch could provide a stable level of nicotine necessary to achieve and sustain cessation, and the subsequent use of short-acting forms is expected to deal with emergent nicotine cravings. The rationale for concurrent combination NRT is that provision of nicotine using different forms may improve symptom relief and enhance cessation outcomes than either product used alone [99]. Theoretically, NRT may have a negative impact on glucose homeostasis and on glycemic control in patients with diabetes, given that nicotine was associated with increased insulin resistance in non-diabetic subjects [100]. However, NRT (given as a gum or lozenge) demonstrated an acceptable safety profile in a 12-week study performed in 901 smokers with either diabetes mellitus (n = 270; 30%) or other underlying medical conditions (i.e., cardiac disease, uncontrolled hypertension), with the most common adverse events being nausea, hiccups, and headache [101].

Table 3
First-line medications used by the French-Speaking Society of Tobaccology (Société Francophone de Tabacologie) and the French-Speaking Society of Diabetes (Société Francophone du Diabète) to treat tobacco dependence in people with diabetes

Drug	Reimbursement status in France	Advantages	Disadvantages and precautions
Nicotine patch	Reimbursed	- Long-acting product that provides steady nicotine levels - Tapering dose is not required - Very easy to use	- Dose of nicotine to be released cannot be adjusted to respond to nicotine cravings and withdrawal symptoms - Nicotine can cross the placenta
Nicotine gum	Reimbursed	- Available in several flavors - Possible to control nicotine dose	- Short-acting preparation requiring repeated use throughout the day - Proper chewing of gum is important for optimal results - Can damage or adhere to dental appliances
Nicotine lozenge	Reimbursed	- Available in several flavors - Can be used by smokers with poor dentition or dentures - Possible to control nicotine dose	Short-acting preparation requiring repeated use throughout the day
Nicotine sublingual tablet	Reimbursed	- Can be used by smokers with poor dentition or dentures - Possible to control nicotine dose	Short-acting preparation requiring repeated use throughout the day
Nicotine mouth spray	Reimbursed	- Can be used by smokers with poor dentition or dentures - Possible to control nicotine dose	- Unpleasant taste - Short-acting preparation requiring repeated use throughout the day - Contains a small amount of alcohol and should thus not be used in pregnancy
Nicotine inhaler	Not reimbursed	- Can be used by smokers with poor dentition or dentures - Possible to control nicotine dose	- Frequent puffing required to obtain adequate nicotine delivery - Inhaled nicotine may cause bronchospasm
Varenicline	Reimbursed	- Limited weight gain - Dual action: reduces the symptoms of nicotine withdrawal and reduces the rewarding aspects of cigarette smoking	Dose reduction is required if creatinine clearance <30 mL/minute because varenicline is excreted almost entirely by the kidneys
Bupropion sustained release	Not reimbursed	Limited weight gain	- Bupropion can cross the placenta - Contraindicated in patients with seizure disorder or predisposition

The high-affinity $\alpha4\beta2$ nicotinic acetylcholine receptor partial agonist varenicline is another approved smoking cessation medication. Varenicline has a dual action; it reduces craving and withdrawal symptoms by stimulating dopamine release through its agonist property and reduces the rewarding aspects of smoking by blocking nicotine binding to the receptor through its antagonist property. To date, no large-scale clinical trials reporting the efficacy and safety of varenicline in patients with diabetes have been published. However, a retrospective analysis [102] of data extracted from 15 placebo-controlled trials with varenicline showed that the incidences of adverse events were comparable in participants with diabetes (n = 323) and without diabetes (n = 6,448). The most commonly reported adverse events for varenicline in participants with and without diabetes were, respectively, nausea (27.2% versus 29.6%), headache (9.3% versus 13.4%), and insomnia (8.6% versus 11.4%). Weight gain from baseline to week 12 was also limited in varenicline-treated quitters with (1.7 kg) and without (2.1 kg) diabetes. Varenicline was additionally found to be effective in promoting smoking cessation in the subgroup of participants with diabetes, as it was associated with a continuous abstinence rate at 12 weeks of 43.8% versus 24.8% for placebo (OR, 2.36; 95% CI, 1.47–3.79) [102].

The antidepressant bupropion can also be used as a smoking cessation medication, even if not reimbursed in France. Bupropion reduces withdrawal symptoms by inhibiting the re-uptake of norepinephrine and dopamine at the level of neuronal synapses in the central nervous system, acting as a non-competitive antagonist of nicotine receptors. However, no studies of bupropion are available in patients with diabetes.

Although classified as consumer products and not medicinal products, electronic cigarettes (e-cigarettes) are battery-powered devices that are intended to deliver aerosolized nicotine. They may thus reduce the severity of nicotine withdrawal symptoms. Although e-cigarettes are likely to be less toxic than smoked tobacco, their safety remains uncertain and their benefit-risk ratio is not established [103,104]. There is also no conclusive evidence that e-cigarette use facilitates smoking cessation in both the general and diabetic populations. Therefore, e-cigarette should not be prescribed to smokers with or without diabetes for smoking cessation. However, if smokers themselves are deliberately switching to exclusive e-cigarette use to treat their nicotine dependence, e-cigarette use should be of limited duration, once abstinence from conventional tobacco products is achieved and the urge to smoke is suppressed [103].

