



**HAL**  
open science

## Smoking and Diabetes: Sex and Gender Aspects and Their Effect on Vascular Diseases

Blandine Tramunt, Alexia Rouland, Vincent Durlach, Bruno Vergès, Daniel Thomas, Ivan Berlin, Carole Clair

► **To cite this version:**

Blandine Tramunt, Alexia Rouland, Vincent Durlach, Bruno Vergès, Daniel Thomas, et al.. Smoking and Diabetes: Sex and Gender Aspects and Their Effect on Vascular Diseases. Canadian Journal of Cardiology, 2023, 39 (5), pp.681 - 692. 10.1016/j.cjca.2023.01.018 . hal-04937895

**HAL Id: hal-04937895**

**<https://ut3-toulouseinp.hal.science/hal-04937895v1>**

Submitted on 10 Feb 2025

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License



## Review

# Smoking and Diabetes: Sex and Gender Aspects and Their Effect on Vascular Diseases

Blandine Tramunt, MD,<sup>a,b</sup> Alexia Rouland, MD,<sup>c</sup> Vincent Durlach, MD, PhD,<sup>d</sup>  
Bruno Vergès, MD, PhD,<sup>c</sup> Daniel Thomas, MD,<sup>e</sup> Ivan Berlin, MD, PhD,<sup>f</sup> and  
Carole Clair, MD, MSc<sup>g</sup>

<sup>a</sup>Institute of Metabolic and Cardiovascular Diseases, UMR1297 INSERM/UPS, Toulouse University, Toulouse, France

<sup>b</sup>Department of Diabetology, Metabolic Diseases and Nutrition, Toulouse University Hospital, Toulouse, France

<sup>c</sup>Department of Endocrinology, Diabetology and Metabolic Diseases, CHU Dijon, Dijon, France

<sup>d</sup>Champagne-Ardenne University, UMR CNRS 7369 MEDyC and Cardio-Thoracic Department, Reims University Hospital, Reims, France

<sup>e</sup>Institute of Cardiology, Pitié-Salpêtrière University Hospital, Sorbonne University, Paris, France

<sup>f</sup>Department of Pharmacology, Pitié-Salpêtrière University Hospital, Paris, France

<sup>g</sup>Department of Ambulatory Care, Center for Primary Care and Public Health University of Lausanne, Lausanne, Switzerland

## ABSTRACT

Smoking and diabetes mellitus (DM) have been identified as 2 major cardiovascular risk factors for many years. In the field of cardiovascular diseases, considering sex differences, or gender differences, or both has become an essential element in moving toward equitable and quality health care. We reviewed the effect of sex or gender on the link between smoking and DM. The risk of type 2 DM due to smoking has been established in both sexes at the same level. As is the case in the general population, the prevalence of smoking in those with DM is higher in men than in women, although the decrease in smoking

## RÉSUMÉ

Le tabagisme et le diabète sucré (DS) sont considérés comme les deux principaux facteurs de risque cardiovasculaire depuis plusieurs années. Dans le domaine des maladies cardiovasculaires, les différences entre les sexes ou les différences entre les genres, ou les deux, sont maintenant des éléments importants à prendre en considération pour évoluer vers des soins de santé équitables et de qualité. Nous passons en revue les effets du sexe ou du genre sur le lien entre le tabagisme et le DS. Le risque de DS de type 2 en raison du tabagisme a été établi au même niveau dans les deux sexes. Comme c'est le cas

Sex and gender dimensions have become a major concern in health and health care in recent years, particularly in the field of metabolic and chronic diseases.<sup>1-3</sup> The interplay between smoking and diabetes mellitus (DM) is complex; both are major cardiovascular risk factors and are preventable. Sex dimensions (biological differences that influence physiological and/or physiopathological processes between men and women) and gender dimensions (socially constructed roles, behaviours, and expressions of women, men, and gender-diverse people) influence the association of smoking with DM at different levels (Figs. 1-3).<sup>4,5</sup>

The prevalence of type 1 DM (T1DM) and type 2 DM (T2DM) differs among men and women. According to the 10th edition of the International Diabetes Federation Atlas, the estimated prevalence of DM in women is slightly lower than that in men (10.2% vs 10.8%, respectively).<sup>6</sup> Sex steroids and genetic factors have an influence on energy balance and glucose homeostasis, and partly explain these differences.<sup>7</sup> However, gendered health behaviours (ie, behaviours that are influenced socially on the basis of gender norms) such as diet, smoking, or physical activity, also contribute strongly to these differences in prevalence among men and women.

Cigarette smoking is the main avoidable cause of death in high- and middle-income countries. It is responsible for cancers, cardiovascular and respiratory diseases, and has been associated with an increasing number of other diseases, including T2DM.<sup>8</sup> Smoking behaviour is socially influenced and the tobacco industry has played an important role in changing gender norms, resulting in a sharp increase in smoking prevalence among women.<sup>9</sup>

Received for publication July 9, 2022. Accepted January 17, 2023.

Corresponding author: Dr Carole Clair, Department of Ambulatory Care, Center for Primary Care and Public Health, University of Lausanne, Rue du Bugnon 44, 1011 Lausanne, Switzerland. Tel.: +41795568146.

E-mail: [carole.clair@unisante.ch](mailto:carole.clair@unisante.ch)

See page 689 for disclosure information.

observed in recent years is more pronounced in men than in women. Regarding chronic DM complications, smoking is an independent risk factor for all-cause mortality, as well as macrovascular and microvascular complications, in both sexes. Nevertheless, in type 2 DM, the burden of smoking appears to be greater in women than in men for coronary heart disease morbidity, with women having a 50% greater risk of fatal coronary event. Women are more dependent to nicotine, cumulate psychosocial barriers to quitting smoking, and are more likely to gain weight, which might make it more difficult for them to quit smoking. Smoking cessation advice and treatments should take into account gender differences to improve the success and long-term maintenance of abstinence in people with and without DM. This might include interventions that address emotions and stress in women or designed to reach specific populations of men.

Regarding the association of smoking with DM, sex and gender might have an influence (Fig. 1). Smoking and smoking cessation might have a differential action on the risk of DM and its complications in men and women, related to behavioural differences (gender) and differences due to biological factors (sex).<sup>10,11</sup>

Taking into account gender and sex dimensions makes it possible to better adapt care for populations in terms of prevention, diagnosis, and the therapeutic approach and thus to move toward socially equitable medicine.<sup>12</sup>

This article focuses on sex and gender differences in the interplay of smoking and DM; we discuss the effect of smoking on the incidence of T2DM, the prevalence of smoking in people with DM, the effect of smoking on DM complications, smoking cessation interventions, and the benefits and risks of smoking cessation in people with T2DM. The consequences of smoking in pregnant women with DM and the association of smoking with gestational DM are not discussed.

### Association of Smoking With Incident T2DM in Men and Women

An association of smoking and the incidence of T2DM has been shown for several decades. Meta-analyses have shown an increased risk of approximately 40% in developing T2DM in smokers.<sup>8,13-15</sup> Moreover, some authors have reported differential effect of nicotine on  $\beta$ -cell function according to sex.<sup>16</sup> Many studies have evaluated the association of smoking, sex, and the risk of developing T2DM.

Meta-analyses published in the past 2 decades support the link between smoking and T2DM in men and women.<sup>13,14</sup> A meta-analysis published in 2015, which included 88 studies with more than 5 million participants and more than 220,000 cases of incident DM, showed a relative risk (RR) of T2DM in smokers compared with nonsmokers of 1.42 (95% confidence interval [CI], 1.34-1.50) and 1.33 (95% CI, 1.26-1.41)

dans la population générale, la prévalence du tabagisme chez les personnes atteintes du DS est plus élevée chez les hommes que chez les femmes, bien que la diminution observée du tabagisme au cours des dernières années soit plus marquée chez les hommes que chez les femmes. En ce qui concerne les complications à long terme du DS, le tabagisme est un facteur de risque indépendant de la mortalité toutes causes confondues, ainsi que des complications macrovasculaires et microvasculaires, dans les deux sexes. Néanmoins, lors de DS de type 2, le fardeau du tabagisme semble plus important chez les femmes que chez les hommes en ce qui concerne la morbidité liée à la maladie coronarienne, puisque les femmes montrent un risque 50 % plus élevé de subir un événement coronarien mortel. Les femmes sont plus dépendantes à la nicotine, cumulent les obstacles psychosociaux à la cessation du tabagisme et sont plus susceptibles de prendre du poids. Par conséquent, la cessation du tabagisme pourrait être plus difficile pour elles. Dans les conseils et les traitements pour cesser de fumer, il faudrait tenir compte des différences de genre afin d'accroître la réussite et de favoriser le maintien à long terme de l'abstinence chez les personnes qui sont atteintes ou non du DS. Il pourrait s'agir par exemple d'interventions qui portent sur les émotions et le stress chez les femmes, ou qui sont conçues pour rejoindre des populations particulières d'hommes.