In sum, there are very limited data on smoking cessation pharmacotherapies in people with diabetes. However, as in the general population, clinicians should encourage the use of pharmacotherapy by all patients with diabetes attempting to quit smoking, except when medically contraindicated or in specific populations for which there is insufficient evidence of safety and efficacy (i.e., pregnant women, light smokers, and adolescents) [105].

- The application of NRT for smoking cessation should be the same for people with diabetes as for those without diabetes (level of evidence 4).
- The application of varenicline for smoking cessation should be the same for people with diabetes as for those without diabetes (level of evidence 3).
- The application of bupropion and e-cigarettes for smoking cessation should be the same for people with diabetes as for those without diabetes (level of evidence 4).

Conclusions

Smoking is a risk factor for the development of both pre-diabetes and diabetes. Smokers with diabetes in turn have an increased risk of poor glycemic control and high morbidity and mortality risks. Hence, healthcare providers have a responsibility to educate all individuals with diabetes on the risks of smoking and advise them not to initiate

Table 4
The French-Speaking Society of Tobaccology (Société Francophone de Tabacologie) and the French-Speaking Society of Diabetes (Société Francophone du Diabète) joint position statement on smoking and diabetes

Healthcare providers should routinely educate all individuals with diabetes on the risks of smoking and advise them not to initiate tobacco use (grade A, level of evidence 1).
All individuals with diabetes who smoke should be advised to quit smoking and should be informed about the health benefits of smoking cessation (grade A, level of evidence 1).
In women with diabetes, smoking cessation should be advised before pregnancy (grade A, level of evidence 2).
It is important to promote new smoking prevention and cessation programs specifically tailored to the needs of women living with diabetes, as their coping mechanisms and social contexts may be different from those of men with diabetes (grade C, level of evidence 4).
Smoking cessation efforts should be accompanied by a proactive review of glycemic control and lifestyle interventions, such as increasing physical activity and reducing body weight (grade A, level of evidence 2).
The most effective way to promote smoking cessation is to combine both behavioral and pharmacologic therapies (grade C, level of evidence 3). In pregnant women, however, a behavioral counseling program is recommended alone, because of the lack of safety information on pharmacotherapies during pregnancy (grade C, level of evidence 4).
First-line pharmacologic therapies for smoking cessation include nicotine replacement therapy, varenicline, and bupropion (grade C, level of evidence 3).
Pharmacotherapy for smoking cessation is recommended for at least 3 months (grade C, level of evidence 4).
For patients wishing to use nicotine replacement therapy, it is preferable to use a combination of long- and short-acting nicotine replacement products (e.g., nicotine patch plus nicotine gum or lozenges) (grade C, level of evidence 4).
E-cigarette use aiming at smoking cessation should be of limited duration, once abstinence is achieved and the urge to smoke is suppressed (grade C, level of evidence 4).

tobacco use of any kind. Tobacco dependence is overall managed in patients with diabetes in the same way as in the general population, with current first-line therapies for smoking cessation including behavioral interventions and pharmacological options, such as NRT, varenicline, and bupropion (Table 4). There is however very limited evidence regarding the efficacy and safety of pharmacotherapies in patients with diabetes. Smoking cessation in diabetes therefore remains a highly relevant topic for future research, particularly in T1DM, for which there is a notable paucity of data.

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Authors' Contribution

All authors participated in the drafting and critical revision of the manuscript.

Declaration of Competing Interest

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References

[1] International diabetes federation. IDF Diabetes Atlas; 202110th edition https://diabetesatlas.org/idfawp/resource-files/2021/07/IDF_Atlas_10th_Edition_2021.pdf [accessed 10 February 2022].
[2] French National Authority for Health (Haute Autorité de Santé). Level of evidence and grading of best practice recommendations [Niveau de preuve et gradation des recommandations de bonne pratique], https://www.has-sante.fr/upload/docs/application/pdf/2013-06/etat_des_lieux_niveau_preuve_gradation.pdf; 2013 [accessed 15 March 2022].
[3] Roderick P, Turner V, Readshaw A, Dogar O, Siddiqi K. The global prevalence of tobacco use in type 2 diabetes mellitus patients: A systematic review and meta-analysis. Diabetes Res Clin Pract 2019;154:52–65. doi: 10.1016/j.diabres.2019.05.035.
[4] Dorner TE, Brath H, Kautzky-Willer A. Sex-specific trends in smoking prevalence over seven years in different Austrian populations: results of a time-series cross-sectional analysis. BMJ Open 2020;10:e035235. doi: 10.1136/bmjopen-2019-035235.
[5] Reynolds K, Liese AD, Anderson AM, Dabelea D, Standiford D, Daniels SR, et al. Prevalence of tobacco use and association between cardiometabolic risk factors and cigarette smoking in youth with type 1 or type 2 diabetes mellitus. J Pediatr 2011;158:594–601 e1. doi: 10.1016/j.jpeds.2010.10.011.
[6] Shah AS, Dabelea D, Talton JW, Urbina EM, Agostino D, RB J, Wadwa RP, et al. Smoking and arterial stiffness in youth with type 1 diabetes: the SEARCH Cardiovascular Disease Study. J Pediatr 2014;165:110–6. doi: 10.1016/j.jpeds.2014.02.024.
[7] Miller RG, Costacou T, Orchard TJ. Risk factor modeling for cardiovascular disease in type 1 diabetes in the Pittsburgh Epidemiology of Diabetes Complications (EDC) study: A comparison with the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study (DCCT/EDIC). Diabetes 2019;68:409–19. doi: 10.2337/db18-0515.
[8] Livingstone SJ, Looker HC, Hothersall EJ, Wild SH, Lindsay RS, Chalmers J, et al. Risk of cardiovascular disease and total mortality in adults with type 1 diabetes: Scottish registry linkage study. PLoS Med 2012;9:e1001321. doi: 10.1371/journal.pmed.1001321.
[9] Fagot-Campagna A, Fosse S, Roudier C, Romon I, Penfornis A, Lecomte P, et al. Caractéristiques, risque vasculaire et complications chez les personnes diabétiques en France métropolitaine: d'importantes évolutions entre Entred 2001 et Entred 2007. Bull Epidemiol Hebd 2009:450–5 42-43 http://beh.santepubliquefrance.fr/beh/2009/42_43/beh_42_43_2009.pdf.
[10] Dossou Y, Roudier C, Penfornis A, Fagot Campagna A, Druet C. Diabète de type 1 en France métropolitaine: caractéristiques, risque vasculaire, fréquence des complications et qualité des soins. Entred 2001 et Entred 2007. Bull Epidemiol Hebd 2013;37-38:477–84 http://beh.santepubliquefrance.fr/beh/2013/37-38/2013_37-38_4.html.
[11] Multicenter survey of diabetic pregnancy in France. Gestation and diabetes in France study group. Diabetes Care 1991;14:994–1000. doi: 10.2337/diacare.14.11.994.
[12] Ford ES, Mokdad AH, Gregg EW. Trends in cigarette smoking among US adults with diabetes: findings from the behavioral risk factor surveillance system. Prev Med 2004;39:1238–42. doi: 10.1016/j.ypmed.2004.04.039.
[13] Plotnikoff RC, Lippke S, Prodaniuk T, Wild TC, Barrett JE. Demographic, health, and behavioral factors associated with smoking in adults with type 1 or type 2 diabetes. Am J Health Behav 2007;31:13–23. doi: 10.5555/ajhb.2007.31.1.13.
[14] Romon I, Fosse S, Eschwège E, Simon D, Weill A, Varroud-Vial M, et al. Prevalence of macrovascular complications and cardiovascular risk factors in people treated for diabetes and living in France: the ENTRED study 2001. Diabetes Metab 2008;34:140–7. doi: 10.1016/j.diabet.2007.11.002.
[15] Schipf S, Schmidt CO, Alte D, Werner A, Scheidt-Nave C, John U, et al. Smoking prevalence in Type 2 diabetes: results of the Study of Health in Pomerania (SHIP) and the German National Health Interview and Examination Survey (GNHIES). Diabet Med 2009;26:791–7. doi: 10.1111/j.1464-5491.2009.02784.x.

[16] Aeschbacher S, Schoen T, Clair C, Schillinger P, Schönenberger S, Risch M, et al. Association of smoking and nicotine dependence with pre-diabetes in young and healthy adults. Swiss Med Wkly 2014;144:w14019. doi: 10.4414/smw.2014.14019.

[17] Willi C, Bodenmann P, Ghali WA, Faris PD, Cornuz J. Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis. JAMA 2007;298:2654–64. doi: 10.1001/jama.298.22.2654.

[18] Pan A, Wang Y, Talaei M, Hu FB, Wu T. Relation of active, passive, and quitting smoking with incident type 2 diabetes: a systematic review and meta-analysis. Lancet Diabetes Endocrinol 2015;3:958–67. doi: 10.1016/S2213-8587(15)00316-2.

[19] 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;30:540–6. doi: 10.1093/ije/30.3.540.

[20] Yuan S, Xue HL, Yu HJ, Huang Y, Tang BW, Yang XH, et al. Cigarette smoking as a risk factor for type 2 diabetes in women compared with men: a systematic review and meta-analysis of prospective cohort studies. J Public Health 2019;41:e169–e76. doi: 10.1093/pubmed/fdy106.

[21] Magnus MC, Tapia G, Olsen SF, Granstrom C, Mårild K, Ueland PM, et al. Parental smoking and risk of childhood-onset type 1 diabetes. Epidemiology 2018;29:848–56. doi: 10.1097/EDE.0000000000000911.

[22] Magalhães E, Sousa BA, Lima NP, Horta BL. Maternal smoking during pregnancy and offspring body mass index and overweight: a systematic review and meta-analysis. Cad Saude Publica 2019;35:e00176118. doi: 10.1590/0102-311X00176118.

[23] Rogers JM. Smoking and pregnancy: Epigenetics and developmental origins of the metabolic syndrome. Birth Defects Res 2019;111:1259–69. doi: 10.1002/bdr2.1550.

[24] Masalin S, Kautiainen H, Gissler M, Pennanen P, Eriksson JG, Laine MK. Impact of smoking on gestational diabetes mellitus and offspring birthweight in primiparous women. Acta Obstet Gynecol Scand 2020;99:1632–9. doi: 10.1111/aogs.13924.

[25] Leng J, Wang P, Shao P, Zhang C, Li W, Li N, et al. Passive smoking increased risk of gestational diabetes mellitus independently and synergistically with prepregnancy obesity in Tianjin, China. Diabetes Metab Res Rev 2017;33:e2861. doi: 10.1002/dmrr.2861.

[26] Hu Y, Zong G, Liu G, Wang M, Rosner B, Pan A, et al. Smoking cessation, weight change, type 2 diabetes, and mortality. N Engl J Med 2018;379:623–32. doi: 10.1056/NEJMoa1803626.