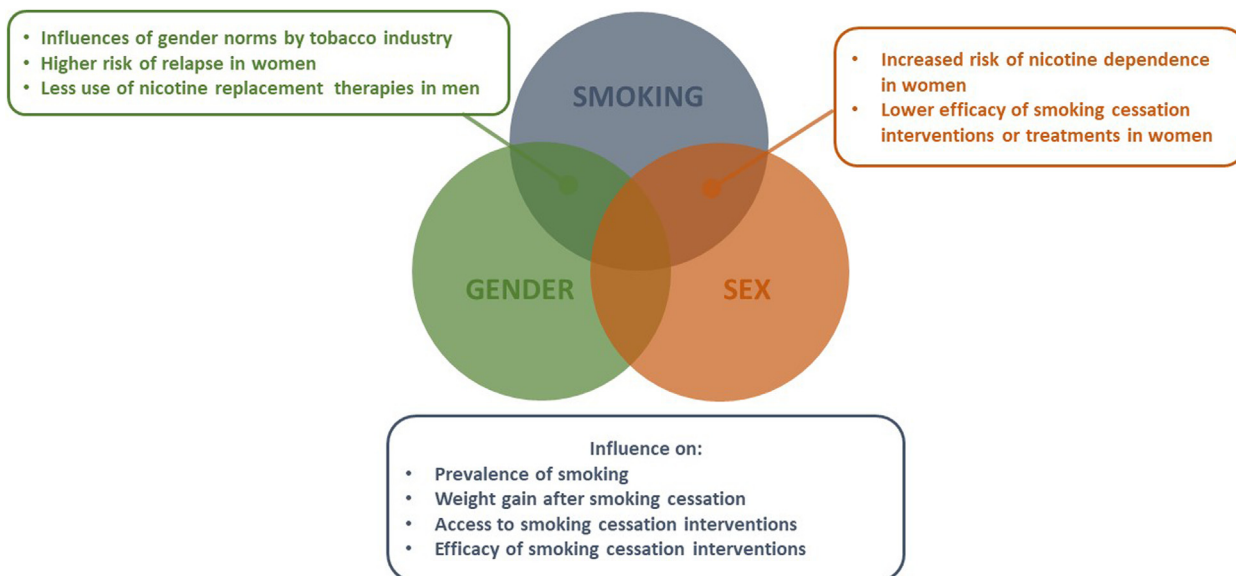
in men and women, respectively.<sup>14</sup> The authors estimated that, on the basis of the assumption that the association of smoking with T2DM is causal, 11.7% of T2DM cases in men and 2.4% of T2DM cases in women could be attributed to active smoking. This figure is likely an underestimate, because passive smoking was not taken into account.<sup>14</sup> According to some authors, this excess risk appears after age of 35 in men and women.<sup>17</sup> Because of the equivalent RR for men and women, it would seem that this risk is equivalent among the 2 sexes. More recently, Yuan et al. published a meta-analysis on the risk of smoking-related T2DM in women compared with that in men. After inclusion of 20 prospective cohort studies with more than 5 million participants and more than 220,000 cases of incident DM, the authors still reported a positive association of smoking with T2DM with an increased risk of 35% and 27% in male and female smokers, respectively, compared with that in nonsmokers. The RR ratio for men and women was nonsignificant at 0.98 (95% CI, 0.96-1.01). The authors therefore concluded that there was no sexual dimorphism in the association of active smoking with the risk of developing T2DM.<sup>15</sup> Although active smoking is associated with the risk of T2DM, passive smoking has also been shown to be a risk factor for T2DM in men and women.<sup>14,18</sup>

#### Highlight

- An association of smoking (active and passive) and the development of T2DM has been established in women and men.
- The excess risk of T2DM conferred by smoking appears to be comparable for men and women.

### Differences in the Prevalence of Smoking for Men and Women With DM

The prevalence of smoking among people with DM is 20%-30%, similar to that observed in the general

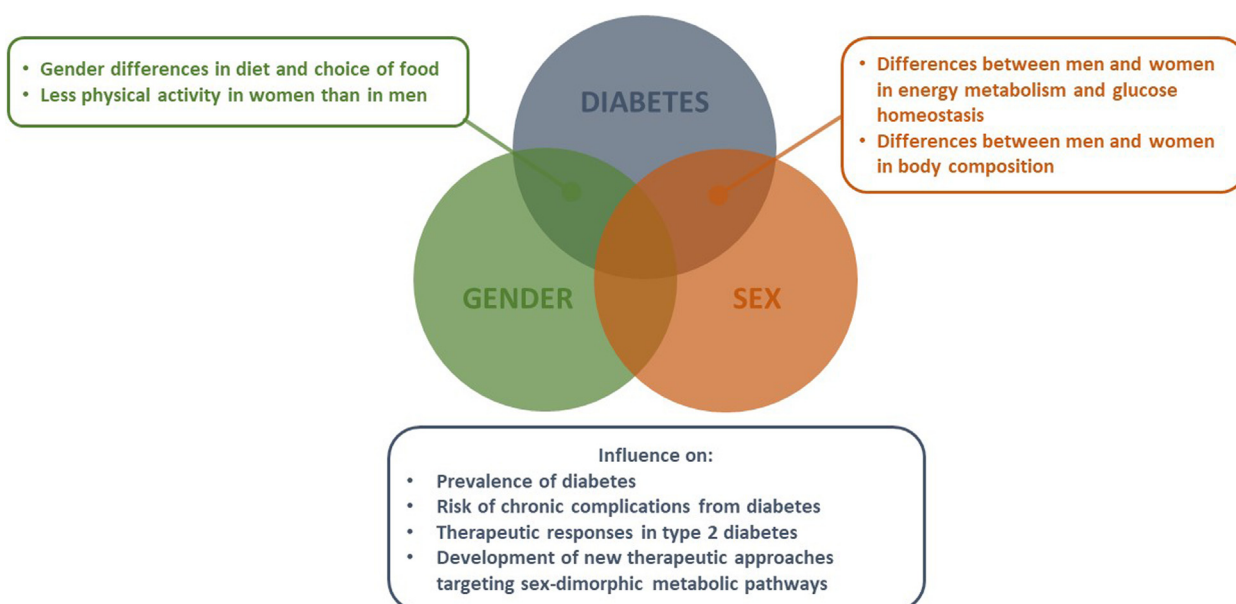


**Figure 1.** Sex and gender aspects in smoking and diabetes; a complex interplay: smoking.

population.<sup>19</sup> A recent review shows that patients with T2DM are 26% less likely to smoke compared with those without T2DM.<sup>20</sup> Age, geographic region, and socioeconomic level are factors that influence smoking prevalence rates.<sup>21</sup> Overall it seems that the prevalence of smoking among men is higher than that of women, regardless of the type of DM.<sup>20,22</sup> Because of different sociocultural behaviours and norms, disparities in prevalence are observed according to geographic region. In a study conducted by the World Health Organization on vascular complications among people with DM between 1983 and 1990, the prevalence of smoking among men had decreased remarkably, whereas it had remained

stable among women (10.7% decrease in men vs 0.5% decrease in women).<sup>23,24</sup>

The intersectionality between sex or gender, ethnicity, and socioeconomic level is of interest. For example, in a population of 1899 patients with DM (16% smokers, 31% ex-smokers, and 51% nonsmokers) in London, Gulliford et al. observed that smoking was more prevalent among people of Caucasian origin than it was among people of African or Afro-Caribbean origin.<sup>21</sup> Few differences were observed for men and women among people of Caucasian origin (22% vs 20%, respectively), whereas a greater difference existed among men and women of Afro-Caribbean (15% vs 10%, respectively) or



**Figure 2.** Sex and gender aspects in smoking and diabetes; a complex interplay: diabetes.

African (8 vs 2%, respectively) origin.<sup>21</sup> A Centers for Disease Control and Prevention study conducted between 2001 and 2010 showed a decrease in smoking prevalence in all ethnic subgroups.<sup>25</sup> However, the decrease was less pronounced in people with DM, especially women with DM compared with men with DM (−2.2% in men and −0.8% in women). In contrast to many studies that showed a male preponderance in the prevalence of smoking in people with DM, a Canadian study showed that female sex was more frequently associated with the risk of being a smoker, regardless of the type of DM.<sup>26</sup> One of the explanations put forward by the authors was the greater decline in smoking prevalence among men than among women. Similarly, studies in young populations with or without DM have shown that young girls were more exposed to tobacco than were young boys.<sup>26,27</sup> In a recent Austrian study, an increase in smoking prevalence was observed among women between 2007 and 2014, whereas it remained stable among men.<sup>28</sup> Furthermore, in this study, analyses of people with DM revealed that the most notable increase was observed in populations of women with DM, more specifically in women between 30 and 64 years old and in those older than 65 years old, with the prevalence increasing from 9.9% to 16.9%.

Thus, although the prevalence of smoking is globally higher among men than it is among women with DM, some data tend to show that women with DM have increased their smoking prevalence in recent years, particularly the younger generations, or at least that the decrease in smoking prevalence is less pronounced in women than in men. This phenomenon can be explained by the tobacco industry's advertising campaigns targeting women.<sup>29,30</sup> Moreover, countries with higher gender empowerment have a higher proportion of women who smoke, in keeping with the industry's use of female empowerment to promote smoking behaviour.<sup>31</sup> Women entering the workforce have not only assumed more traditional male roles, but they have also combined family care and paid work, resulting in stressful life experiences that women try to cope with by using cigarettes.<sup>32</sup> In high-income countries, it has been reported that smoking affects more people of low socioeconomic classes and women with stress, mental health disorders, or with histories of violence, resulting in increasing health inequalities.<sup>33</sup> It is therefore important that health and prevention policies target particularly women.

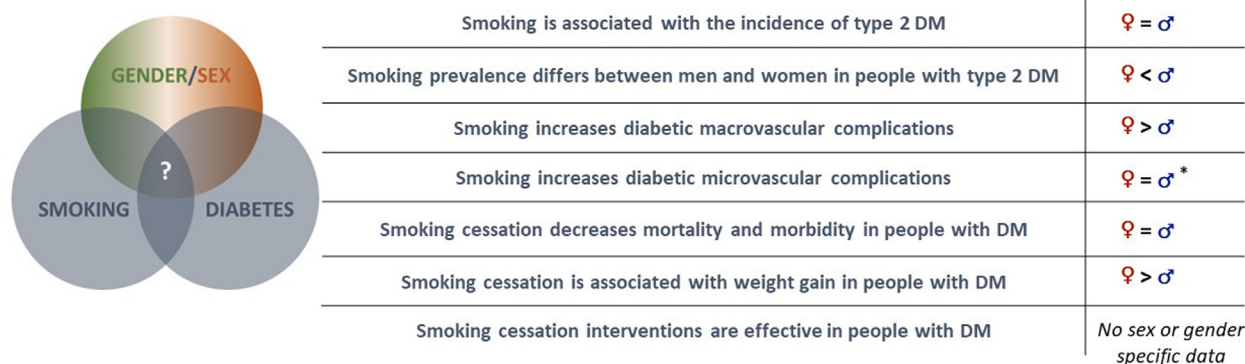
### Highlight

- As observed in the general population, the prevalence of smoking varies among men and women with DM, it being overall higher in men than in women.
- The trend toward a decrease in smoking observed in men in recent years seems to be less pronounced in women.

### Influence of Sex and Gender in Interaction With Smoking on Complications of Chronic DM

The role of smoking in all-cause mortality and developing macrovascular and microvascular complications in the population with DM has been shown by numerous studies, smoking being the strongest predictor of death among all risk factors.<sup>34</sup> Studies in the general population have shown a greater negative health effect of smoking in women than in men for cardiovascular diseases.<sup>35</sup> In people with DM, studies show sex differences in the occurrence of several chronic diabetic complications, especially a higher burden of DM on cardiovascular risk in women<sup>1,36-40</sup> (Table 1). In a meta-analysis of 37 prospective studies that included people with and without T2DM, Huxley et al. reported a higher RR of fatal coronary events in women than in men with DM compared with women and men without DM.<sup>41</sup> The RR ratio between women and men with DM was 1.46 (95% CI, 1.14-1.88), indicating that women with DM had approximately a 50% higher risk of a fatal coronary event than did men with DM. For T1DM, the same authors reported an excess risk of all-cause mortality of approximately 40% in women compared with men. The risk of fatal and nonfatal vascular events was twice as high in women as in men.<sup>36</sup> Similar results were reported for the risk of stroke in another study.<sup>42</sup>

Regarding the sex-specific effect of smoking on cardiovascular and some microvascular complications in populations with DM, the deleterious effect of smoking is greater among women than men (summarized in Table 2 and Fig. 4). As early as 1990, Moy et al. described the deleterious role of tobacco in women with DM in a US cohort of 723 participants with T1DM.<sup>43</sup> In this cohort, smoking was an independent risk factor for mortality in women but not in men. The excess mortality in women with DM could be explained



**Figure 3.** Sex and gender aspects in smoking and diabetes; a complex interplay: the association of smoking and diabetes. DM, diabetes mellitus.

\* Except for microalbuminuria: ♀ > ♂.



**Table 1. Sex-stratified effect of diabetes on chronic macro- and microvascular complications**

Reference	Type of diabetes	Outcome	Women RR (95% CI)*	Men RR (95% CI)*	Men HR (95% CI)†	Women:men ratio of RR (95% CI)
Macrovascular complications						
Huxley et al. <sup>41</sup>	T2DM	CHD mortality (37 studies)	3.50 (2.70-4.53)	2.06 (1.81-2.34)	—	1.70 (1.27-2.27)
		CHD mortality (multiple adjusted; 29 studies;)	2.95 (2.39-3.65)	2.02 (1.76-2.31)	—	1.46 (1.14-1.88)
Peters et al. <sup>42</sup>	T2DM	Stroke (64 studies)	2.28 (1.93-2.69)	1.83 (1.60-2.08)	—	1.27 (1.10-1.46)
Microvascular complications						
Singh et al. <sup>60</sup>	T2DM	Microalbuminuria	—	—	1.64 (1.21-2.24)	—
		Retinopathy	—	—	1.27 (0.93-1.74)‡	—
		Neuropathy	—	—	1.35 (0.99-1.83)‡	—

CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio; RR, relative risk; T2DM, type 2 diabetes mellitus.

\* People without diabetes are the reference group.

† Women are the reference group.