[27] Luo J, Rossouw J, Tong E, Giovino GA, Lee CC, Chen C, et al. Smoking and diabetes: does the increased risk ever go away? Am J Epidemiol 2013;178:937–45. doi: 10.1093/aje/kwt071.

[28] Oba S, Noda M, Waki K, Nanri A, Kato M, Takahashi Y, et al. Smoking cessation increases short-term risk of type 2 diabetes irrespective of weight gain: the Japan Public Health Center-Based Prospective Study. PLoS One 2012;7:e17061. doi: 10.1371/journal.pone.0017061.

[29] Park SE, Seo MH, Cho JH, Kwon H, Kim YH, Han KD, et al. Dose-dependent effect of smoking on risk of diabetes remains after smoking cessation: a nationwide population-based cohort study in Korea. Diabetes Metab J 2021;45:539–46. doi: 10.4093/dmj.2020.0061.

[30] Benowitz NL. Nicotine addiction. N Engl J Med 2010;362:2295–303. doi: 10.1056/NEJMra0809890.

[31] Andersson K, Arner P. Systemic nicotine stimulates human adipose tissue lipolysis through local cholinergic and catecholaminergic receptors. Int J Obes Relat Metab Disord 2001;25:1225–32. doi: 10.1038/sj.ijo.0801654.

[32] Clair C, Chiolero A, Faeh D, Cornuz J, Marques-Vidal P, Paccaud F, et al. Dose-dependent positive association between cigarette smoking, abdominal obesity and body fat: cross-sectional data from a population-based survey. BMC Public Health 2011;11:23. doi: 10.1186/1471-2458-11-23.

[33] Barr J, Sharma CS, Sarkar S, Wise K, Dong L, Periyakaruppan A, et al. Nicotine induces oxidative stress and activates nuclear transcription factor kappa B in rat mesencephalic cells. Mol Cell Biochem 2007;297:93–9. doi: 10.1007/s11010-006-9333-1.

[34] Morimoto A, Tatsumi Y, Deura K, Mizuno S, Ohno Y, Watanabe S. Impact of cigarette smoking on impaired insulin secretion and insulin resistance in Japanese men: The Saku Study. J Diabetes Investig 2013;4:274–80. doi: 10.1111/jdi.12019.

[35] Ostgren CJ, Lindblad U, Ranstam J, Melander A, Råstam L. Associations between smoking and beta-cell function in a non-hypertensive and non-diabetic population. Skaraborg Hypertension and Diabetes Project. Diabet Med 2000;17:445–50. doi: 10.1046/j.1464-5491.2000.00294.x.

[36] Chen C, Tu YQ, Yang P, Yu QL, Zhang S, Xiong F, et al. Assessing the impact of cigarette smoking on β-cell function and risk for type 2 diabetes in a non-diabetic Chinese cohort. Am J Transl Res 2018;10:2164–74 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6079127/.

[37] Qin R, Chen T, Lou Q, Yu D. Excess risk of mortality and cardiovascular events associated with smoking among patients with diabetes: meta-analysis of observational prospective studies. Int J Cardiol 2013;167:342–50. doi: 10.1016/j.ijcard.2011.12.100.

[38] Pan A, Wang Y, Talaei M, Hu FB. Relation of smoking with total mortality and cardiovascular events among patients with diabetes mellitus: a meta-analysis and systematic review. Circulation 2015;132:1795–804. doi: 10.1161/CIRCULATIONAHA.115.017926.

[39] Al-Delaimy WK, Willett WC, Manson JE, Speizer FE, Hu FB. Smoking and mortality among women with type 2 diabetes: The Nurses' Health Study cohort. Diabetes Care 2001;24:2043–8. doi: 10.2337/diacare.24.12.2043.

[40] Al-Delaimy WK, Manson JE, Solomon CG, Kawachi I, Stampfer MJ, Willett WC, et al. Smoking and risk of coronary heart disease among women with type 2 diabetes mellitus. Arch Intern Med 2002;162:273–9. doi: 10.1001/archinte.162.3.273.

[41] Feodoroff M, Harjutsalo V, Forsblom C, Groop PH. Dose-dependent effect of smoking on risk of coronary heart disease, heart failure and stroke in individuals with type 1 diabetes. Diabetologia 2018;61:2580–9. doi: 10.1007/s00125-018-4725-9.

[42] Jónsdóttir LS, Sigfússon N, Gudnason V, Sigvaldason H, Thorgeirsson G. Do lipids, blood pressure, diabetes, and smoking confer equal risk of myocardial infarction in women as in men? The Reykjavik Study. J Cardiovasc Risk 2002;9:67–76.

[43] Liao D, Ma L, Liu J, Fu P. Cigarette smoking as a risk factor for diabetic nephropathy: A systematic review and meta-analysis of prospective cohort studies. PLoS One 2019;14:e0210213. doi: 10.1371/journal.pone.0210213.

[44] Feodoroff M, Harjutsalo V, Forsblom C, Thorn L, Wadén J, Tolonen N, et al. Smoking and progression of diabetic nephropathy in patients with type 1 diabetes. Acta Diabetol 2016;53:525–33. doi: 10.1007/s00592-015-0822-0.