‡ Not significant.

by the higher rate of coronary heart disease (CHD) and mediated by greater contribution of cardiovascular risk factors such as high blood pressure and higher plasma lipid levels in women with DM than in men with DM.<sup>41</sup> Several mechanisms might explain the greater toxicity of smoking in women, but they are not fully understood. First, women have on average a smaller body surface than men and so they might extract more carcinogens and toxic substances from tobacco smoke than do men.<sup>44</sup> Second, hormones such as estrogens have an influence on the metabolism of nicotine, increasing its clearance.<sup>45</sup> As a consequence women might smoke more intensely to compensate, leading to an increase in toxicity.<sup>46</sup> Third, women are more exposed to secondhand smoke than are men.<sup>47</sup> Thus, women who smoke are more likely to be doubly exposed to secondhand smoke and to their own consumption, leading to higher total exposure than occurs for men. Nevertheless, this excess risk is not reported in all studies; for example, in several studies that reported an increased risk of cardiovascular disease in women with T1DM compared with that in men, smoking was not considered to be an explanation for the sex difference.<sup>48-50</sup> Furthermore, in the **Europe and Diabetes (EURODIAB) Prospective Complications Study**, current smoking was identified as a risk factor for CHD only in men, although the difference between men and

women was not statistically significant after multivariate adjustment.<sup>51</sup> In the **Finnish Diabetic Nephropathy (Finn-Diane)** study, which included 4506 individuals with T1DM, no interaction was shown between smoking and sex in cardiovascular disease risk with the exception of stroke.<sup>52</sup> This risk was greater in current and former smokers than in never-smokers in men only.

In T1DM, data are scarce and conflicting concerning the role of smoking in the sex-specific cardiovascular morbidity-mortality. In a British prospective study of women, with a mean follow-up of 6.1 years, smoking was the strongest modifiable cardiovascular risk factor in middle-aged women with DM, particularly in those treated with insulin, compared with women of the same age without DM.<sup>53</sup> The 5-year incidence rate of cardiovascular disease was 4.6 per 100 nonsmoking women with DM, 5.9 in non-insulin-treated smoking women with DM, and 11.0 in insulin-treated smoking women with DM, all aged 50-69 years.<sup>53</sup> In a Swedish cohort of T2DM, the hazard ratio (HR) for the risk of heart attack (fatal or not) attributable to smoking was greater in women than in men (HR, 2.17 [95% CI, 1.69-2.79] vs 1.45 [95% CI, 1.19-1.77], respectively).<sup>54</sup> In a Finnish cohort of people with and without T2DM that included 28,712 men and 30,700 women aged 25-64 years, smokers

**Table 2. Sex-stratified effect of smoking on chronic macro- and microvascular complications in people with diabetes**

Study	Type of diabetes	Outcome	Women RR or HR (95% CI)	Men RR or HR (95% CI)	Women:men ratio of HR (95% CI)
Macrovascular complications					
Moy et al. <sup>43</sup>	T1DM	Mortality	RR, 2.57 (1.04-6.36)*	RR, 1.21 (0.57-2.55)*,†	—
		CHD mortality	RR, 5.16 (1.29-20.57)*	RR, 0.78 (0.21-2.86)*,†	—
Nilsson et al. <sup>54</sup>	T2DM	Fatal/nonfatal MI	HR, 2.17 (1.69-2.79)*	HR, 1.45 (1.19-1.77)*	—
Barengo et al. <sup>55</sup>	T2DM	All-cause mortality	HR, 4.51 (2.91-7.00)‡	HR, 3.76 (2.95-4.78)‡	—
		CHD mortality	HR, 6.92 (2.79-17.19)‡	HR, 2.62 (1.60-4.29)‡	—
		CHD incidence	HR, 4.55 (2.48-8.33)‡	HR, 3.27 (2.45-4.36)‡	—
Blomster et al. <sup>56</sup>	T2DM	Major coronary events	—	—	1.64 (0.83-3.26)†,§
Microvascular complications					
Blomster et al. <sup>56</sup>	T2DM	Nephropathy	—	—	1.04 (0.57-1.89)†,§

CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; RR, relative risk; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

\* Cox regression analysis.

† Not significant.

‡ People without diabetes and without smoking are the reference group (HR = 1). In the table, results are for women or men with T2DM and smokers. In women with T2DM and nonsmokers, HRs (95% CI) were 2.11 (1.71-2.59), 4.06 (2.83-5.82), and 2.60 (2.02-3.35) for all-cause mortality, CHD mortality, and CHD incidence, respectively. In men with T2DM and nonsmokers, HRs (95% CI) were 2.03 (1.51-2.74), 2.62 (1.60-4.29), and 1.56 (1.08-2.24) for all-cause mortality, CHD mortality, and CHD incidence, respectively.

§ Ratio of the HRs (women:men) for daily smoking vs never smoking.

with DM had greater all-cause and CHD mortality than nonsmokers with DM, regardless of sex. In addition, the HRs for coronary mortality or incidence of CHD were higher in female smokers with DM than in male smokers with DM, suggesting a more deleterious role of smoking in women with DM.<sup>55</sup>

In the **Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE)** study, which included 11,140 people with T2DM, 17% of men and 9% of women were smokers, whereas 38% of men and 14% of women had stopped smoking.<sup>56</sup> Smoking was a risk factor for all cardiovascular events (except major cerebrovascular events), as well as for all-cause mortality, nephropathy, and cancer. The female-to-male HR for smokers vs nonsmokers did not reach significance for any of the events, but tended to be higher in women for major coronary events (HR, 1.64 [95% CI, 0.83-3.26];  $P = 0.08$ ). Although this result did not reach significance, the authors concluded that there was a signal in favour of an increased risk of smoking in women with T2DM compared with that in men with T2DM who were smokers.

Results are contradictory as to the incidence of microvascular complications. Some authors reported a greater incidence in men than in women, whereas others reported no difference.<sup>57-59</sup> These studies mainly concern patients with T2DM. Nevertheless, only a few studies evaluated the role of smoking to explain such differences. In the previously mentioned ADVANCE study, a similar effect was observed for active smoking on the risk of diabetic nephropathy for men and women (HR between women and men: 1.04 [95% CI, 0.57-1.89]).<sup>56</sup> The authors acknowledged the lack of statistical power to detect a sex-differentiated effect of smoking. Indeed, the number of women smokers or ex-smokers was 434 and 658, respectively, compared with 1116 and 2466 male smokers or ex-smokers, respectively.<sup>56</sup> In a Dutch prospective cohort of 1886 patients with T2DM with a mean follow-up of approximately 7 years, the incidence of microalbuminuria was significantly higher in men than in women (HR, 1.64 [95% CI, 1.21-2.24]).<sup>60</sup> No sex difference was shown in the incidence of diabetic retinopathy or diabetic neuropathy. When the effect of smoking on microvascular complications was assessed, the interaction analyses indicated a more deleterious effect of smoking on microalbuminuria in

women than in men. No interaction was found in the assessment of the role of smoking on the occurrence of other microvascular complications.

Few data of this type are available in populations with T1DM, making it difficult to conclude that smoking has a differentially deleterious effect on microvascular complications according to sex.

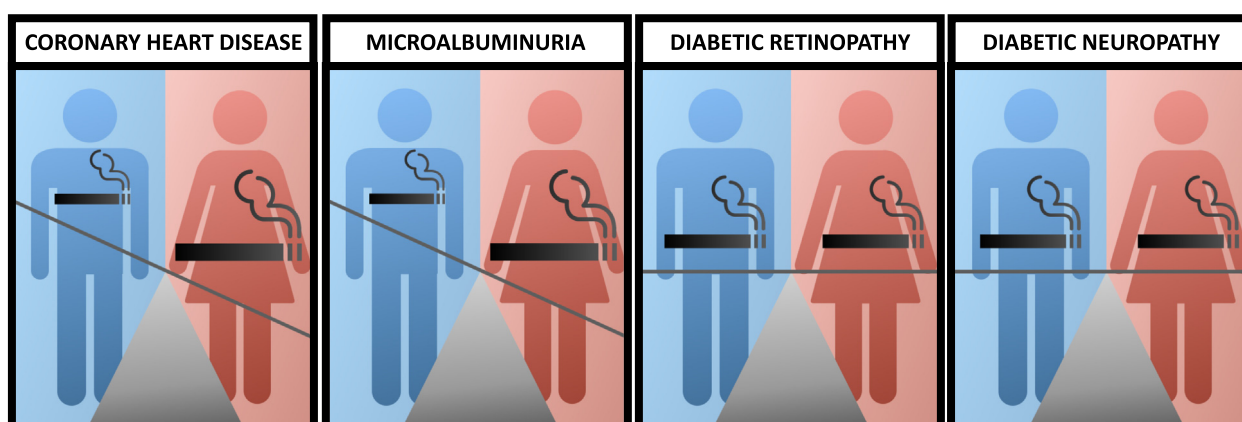
### Highlight

- In people with DM, smoking is an independent risk factor for all-cause mortality and macrovascular and microvascular complications in women and men.
- In people with T2DM, the burden of smoking appears to be greater in women than in men in terms of coronary morbidity.
- In people with T1DM, it is difficult to conclude whether smoking has a different effect on men or women because of the scarce and conflicting data.

## Smoking Cessation in People With DM: Sex and Gender Specificities

### Benefits of smoking cessation in people with DM

Smoking cessation in the population with DM is associated with a reduced risk of mortality and chronic diabetic complications, macrovascular and microvascular.<sup>14,38,61-64</sup> Some studies have focused exclusively on populations of women with DM, showing a clear benefit of smoking cessation in this population, particularly in terms of cardiovascular disease.<sup>63-65</sup> Few studies have reported sex-stratified data that compared the benefits of smoking cessation in men and women. In the previously mentioned ADVANCE study, no difference in the benefit of smoking cessation in terms of all-cause mortality, cardiovascular morbidity, nephropathy, or cancer was found between men and women with T2DM.<sup>56</sup> Notably, however, in that study, only the benefit for all-cause mortality after smoking cessation was significant (30% risk reduction) in both sexes.<sup>56</sup> Similarly, in the Finnish study by Barengo et al., ex-smokers with DM showed a reduction in the risk of all-cause and coronary mortality compared with that for



**Figure 4.** Effect of smoking on chronic complications of type 2 diabetes mellitus according to sex.

smokers with DM, and this was comparable for men and women.<sup>55</sup> However, in both sexes, an excess risk persisted compared with nonsmoking people with DM. However, in terms of the incidence of CHD, the benefit of quitting smoking compared with continuing to smoke was greater in women than in men.<sup>55</sup> At the microvascular level, the data are even more scarce. In T2DM, sex was not found to be an independent predictor of the absence of microalbuminuria at 1 year after smoking cessation.<sup>66</sup> Thus, even if the data are tenuous, it seems that smoking cessation is beneficial in the population with DM in a comparable manner for men and women. Moreover, this benefit of smoking cessation persists beyond the associated weight gain secondary to cessation in both sexes, even if an attenuation is sometimes described.<sup>61,66,67</sup>

### Weight gain after smoking cessation in people with DM

Weight gain after cessation is a major concern and often constitutes an obstacle to smoking cessation.<sup>68</sup> In this context, the question of a difference in weight gain for men and women might be raised. This question is all the more important in the context of metabolic disease such as DM. Patients with DM do not seem to have a greater weight gain after smoking cessation than that observed in the general population.<sup>67,69</sup> The observations concerning the gender difference in weight gain secondary to cessation might sometimes be contradictory.<sup>70,71</sup> Some authors observed a greater average weight gain in women than in men. Thus, Williamson et al. reported a mean weight gain attributable to smoking cessation at 1 year after cessation of 2.8 kg in men and 3.8 kg in women after adjustment for confounding factors.<sup>72</sup> Significant weight gain (> 13 kg) was observed in 9.8% of men and in 13.4% of women.<sup>72</sup> In another study on weight change in the 5 years after smoking cessation, women observed an average weight gain of 5.2 kg in the first year and 3.4 kg between 1 and 5 years, whereas for men these figures were 4.9 and 2.6 kg, respectively.<sup>73</sup> Conversely, some authors have reported a greater weight gain in men than in women. In one study, the average weight gain at 1 year after quitting was 3.3 kg for women vs 3.9 kg for men. In addition, in this study, male sex was associated with greater weight gain after smoking cessation.<sup>74</sup> Another study showed an interaction between weight gain after quitting, sex, and prequitting smoking status. Specifically, men with a low level of smoking (about 10 cigarettes per day) gained more weight at 1 year after quitting than did women, whereas with a higher level of smoking (25 cigarettes per day), the opposite was observed.<sup>75</sup> However, no study to date has specifically evaluated the difference in weight between men and women with DM. Beyond the actual weight gain, fear of weight gain constitutes a barrier to the quitting process, particularly among women in the general population. Indeed, one study compared the weight gain tolerated after smoking cessation by male and female smokers.<sup>76</sup> Men reported a weight gain of 4.9 kg ( $\pm$  3.5 kg), whereas women reported a weight gain of 2.3 kg ( $\pm$  2.6 kg).

### Motivations and barriers to quitting in people with DM

In addition to weight gain, there are other sex- or gender-related barriers to quitting. In a Dutch qualitative study of 11 female and 9 male smokers, the main barriers to smoking

cessation were psychosocial (emotion and stress) among women, but more related to environmental factors among men.<sup>77</sup> Thus, the authors emphasized the need to adapt cessation strategies according to gender, notably by targeting internal problems in women vs external problems in men.<sup>77</sup> Nevertheless, such findings are not necessarily transposable to people with DM. In this specific population, barriers to quitting smoking for men and women might differ, and specificities inherent to diabetic status are observed.<sup>78</sup> In people with DM, apprehension about weight gain could be exacerbated because of its possible effect on glycemic control. Furthermore, health professionals might also be more likely to focus on the weight objective after smoking cessation.<sup>79</sup> In patients with T1DM, weight concern was more prevalent in women than in men, as well as in patients with poor glycemic control.<sup>79</sup> However, on the question of the link between smoking cessation and DM management or control, there was no difference between men and women. Furthermore, in another study of barriers to smoking cessation in T2DM according to gender, weight gain did not emerge as a major concern.<sup>78</sup> Moreover, in this study, DM significantly modulated the barriers to smoking cessation compared with that in the general population, making it difficult to generalize to people with DM.<sup>78</sup> Studies specifically targeting people with DM are needed. Furthermore, in T2DM, several studies report a lack of knowledge concerning the links between smoking and T2DM.<sup>78,80</sup> Thus, smoking cessation strategies must take into account gender differences to improve the success and long-term maintenance of abstinence.

### Smoking cessation interventions in people with DM

Regarding nonpharmacological smoking cessation strategies, some authors reported sex and gender differences in their effectiveness. However, no data are available to date for people with DM. This was the objective of the **Diabetes and Smoking Cessation: A Gender-Oriented Randomised Controlled Trial (DISCOG-RCT)** study, in which the effectiveness of smoking cessation interventions in the T2DM population was evaluated by also integrating gender specificities.<sup>81</sup> Concerning pharmacological strategies, in the general population, the literature shows differences according to sex or gender. Nicotine replacement therapies or bupropion are more effective in men, whereas varenicline is more efficient in women.<sup>82-86</sup> These differences are linked to pharmacogenetic factors.<sup>87</sup> As reviewed in this article, sex affects enzymes that metabolize drugs such as cytochrome P450 family 2 subfamily B member 6 (CYP2B6), or genes that influence dopamine concentrations such as *DRD2* or *COMT*.<sup>87,88</sup> Such observations have not been tested specifically in people with DM. Differences between men and women in barriers or responses to smoking cessation strategies have an effect on the success of smoking cessation. In the general population, data are divergent among studies, but it seems that there is no difference in the proportion of women initiating cessation compared with men, nor in the success of cessation. However, a difference in the ability to maintain abstinence over the long term has been observed.<sup>88</sup> Another study has reported a higher rate of cessation at 1 year among women than among men, particularly among young people, whereas this rate is higher among men as they get older.<sup>89</sup> To date, such observations have not



been published for people with DM. Finally, the management of smoking cessation by health professionals might vary according to the sex or gender of patients. Indeed, the management of cardiovascular risk factors was more aggressive in men than in women, whether in patients with T2DM or T1DM.<sup>90,91</sup> However, these data mainly concern the management of dyslipidemia or hypertension on the basis of prescription data for lipid-lowering and antihypertensive medications. In these studies, the occurrence of smoking cessation advice according to sex or gender was not reported. In a study published in 1995 in the United States, the percentage of people with DM who received advice to stop or reduce smoking from their doctor was approximately the same among men and women.<sup>92</sup> Thus, it is important to draw the attention of health professionals to the management of cardiovascular risk factors, especially smoking cessation, in both sexes.