[45] Jiang N, Huang F, Zhang X. Smoking and the risk of diabetic nephropathy in patients with type 1 and type 2 diabetes: a meta-analysis of observational studies. Oncotarget 2017;8:93209–18. doi: 10.18632/oncotarget.21478.

[46] Braffett BH, Rice MM, Young HA, Lachin JM. Mediation of the association of smoking and microvascular complications by glycemic control in type 1 diabetes. PLoS One 2019;14:e0210367. doi: 10.1371/journal.pone.0210367.

[47] Cai X, Chen Y, Yang W, Gao X, Han X, Ji L. The association of smoking and risk of diabetic retinopathy in patients with type 1 and type 2 diabetes: a meta-analysis. Endocrine 2018;62:299–306. doi: 10.1007/s12020-018-1697-y.

[48] Boretsky A, Gupta P, Tirgan N, Liu R, Godley BF, Zhang W, et al. Nicotine accelerates diabetes-induced retinal changes. Curr Eye Res 2015;40:368–77. doi: 10.3109/02713683.2014.924147.

[49] Clair C, Cohen MJ, Eichler F, Selby KJ, Rigotti NA. The effect of cigarette smoking on diabetic peripheral neuropathy: a systematic review and meta-analysis. J Gen Intern Med 2015;30:1193–203. doi: 10.1007/s11606-015-3354-y.

[50] Ahmad A, Moinuddin A, Ahsan A, Goel A. Study of electrophysiological changes in sensory nerves among diabetic smokers. J Clin Diagn Res 2016;10:Cc09–11. doi: 10.7860/JCDR/2016/16673.7103.

[51] Sen P, Demirdal T, Emir B. Meta-analysis of risk factors for amputation in diabetic foot infections. Diabetes Metab Res Rev 2019;35:e3165. doi: 10.1002/dmrr.3165.

[52] Singh SS, Roeters-van Lennep JE, Lemmers RFH, van Herpt TTW, Lieverse AG, Sijbrands EJG, et al. Sex difference in the incidence of microvascular complications in patients with type 2 diabetes mellitus: a prospective cohort study. Acta Diabetol 2020;57:725–32. doi: 10.1007/s00592-020-01489-6.

[53] Blomster JI, Woodward M, Zoungas S, Hillis GS, Harrap S, Neal B, et al. The harms of smoking and benefits of smoking cessation in women compared with men with type 2 diabetes: an observational analysis of the ADVANCE (Action in Diabetes and Vascular Disease: preterax and diamicron modified release controlled evaluation) trial. BMJ Open 2016;6:e009668. doi: 10.1136/bmjopen-2015-009668.

[54] Iwase M, Fujii H, Idewaki Y, Nakamura U, Ohkuma T, Ide H, et al. Prospective study of cancer in Japanese patients with type 2 diabetes: the Fukuoka Diabetes Registry. Diabetol Int 2019;10:260–7. doi: 10.1007/s13340-019-00390-0.

[55] Magliano DJ, Davis WA, Shaw JE, Bruce DG, Davis TM. Incidence and predictors of all-cause and site-specific cancer in type 2 diabetes: the Fremantle Diabetes Study. Eur J Endocrinol 2012;167:589–99. doi: 10.1530/EJE-12-0053.

[56] Tseng CH. Factors associated with cancer- and non-cancer-related deaths among Taiwanese patients with diabetes after 17 years of follow-up. PLoS One 2016;11:e0147916. doi: 10.1371/journal.pone.0147916.

[57] Ansary-Moghaddam A, Huxley R, Barzi F, Lawes C, Ohkubo T, Fang X, et al. The effect of modifiable risk factors on pancreatic cancer mortality in populations of the Asia-Pacific region. Cancer Epidemiol Biomarkers Prev 2006;15:2435–40. doi: 10.1158/1055-9965.EPI-06-0368.

[58] Hassan MM, Bondy ML, Wolff RA, Abbruzzese JL, Vauthey JN, Pisters PW, et al. Risk factors for pancreatic cancer: case-control study. Am J Gastroenterol 2007;102:2696–707. doi: 10.1111/j.1572-0241.2007.01510.x.

[59] Miele L, Bosetti C, Turati F, Rapaccini G, Gasbarrini A, La Vecchia C, et al. Diabetes and insulin therapy, but not metformin, are related to hepatocellular cancer risk. Gastroenterol Res Pract 2015;2015:570356. doi: 10.1155/2015/570356.

[60] Chiang CH, Lu CW, Han HC, Hung SH, Lee YH, Yang KC, et al. The relationship of diabetes and smoking status to hepatocellular carcinoma mortality. Medicine (Baltimore) 2016;95:e2699. doi: 10.1097/MD.0000000000002699.

[61] Lee JM, Lee KM, Kim DB, Ko SH, Park YG. Colorectal cancer risks according to sex differences in patients with type II diabetes mellitus: a Korean nationwide population-based cohort study. Clin Transl Gastroenterol 2019;10:e00090. doi: 10.14309/ctg.0000000000000090.

[62] Tseng CH. Diabetes but not insulin is associated with higher colon cancer mortality. World J Gastroenterol 2012;18:4182–90. doi: 10.3748/wjg.v18.i31.4182.

[63] Luk AOY, Lau ESH, Cheung KKT, Kong APS, Ma RCW, Ozaki R, et al. Glycaemia control and the risk of hospitalisation for infection in patients with type 2 diabetes: Hong Kong Diabetes Registry. Diabetes Metab Res Rev 2017;33:e2923. doi: 10.1002/dmrr.2923.

[64] Carey IM, Critchley JA, DeWilde S, Harris T, Hosking FJ, Cook DG. Risk of infection in type 1 and type 2 diabetes compared with the general population: a matched cohort study. Diabetes Care 2018;41:513–21. doi: 10.2337/dc17-2131.

[65] Reed GW, Choi H, Lee SY, Lee M, Kim Y, Park H, et al. Impact of diabetes and smoking on mortality in tuberculosis. PLoS One 2013;8:e58044. doi: 10.1371/journal.pone.0058044.

[66] Katon W, von Korff M, Ciechanowski P, Russo J, Lin E, Simon G, et al. Behavioral and clinical factors associated with depression among individuals with diabetes. Diabetes Care 2004;27:914–20. doi: 10.2337/diacare.27.4.914.

[67] McGihon RE, Burns RJ, Deschênes SS, Schmitz N. Longitudinal associations between number of cigarettes per day and depressive symptoms in adult smokers with type 2 diabetes: A path analysis approach. J Psychosom Res 2019;125:109737. doi: 10.1016/j.jpsychores.2019.109737.

[68] Contreras KR, Kominiarek MA, Zollinger TW. The impact of tobacco smoking on perinatal outcome among patients with gestational diabetes. J Perinatol 2010;30:319–23. doi: 10.1038/jp.2009.175.

[69] Beyerlein A, Lack N, von Kries R. No further improvement in pregnancy-related outcomes in the offspring of mothers with pre-gestational diabetes in Bavaria, Germany, between 2001 and 2016. Diabet Med 2018;35:1420–4. doi: 10.1111/dme.13691.

[70] Hong M, Kim HY, Seok H, Yeo CD, Kim YS, Song JY, et al. Prevalence and risk factors of periodontitis among adults with or without diabetes mellitus. Korean J Intern Med 2016;31:910–9. doi: 10.3904/kjim.2016.031.

[71] Jørgensen L, Joakimsen R, Ahmed L, Størmer J, Jacobsen BK. Smoking is a strong risk factor for non-vertebral fractures in women with diabetes: the Tromsø Study. Osteoporos Int 2011;22:1247–53. doi: 10.1007/s00198-010-1340-0.

[72] Peng K, Chen G, Liu C, Mu Y, Ye Z, Shi L, et al. Association between smoking and glycemic control in diabetic patients: results from the risk evaluation of cAncers in Chinese diabeTic Individuals: A lONgitudinal (REACTION) study. J Diabetes 2018;10:408–18. doi: 10.1111/1753-0407.12625.

[73] Kar D, Gillies C, Zaccardi F, Webb D, Seidu S, Tesfaye S, et al. Relationship of cardiometabolic parameters in non-smokers, current smokers, and quitters in diabetes: a systematic review and meta-analysis. Cardiovasc Diabetol 2016;15:158. doi: 10.1186/s12933-016-0475-5.

[74] Gerber PA, Locher R, Schmid B, Spinas GA, Lehmann R. Smoking is associated with impaired long-term glucose metabolism in patients with type 1 diabetes mellitus. Nutr Metab Cardiovasc Dis 2013;23:102–8. doi: 10.1016/j.numecd.2011.08.007.

[75] Melin EO, Thunander M, Svensson R, Landin-Olsson M, Thulesius HO. Depression, obesity, and smoking were independently associated with inadequate glycemic control in patients with type 1 diabetes. Eur J Endocrinol 2013;168:861–9. doi: 10.1530/EJE-13-0137.

[76] Hirai FE, Moss SE, Klein BE, Klein R. Severe hypoglycemia and smoking in a long-term type 1 diabetic population: Wisconsin Epidemiologic Study of Diabetic Retinopathy. Diabetes Care 2007;30:1437–41. doi: 10.2337/dc06-2264.

[77] Jensen MH, Cichosz SL, Hirsch IB, Vestergaard P, Hejlesen O, Seto E. Smoking is associated with increased risk of not achieving glycemic target, increased glycemic variability, and increased risk of hypoglycemia for people with type 1 diabetes. J Diabetes Sci Technol 2021;15:827–32. doi: 10.1177/1932296820922254.

[78] Aulinas A, Colom C, García Patterson A, Ubeda J, María MA, Orellana I, et al. Smoking affects the oral glucose tolerance test profile and the relationship between glucose and HbA1c in gestational diabetes mellitus. Diabet Med 2016;33:1240–4. doi: 10.1111/dme.12966.

[79] Robertson H, Pearson DW, Gold AE. Severe hypoglycaemia during pregnancy in women with Type 1 diabetes is common and planning pregnancy does not decrease the risk. Diabet Med 2009;26:824–6. doi: 10.1111/j.1464-5491.2009.02769.x.

[80] Taylor GM, Lindson N, Farley A, Leinberger-Jabari A, Sawyer K, Te Water Naudé R, et al. Smoking cessation for improving mental health. Cochrane Database Syst Rev 2021;3:CD013522. doi: 10.1002/14651858.CD013522.pub2.

[81] Clair C, Rigotti NA, Porneala B, Fox CS, D'Agostino RB, Pencina MJ, et al. Association of smoking cessation and weight change with cardiovascular disease among adults with and without diabetes. JAMA 2013;309:1014–21. doi: 10.1001/jama.2013.1644.