Smoking cessation advice and treatments should be systematically proposed to every smoker with DM regardless of sex or gender. Interventions that have been proven effective in people without DM, such as behavioural interventions, nicotine replacement therapy, and the administration of bupropion or varenicline, are also effective in smokers with DM.<sup>18</sup> Few data exist on sex or gender specificities in people with DM regarding smoking cessation. Interventions might be tailored to better reach patients on the basis of their sex or gender specificities, as well as their DM specificities.<sup>93</sup> This includes interventions that address emotions and stress in women<sup>94</sup> or an implementation design to reach specific populations of men.<sup>93</sup>

### Highlight

- The benefit of smoking cessation appears to be similar among men and women with DM.
- As in the general population, weight change after smoking cessation in people with DM appears to be greater in women than in men.
- No data are available to date regarding a sex or gender difference in the effectiveness of smoking cessation interventions specifically in people with DM.
- Smoking cessation advice and treatments should be systematically proposed to every smoker with DM regardless of sex or gender.

### Electronic Nicotine Delivery Systems

Few data exist on the use and health effects of electronic nicotine delivery systems (ENDS or e-cigarettes) and the potential differences between men and women with DM. In populations without DM, a higher prevalence of ENDS use has been shown in men, especially in younger populations.<sup>95,96</sup> The trends might change, but limited data suggest that men are early adopters, similar to what has been observed with cigarette smoking. Regarding the association between ENDS use and the incidence of T2DM or prediabetes in never cigarette smokers, studies suggest that, similar to smokers, ENDS users are at increased risk of impaired glucose tolerance compared with nonusers.<sup>97-99</sup> It is important to note that most of the available studies have short follow-ups and consist mainly of dual cigarette smokers and

ENDS users, making it difficult to isolate the health effect associated with ENDS use. In a study that used data from the Behavioral Risk Factor Surveillance System (BRFSS) survey, the odds ratio (OR) of self-reported prediabetes for nonsmoking ENDS users compared with never ENDS users was higher in men than in women (OR, 2.36 [95% CI, 1.26-4.40] vs OR, 1.88 [95% CI, 1.00-3.53], respectively).<sup>99</sup> Animal studies suggest that glycerol contained in ENDS liquids can affect glucose homeostasis in men and women.<sup>100</sup> Finally, regarding the effects of ENDS use on diabetic complications few studies exist and none with sex- or gender-specific data. One Chinese study showed that ENDS use was associated with impaired angiogenesis and wound healing in people with DM because of increased endothelial oxidative stress and reduced nitric oxide bioavailability, but sex specificities were not assessed.<sup>101</sup>

### Highlight

- Few data exist on the use and health effects of ENDS in men and women with DM.
- ENDS use aiming at smoking cessation should be of limited duration, when abstinence is achieved and the urge to smoke is suppressed, regardless of sex and gender.

### Conclusion

In this article, we reviewed available data on sex or gender differences in the interplay between smoking and DM. Smoking is a risk factor for the development of T2DM in men and women and the risk conferred by smoking appears to be comparable among them. As observed in the general population, the prevalence of smoking varies among men and women with DM, being overall higher in men than in women. However, the trend toward a decrease in smoking observed in men in recent years seems to be less pronounced in women. Tobacco prevention policies should target people with DM with specific attention on women who might be especially exposed to the tobacco industry's marketing strategies.

Smoking is an independent risk factor for all-cause mortality and macrovascular and microvascular complications in women and men with DM. However, in people with T2DM, the burden of smoking appears to be greater in women than in men in terms of coronary morbidity. Even if mechanisms are not all understood, the greater susceptibility of women to smoking toxicity argues for special attention from health professionals in the management of cardiovascular risk factors and diabetes complications in women with DM.

Regarding smoking cessation, women with DM tend to be more dependent to nicotine and to have more stress and psychosocial barriers to quitting smoking. Weight change after smoking cessation also appears to be greater in women than in men. These factors might hinder smoking cessation and should be addressed when managing smokers with DM. People with DM should be offered the same first-line therapies as the general population for smoking cessation treatment, including behavioural interventions and pharmacological treatments (such as nicotine replacement

therapies, varenicline, and bupropion). There is to date limited evidence regarding the efficacy and safety of pharmacotherapies in patients with DM and sex- or gender-specific data are even more scarce or lacking, particularly in people with T1DM.

Smoking cessation should be proposed to all patients with diabetes, regardless of their sex or gender. Further research that takes into account sex or gender dimensions are required. This could help tailor smoking prevention and smoking cessation interventions to better reach people with DM on the basis of their sex or gender specificities.

### Acknowledgements

We thank the Société Francophone du Diabète, Société Francophone de Tabacologie, the Fédération Française des Diabétiques, and all members of the study group “Tabac et Diabète.”

### Funding Sources

None.

### Disclosures

Blandine Tramunt reports personal fees from Novo Nordisk and Lilly. Vincent Durlach has acted as an advisory board member, speaker, or consultant for Amgen, Sanofi, Lilly, Servier, and Bioprojet. Bruno Verges reports grants, honoraria, and institutional funding from Amgen, AstraZeneca, Bayer Pharma, Boehringer-Ingelheim, LifeScan, Lilly, MSD, Novo Nordisk, and Recordati. Daniel Thomas has received honoraria from Pfizer for punctual consulting, lectures, and presentations, and support for attending meetings/travel. Carole Clair has acted as a speaker for Eli-Lilly. The remaining authors have no conflicts of interest to disclose.

### References

1. Tannenbaum C, Ellis RP, Eyssel F, Zou J, Schiebinger L. Sex and gender analysis improves science and engineering. *Nature* 2019;575:137-46.
2. Kautzky-Willer A, Harreiter J, Pacini G. Sex and gender differences in risk, pathophysiology and complications of type 2 diabetes mellitus. *Endocr Rev* 2016;37:278-316.
3. Harreiter J, Kautzky-Willer A. Sex and gender differences in prevention of type 2 diabetes. *Front Endocrinol (Lausanne)* 2018;9:220.
4. Clayton JA, Tannenbaum C. Reporting sex, gender, or both in clinical research? *JAMA* 2016;316:1863-4.
5. Connelly PJ, Azizi Z, Alipour P, Delles C, Pilote L, Raparelli V. The importance of gender to understand sex differences in cardiovascular disease. *Can J Cardiol* 2021;37:699-710.
6. International Diabetes Federation. *IDF Diabetes Atlas 2021*. 10th Ed. Brussels, Belgium: International Diabetes Federation, 2021. Available at: <https://www.diabetesatlas.org>. Accessed April 4, 2023.
7. Tramunt B, Smati S, Grandgeorge N, et al. Sex differences in metabolic regulation and diabetes susceptibility. *Diabetologia* 2020;63:453-61.
8. CDC: Surgeon General's Report: The Health Consequences of Smoking—50 Years of Progress. Available at: <https://www.cdc.gov/tobacco/sgr/50th-anniversary/index.htm>. Accessed September 7, 2022.
9. Barbeau EM, Leavy-Sperounis A, Balbach ED. Smoking, social class, and gender: what can public health learn from the tobacco industry about disparities in smoking? *Tob Control* 2004;13:115-20.
10. Azizi Z, Gisinger T, Bender U, et al. Sex, gender, and cardiovascular health in Canadian and Austrian populations. *Can J Cardiol* 2021;37:1240-7.
11. Longpre-Poirier C, Dougoud J, Jacmin-Park S, et al. Sex and gender and allostatic mechanisms of cardiovascular risk and disease. *Can J Cardiol* 2022;38:1812-27.
12. Mauvais-Jarvis F, Bairey Merz N, Barnes PJ, et al. Sex and gender: modifiers of health, disease, and medicine. *Lancet* 2020;396:565-82.
13. 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.
14. 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.
15. Yuan S, Xue HL, Yu HJ, 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 (Oxf)* 2019;41:e169-76.
16. Ostgren CJ, Lindblad U, Ranstam J, et al. 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.
17. Jankowich M, Choudhary G, Taveira TH, Wu WC. Age-, race-, and gender-specific prevalence of diabetes among smokers. *Diabetes Res Clin Pract* 2011;93:e101-5.
18. Zhang L, Curhan GC, Hu FB, Rimm EB, Forman JP. Association between passive and active smoking and incident type 2 diabetes in women. *Diabetes Care* 2011;34:892-7.
19. Clair C, Meigs JB, Rigotti NA. Smoking behavior among US adults with diabetes or impaired fasting glucose. *Am J Med* 2013;126:e541.e515-48.
20. 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.
21. Gulliford MC, Sedgwick JE, Pearce AJ. Cigarette smoking, health status, socio-economic status and access to health care in diabetes mellitus: a cross-sectional survey. *BMC Health Serv Res* 2003;3:4.
22. Durlach V, Verges B, Al-Salameh A, et al. Smoking and diabetes interplay: a comprehensive review and joint statement. *Diabetes Metab* 2022;48:101370.
23. Lee ET, Keen H, Bennett PH, Fuller JH, Lu M. Follow-up of the WHO Multinational Study of Vascular Disease in Diabetes: general description and morbidity. *Diabetologia* 2001;44(suppl 2):S3-13.
24. Prevalence of small vessel and large vessel disease in diabetic patients from 14 centres. The World Health Organisation Multinational Study of Vascular Disease in Diabetics. *Diabetes Drafting Group. Diabetologia* 1985;28(suppl):615-40.
25. Fan AZ, Rock V, Zhang X, Li Y, Elam-Evans L, Balluz L. Trends in cigarette smoking rates and quit attempts among adults with and without diagnosed diabetes, United States, 2001-2010. *Prev Chronic Dis* 2013;10:E160.