[82] Liu G, Hu Y, Zong G, Pan A, Manson JE, Rexrode KM, et al. Smoking cessation and weight change in relation to cardiovascular disease incidence and mortality in people with type 2 diabetes: a population-based cohort study. Lancet Diabetes Endocrinol 2020;8:125–33. doi: 10.1016/S2213-8587(19)30413-9.

[83] Phisitkul K, Hegazy K, Chuahirun T, Hudson C, Simoni J, Rajab H, et al. Continued smoking exacerbates but cessation ameliorates progression of early type 2 diabetic nephropathy. Am J Med Sci 2008;335:284–91. doi: 10.1097/MAJ.0b013e318156b799.

[84] Bergman BC, Perreault L, Hunerdosse D, Kerege A, Playdon M, Samek AM, et al. Novel and reversible mechanisms of smoking-induced insulin resistance in humans. Diabetes 2012;61:3156–66. doi: 10.2337/db12-0418.

[85] Aubin HJ, Farley A, Lycett D, Lahmek P, Aveyard P. Weight gain in smokers after quitting cigarettes: meta-analysis. BMJ 2012;345:e4439. doi: 10.1136/bmj.e4439.

[86] Lycett D, Nichols L, Ryan R, Farley A, Roalfe A, Mohammed MA, et al. The association between smoking cessation and glycaemic control in patients with type 2 diabetes: a THIN database cohort study. Lancet Diabetes Endocrinol 2015;3:423–30. doi: 10.1016/S2213-8587(15)00082-0.

[87] Chau TK, Fong DY, Chan SS, Wong JY, Li WH, Tan KC, et al. Misconceptions about smoking in patients with type 2 diabetes mellitus: a qualitative analysis. J Clin Nurs 2015;24:2545–53. doi: 10.1111/jocn.12854.

[88] Georges A, Galbiati L, Clair C. Smoking in men and women with type 2 diabetes: A qualitative gender-sensitive exploration of barriers to smoking cessation among people with type 2 diabetes. PLoS One 2019;14:e0221783. doi: 10.1371/journal.pone.0221783.

[89] Nagrebetsky A, Brettell R, Roberts N, Farmer A. Smoking cessation in adults with diabetes: a systematic review and meta-analysis of data from randomised controlled trials. BMJ Open 2014;4:e004107. doi: 10.1136/bmjopen-2013-004107.

[90] Davies MJ, Heller S, Skinner TC, Campbell MJ, Carey ME, Cradock S, et al. Effectiveness of the diabetes education and self management for ongoing and newly diagnosed (DESMOND) programme for people with newly diagnosed type 2 diabetes: cluster randomised controlled trial. BMJ 2008;336:491–5. doi: 10.1136/bmj.39474.922025.BE.

[91] Lawson PJ, Flocke SA, Casucci B. Development of an instrument to document the 5A's for smoking cessation. Am J Prev Med 2009;37:248–54. doi: 10.1016/j.amepre.2009.04.027.

[92] Lancaster T, Stead LF. Individual behavioural counselling for smoking cessation. Cochrane Database Syst Rev 2017;3:CD001292. doi: 10.1002/14651858.CD001292.pub3.

[93] Canga N, De Irala J, Vara E, Duaso MJ, Ferrer A, Martínez-González MA. Intervention study for smoking cessation in diabetic patients: a randomized controlled trial in both clinical and primary care settings. Diabetes Care 2000;23:1455–60. doi: 10.2337/diacare.23.10.1455.

[94] Thankappan KR, Mini GK, Daivadanam M, Vijayakumar G, Sarma PS, Nichter M. Smoking cessation among diabetes patients: results of a pilot randomized controlled trial in Kerala, India. BMC Public Health 2013;13:47. doi: 10.1186/1471-2458-13-47.

[95] Stead LF, Koilpillai P, Fanshawe TR, Lancaster T. Combined pharmacotherapy and behavioural interventions for smoking cessation. Cochrane Database Syst Rev 2016;3:CD008286. doi: 10.1002/14651858.CD008286.pub3.

[96] Leone FT, Zhang Y, Evers-Casey S, Evins AE, Eakin MN, Fathi J, et al. Initiating pharmacologic treatment in tobacco-dependent adults. An official American Thoracic Society clinical practice guideline. Am J Respir Crit Care Med 2020;202:e5–e31. doi: 10.1164/rccm.202005-1982ST.

[97] Anthenelli RM, Benowitz NL, West R, St Aubin L, McRae T, Lawrence D, et al. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. Lancet 2016;387:2507–20. doi: 10.1016/S0140-6736(16)30272-0.

[98] Benowitz NL, Pipe A, West R, Hays JT, Tonstad S, McRae T, et al. Cardiovascular safety of varenicline, bupropion, and nicotine patch in smokers: a randomized clinical trial. JAMA Intern Med 2018;178:622–31. doi: 10.1001/jamainternmed.2018.0397.

[99] Lindson N, Chepkin SC, Ye W, Fanshawe TR, Bullen C, Hartmann-Boyce J. Different doses, durations and modes of delivery of nicotine replacement therapy for smoking cessation. Cochrane Database Syst Rev 2019;4:CD013308. doi: 10.1002/14651858.CD013308.

[100] Eliasson B, Taskinen MR, Smith U. Long-term use of nicotine gum is associated with hyperinsulinemia and insulin resistance. Circulation 1996;94:878–81. doi: 10.1161/01.cir.94.5.878.