26. 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.
27. Raho E, van Oostrom SH, Visser M, et al. Generation shifts in smoking over 20 years in two Dutch population-based cohorts aged 20-100 years. *BMC Public Health* 2015;15:142.
28. 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.
29. Carpenter CM, Wayne GF, Connolly GN. Designing cigarettes for women: new findings from the tobacco industry documents. *Addiction* 2005;100:837-51.
30. Sy D, Mackay J. Women and the Tobacco Industry. Available at: <https://exposetobacco.org/wp-content/uploads/Women-and-the-Tobacco-Industry-3.5.21.pdf>. Accessed September 7, 2022.
31. Hitchman SC, Fong GT. Gender empowerment and female-to-male smoking prevalence ratios. *Bull World Health Organ* 2011;89:195-202.
32. Graham H. *When Life's a Drag: Women, Smoking and Disadvantage*. University of Warwick, UK: Great Britain Department of Health 1993.
33. Greaves L. The meanings of smoking to women and their implications for cessation. *Int J Environ Res Public Health* 2015;12:1449-65.
34. Rawshani A, Rawshani A, Franzen S, et al. Risk Factors, mortality, and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2018;379:633-44.
35. Huxley RR, Woodward M. Cigarette smoking as a risk factor for coronary heart disease in women compared with men: a systematic review and meta-analysis of prospective cohort studies. *Lancet* 2011;378:1297-305.
36. Huxley RR, Peters SA, Mishra GD, Woodward M. Risk of all-cause mortality and vascular events in women versus men with type 1 diabetes: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol* 2015;3:198-206.
37. de Ritter R, de Jong M, Vos RC, et al. Sex differences in the risk of vascular disease associated with diabetes. *Biol Sex Differ* 2020;11:1.
38. 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.
39. Hu G, Jousilahti P, Qiao Q, Katoh S, Tuomilehto J. Sex differences in cardiovascular and total mortality among diabetic and non-diabetic individuals with or without history of myocardial infarction. *Diabetologia* 2005;48:856-61.
40. de Ferranti SD, de Boer IH, Fonseca V, et al. Type 1 diabetes mellitus and cardiovascular disease: a scientific statement from the American Heart Association and American Diabetes Association. *Circulation* 2014;130:1110-30.
41. Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. *BMJ* 2006;332:73-8.
42. Peters SA, Huxley RR, Woodward M. Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775,385 individuals and 12,539 strokes. *Lancet* 2014;383:1973-80.
43. Moy CS, LaPorte RE, Dorman JS, et al. Insulin-dependent diabetes mellitus mortality. The risk of cigarette smoking. *Circulation* 1990;82:37-43.
44. Woodward M, Tunstall-Pedoe H, Smith WC, Tavendale R. Smoking characteristics and inhalation biochemistry in the Scottish population. *J Clin Epidemiol* 1991;44:1405-10.
45. Hukkanen J, Jacob P 3rd, Benowitz NL. Metabolism and disposition kinetics of nicotine. *Pharmacol Rev* 2005;57:79-115.
46. Berlin I. Incidence of lung cancer among young women. *N Engl J Med* 2018;379:988.
47. Oberg M, Jaakkola MS, Woodward A, Peruga A, Pruss-Ustun A. Worldwide burden of disease from exposure to second-hand smoke: a retrospective analysis of data from 192 countries. *Lancet* 2011;377:139-46.
48. Colhoun HM, Rubens MB, Underwood SR, Fuller JH. The effect of type 1 diabetes mellitus on the gender difference in coronary artery calcification. *J Am Coll Cardiol* 2000;36:2160-7.
49. Livingstone SJ, Looker HC, Hothersall EJ, et al. Risk of cardiovascular disease and total mortality in adults with type 1 diabetes: Scottish registry linkage study. *PLoS Med* 2012;9:e1001321.
50. Dabelea D, Kinney G, Snell-Bergeon JK, et al. Effect of type 1 diabetes on the gender difference in coronary artery calcification: a role for insulin resistance? The Coronary Artery Calcification in Type 1 Diabetes (CACTI) study. *Diabetes* 2003;52:2833-9.
51. Soedamah-Muthu SS, Chaturvedi N, Toeller M, et al. Risk factors for coronary heart disease in type 1 diabetic patients in Europe: the EURODIAB Prospective Complications Study. *Diabetes Care* 2004;27:530-7.
52. Feodoroff M, Harjutsalo V, Forsblom C, Groop PH; FinnDiane Study Group. 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.
53. Spencer EA, Pirie KL, Stevens RJ, et al. Diabetes and modifiable risk factors for cardiovascular disease: the prospective Million Women Study. *Eur J Epidemiol* 2008;23:793-9.
54. Nilsson PM, Cederholm J, Eeg-Olofsson K, et al. Smoking as an independent risk factor for myocardial infarction or stroke in type 2 diabetes: a report from the Swedish National Diabetes Register. *Eur J Cardiovasc Prev Rehabil* 2009;16:506-12.
55. Barengo NC, Teuschl Y, Moltchanov V, Laatikainen T, Jousilahti P, Tuomilehto J. Coronary heart disease incidence and mortality, and all-cause mortality among diabetic and non-diabetic people according to their smoking behavior in Finland. *Tob Induc Dis* 2017;15:12.
56. Blomster JI, Woodward M, Zoungas S, 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.
57. Yang JY, Kim NK, Lee YJ, et al. Prevalence and factors associated with diabetic retinopathy in a Korean adult population: the 2008-2009 Korea National Health and Nutrition Examination Survey. *Diabetes Res Clin Pract* 2013;102:218-24.
58. Liu Z, Fu C, Wang W, Xu B. Prevalence of chronic complications of type 2 diabetes mellitus in outpatients - a cross-sectional hospital based survey in urban China. *Health Qual Life Outcomes* 2010;8:62.
59. Pop-Busui R, Lu J, Lopes N, Jones TL, Investigators BD. Prevalence of diabetic peripheral neuropathy and relation to glycemic control

- therapies at baseline in the BARI 2D cohort. *J Peripher Nerv Syst* 2009;14:1-13.
60. Singh SS, Roeters-van Lennep JE, Lemmers RFH, 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.
61. Liu G, Hu Y, Zong G, 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.
62. Chuahirun T, Simoni J, Hudson C, et al. Cigarette smoking exacerbates and its cessation ameliorates renal injury in type 2 diabetes. *Am J Med Sci* 2004;327:57-67.
63. 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.
64. Al-Delaimy WK, Manson JE, Solomon CG, et al. Smoking and risk of coronary heart disease among women with type 2 diabetes mellitus. *Arch Intern Med* 2002;162:273-9.
65. Luo J, Rossouw J, Margolis KL. Smoking cessation, weight change, and coronary heart disease among postmenopausal women with and without diabetes. *JAMA* 2013;310:94-6.
66. Voulgari C, Katsilambros N, Tentolouris N. Smoking cessation predicts amelioration of microalbuminuria in newly diagnosed type 2 diabetes mellitus: a 1-year prospective study. *Metabolism* 2011;60:1456-64.
67. Clair C, Rigotti NA, Porneala B, et al. Association of smoking cessation and weight change with cardiovascular disease among adults with and without diabetes. *JAMA* 2013;309:1014-21.
68. Siahpush M, Singh GK, Tibbits M, Pinard CA, Shaikh RA, Yaroch A. It is better to be a fat ex-smoker than a thin smoker: findings from the 1997-2004 National Health Interview Survey-National Death Index linkage study. *Tob Control* 2014;23:395-402.
69. Driva S, Korkontzelou A, Tonstad S, Tentolouris N, Katsaounou P. The effect of smoking cessation on body weight and other metabolic parameters with focus on people with type 2 diabetes mellitus. *Int J Environ Res Public Health* 2022;19:13222.
70. Aubin HJ, Farley A, Lycett D, Lahmek P, Aveyard P. Weight gain in smokers after quitting cigarettes: meta-analysis. *BMJ* 2012;345:e4439.
71. Harris KK, Zopey M, Friedman TC. Metabolic effects of smoking cessation. *Nat Rev Endocrinol* 2016;12:684.
72. Williamson DF, Madans J, Anda RF, Kleinman JC, Giovino GA, Byers T. Smoking cessation and severity of weight gain in a national cohort. *N Engl J Med* 1991;324:739-45.
73. O'Hara P, Connett JE, Lee WW, Nides M, Murray R, Wise R. Early and late weight gain following smoking cessation in the Lung Health Study. *Am J Epidemiol* 1998;148:821-30.
74. Prod'homme S, Locatelli I, Giraudon K, et al. Predictors of weight change in sedentary smokers receiving a standard smoking cessation intervention. *Nicotine Tob Res* 2013;15:910-6.
75. Locatelli I, Collet TH, Clair C, Rodondi N, Cornuz J. The joint influence of gender and amount of smoking on weight gain one year after smoking cessation. *Int J Environ Res Public Health* 2014;11:8443-55.
76. Pomerleau CS, Kurth CL. Willingness of female smokers to tolerate postcessation weight gain. *J Subst Abuse* 1996;8:371-8.
77. Dieleman LA, van Peet PG, Vos HMM. Gender differences within the barriers to smoking cessation and the preferences for interventions in primary care a qualitative study using focus groups in The Hague, The Netherlands. *BMJ Open* 2021;11:e042623.
78. 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.
79. Haire-Joshu D, Heady S, Thomas L, Schechtman K, Fisher EB Jr. Beliefs about smoking and diabetes care. *Diabetes Educ* 1994;20:410-5.
80. Chau TK, Fong DY, Chan SS, et al. Misconceptions about smoking in patients with type 2 diabetes mellitus: a qualitative analysis. *J Clin Nurs* 2015;24:2545-53.
81. Clair C, Augsburg A, Birrer P, et al. Assessing the efficacy and impact of a personalised smoking cessation intervention among type 2 diabetic smokers: study protocol for an open-label randomised controlled trial (DISCOGO-RCT). *BMJ Open* 2020;10:e040117.
82. Perkins KA, Scott J. Sex differences in long-term smoking cessation rates due to nicotine patch. *Nicotine Tob Res* 2008;10:1245-50.
83. McKee SA, Smith PH, Kaufman M, Mazure CM, Weinberger AH. Sex differences in varenicline efficacy for smoking cessation: a meta-analysis. *Nicotine Tob Res* 2016;18:1002-11.
84. Smith PH, Kasza KA, Hyland A, et al. Gender differences in medication use and cigarette smoking cessation: results from the International Tobacco Control Four Country Survey. *Nicotine Tob Res* 2015;17:463-72.
85. Smith PH, Zhang J, Weinberger AH, Mazure CM, McKee SA. Gender differences in the real-world effectiveness of smoking cessation medications: findings from the 2010-2011 Tobacco Use Supplement to the Current Population Survey. *Drug Alcohol Depend* 2017;178:485-91.
86. Smith PH, Weinberger AH, Zhang J, Emme E, Mazure CM, McKee SA. Sex differences in smoking cessation pharmacotherapy comparative efficacy: a network meta-analysis. *Nicotine Tob Res* 2017;19:273-81.
87. Schnoll RA, Patterson F. Sex heterogeneity in pharmacogenetic smoking cessation clinical trials. *Drug Alcohol Depend* 2009;104(suppl 1):S94-9.
88. Smith PH, Bessette AJ, Weinberger AH, Sheffer CE, McKee SA. Sex/gender differences in smoking cessation: a review. *Prev Med* 2016;92:135-40.
89. Jarvis MJ, Cohen JE, Delnevo CD, Giovino GA. Dispelling myths about gender differences in smoking cessation: population data from the USA, Canada and Britain. *Tob Control* 2013;22:356-60.
90. Wexler DJ, Grant RW, Meigs JB, Nathan DM, Cagliero E. Sex disparities in treatment of cardiac risk factors in patients with type 2 diabetes. *Diabetes Care* 2005;28:514-20.
91. Larkin ME, Backlund JY, Cleary P, et al. Disparity in management of diabetes and coronary heart disease risk factors by sex in DCCT/EDIC. *Diabet Med* 2010;27:451-8.
92. Malarcher AM, Ford ES, Nelson DE, et al. Trends in cigarette smoking and physicians' advice to quit smoking among people with diabetes in the U.S. *Diabetes Care* 1995;18:694-7.
93. Bottorff JL, Haines-Saah R, Kelly MT, et al. Gender, smoking and tobacco reduction and cessation: a scoping review. *Int J Equity Health* 2014;13:114.
94. Torchalla I, Okoli CT, Bottorff JL, Qu A, Poole N, Greaves L. Smoking cessation programs targeted to women: a systematic review. *Women Health* 2012;52:32-54.



95. Cooper M, Day HR, Ren C, et al. Correlates of tobacco product initiation among youth and young adults between waves 1-4 of the population assessment of tobacco and Health (PATH) study (2013-2018). *Addict Behav* 2022;134:107396.
96. Mattingly DT, Zavala-Arciniega L, Hirschtick JL, Meza R, Levy DT, Fleischer NL. Trends in exclusive, dual and polytobacco use among U.S. adults, 2014-2019: results from two nationally representative surveys. *Int J Environ Res Public Health* 2021;18:13092.
97. Zhang Z, Jiao Z, Blaha MJ, et al. The association between e-cigarette use and prediabetes: results from the Behavioral Risk Factor Surveillance System, 2016-2018. *Am J Prev Med* 2022;62:872-7.
98. Gorna I, Napierala M, Florek E. Electronic cigarette use and metabolic syndrome development: a critical review. *Toxics* 2020;8:105.
99. Aruegwu NC, Perez MF, Oncken C, Mead EL, Maheshwari N, Mortensen EM. E-cigarette use is associated with a self-reported diagnosis of prediabetes in never cigarette smokers: results from the behavioral risk factor surveillance system survey. *Drug Alcohol Depend* 2019;205:107692.
100. Lechasseur A, Mouchiroud M, Tremblay F, et al. Glycerol contained in vaping liquids affects the liver and aspects of energy homeostasis in a sex-dependent manner. *Physiol Rep* 2022;10:e15146.
101. Liu Z, Zhang Y, Youn JY, et al. Flavored and nicotine-containing e-cigarettes induce impaired angiogenesis and diabetic wound healing via increased endothelial oxidative stress and reduced NO bioavailability. *Antioxidants (Basel)* 2022;11:904.