[101] Marsh HS, Dresler CM, Choi JH, Targett DA, Gamble ML, Strahs KR. Safety profile of a nicotine lozenge compared with that of nicotine gum in adult smokers with underlying medical conditions: a 12-week, randomized, open-label study. Clin Ther 2005;27:1571–87. doi: 10.1016/j.clinthera.2005.10.008.

[102] Tonstad S, Lawrence D. Varenicline in smokers with diabetes: A pooled analysis of 15 randomized, placebo-controlled studies of varenicline. J Diabetes Investig 2017;8:93–100. doi: 10.1111/jdi.12543.

[103] Le Faou AL, Ruppert AM, Dautzenberg B, Roche N. Joint position of the French speaking society of pulmonology (SPLF) and tabacology (SFT) on e-cigarette use as a smoking cessation tool. Tob Prev Cessation 2020;6:A56. doi: 10.18332/tpc/128426.

[104] French High Council for Public Health (Haut Conseil de la Santé Publique). Report on the benefits and risks of electronic cigarettes [Avis relatif aux bénéfices-risques de la cigarette électronique], https://www.hcsp.fr/Explore.cgi/AvisRapportsDomaine?clefr=1138; 2021 [accessed 19 April 2022].

[105] Selph S, Patnode C, Bailey SR, Pappas M, Stoner R, Chou R. Primary care-relevant interventions for tobacco and nicotine use prevention and cessation in children and adolescents: Updated evidence report and systematic review for the US Preventive Services Task Force. JAMA 2020;323:1599–608. doi: 10.1001/jama.2020.3332.

[106] Lam TH, Li WH, Wang MP, Cheung YT, Cheung DY, Ho KY, et al. A brief, tailored smoking cessation intervention for smokers with diabetes mellitus in Hong Kong. Hong Kong Med J 2017;23(Suppl 2):10–1 https://www.hkmj.org/abstracts/v23%20Suppl%202n3/10.htm.

[107] Sawicki PT, Didjurgeit U, Mühlhauser I, Berger M. Behaviour therapy versus doctor's anti-smoking advice in diabetic patients. J Intern Med 1993;234:407–9. doi: 10.1111/j.1365-2796.1993.tb00763.x.

[108] Ardron M, MacFarlane IA, Robinson C, van Heyningen C, Calverley PM. Anti-smoking advice for young diabetic smokers: is it a waste of breath? Diabet Med 1988;5:667–70. doi: 10.1111/j.1464-5491.1988.tb01077.x.

[109] Aung MN, Yuasa M, Moolphate S, Lorga T, Yokokawa H, Fukuda H, et al. Effectiveness of a new multi-component smoking cessation service package for patients with hypertension and diabetes in northern Thailand: a randomized controlled trial (ESCAPE study). Subst Abuse Treat Prev Policy 2019;14:10. doi: 10.1186/s13011-019-0197-2.

[110] Fowler PM, Hoskins PL, McGill M, Dutton SP, Yue DK, Turtle JR. Anti-smoking programme for diabetic patients: the agony and the ecstasy. Diabet Med 1989;6:698–702. doi: 10.1111/j.1464-5491.1989.tb01260.x.

[111] Hokanson JM, Anderson RL, Hennrikus DJ, Lando HA, Kendall DM. Integrated tobacco cessation counseling in a diabetes self-management training program: a randomized trial of diabetes and reduction of tobacco. Diabetes Educ 2006;32:562–70. doi: 10.1177/0145721706289914.

[112] Ng N, Nichter M, Padmawati RS, Prabandari YS, Muramoto M, Nichter M. Bringing smoking cessation to diabetes clinics in Indonesia. Chronic Illn 2010;6:125–35. doi: 10.1177/1742395310364253.
[113] Pérez-Tortosa S, Roig L, Manresa JM, Martin-Cantera C, Puigdomènech E, Roura P, et al. Continued smoking abstinence in diabetic patients in primary care: a cluster randomized controlled multicenter study. Diabetes Res Clin Pract 2015;107:94–103. doi: 10.1016/j.diabres.2014.09.009.
[114] Persson LG, Hjalmarson A. Smoking cessation in patients with diabetes mellitus: results from a controlled study of an intervention programme in primary healthcare in Sweden. Scand J Prim Health Care 2006;24:75–80. doi: 10.1080/02813430500439395.
[115] Huo X, Spatz ES, Ding Q, Horak P, Zheng X, Masters C, et al. Design and rationale of the Cardiovascular Health and Text Messaging (CHAT) Study and the CHAT-Diabetes Mellitus (CHAT-DM) Study: two randomised controlled trials of text messaging to improve secondary prevention for coronary heart disease and diabetes. BMJ Open 2017;7:e018302. doi: 10.1136/bmjopen-2017-018302.
[116] Martinez SA, Quaife SL, Hasan A, McMillan KA, Beebe LA, Muirhead F. Contingency management for smoking cessation among individuals with type 2 diabetes: protocol for a multi-center randomized controlled feasibility trial. Pilot Feasibility Stud 2020;6:82. doi: 10.1186/s40814-020-00629-7.
[117] Reid RD, Malcolm J, Wooding E, Geertsma A, Aitken D, Arbeau D, et al. Prospective, cluster-randomized trial to implement the Ottawa Model for Smoking Cessation in diabetes education programs in Ontario. Canada. Diabetes Care 2018;41:406–12. doi: 10.2337/dc17-1809.