

Review

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

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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.^{1–3} 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).^{4,5}

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).⁶ Sex steroids and genetic factors have an influence on energy balance and glucose homeostasis, and partly explain these differences.⁷ 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.⁸ 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.⁹

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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).^{10,11}

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.¹²

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.^{8,13-15} Moreover, some authors have reported differential effect of nicotine on β -cell function according to sex.¹⁶ 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.^{13,14} 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.¹⁴ 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.¹⁴ According to some authors, this excess risk appears after age of 35 in men and women.¹⁷ 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.¹⁵ 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.^{14,18}

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

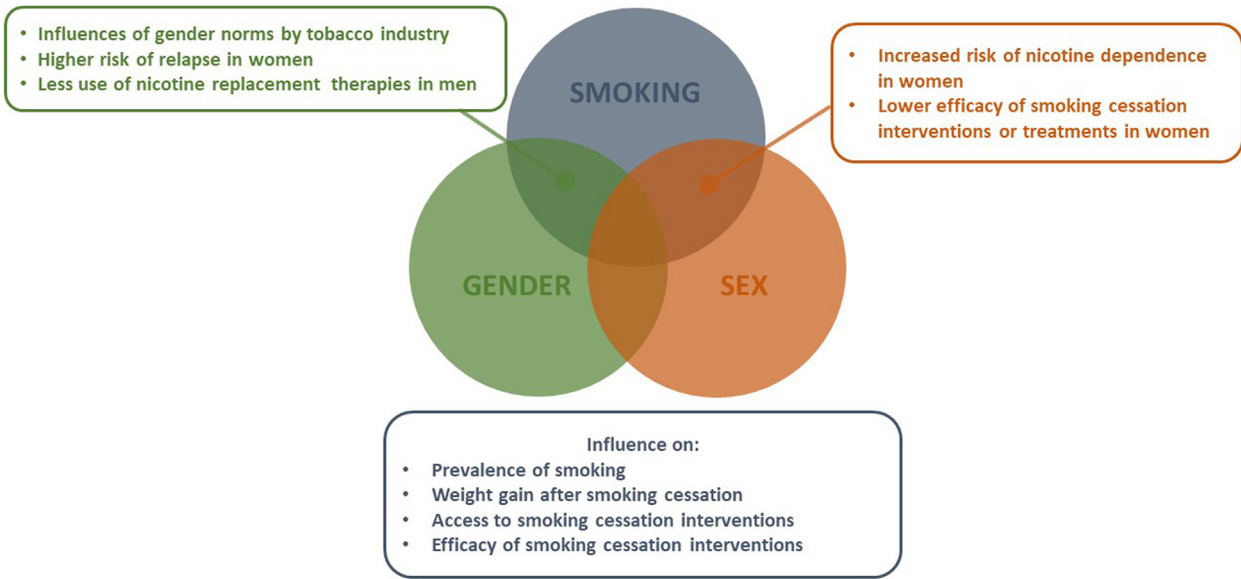


Figure 1. Sex and gender aspects in smoking and diabetes; a complex interplay: smoking.

population.¹⁹ A recent review shows that patients with T2DM are 26% less likely to smoke compared with those without T2DM.²⁰ Age, geographic region, and socioeconomic level are factors that influence smoking prevalence rates.²¹ Overall it seems that the prevalence of smoking among men is higher than that of women, regardless of the type of DM.^{20,22} 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).^{23,24}

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.²¹ 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

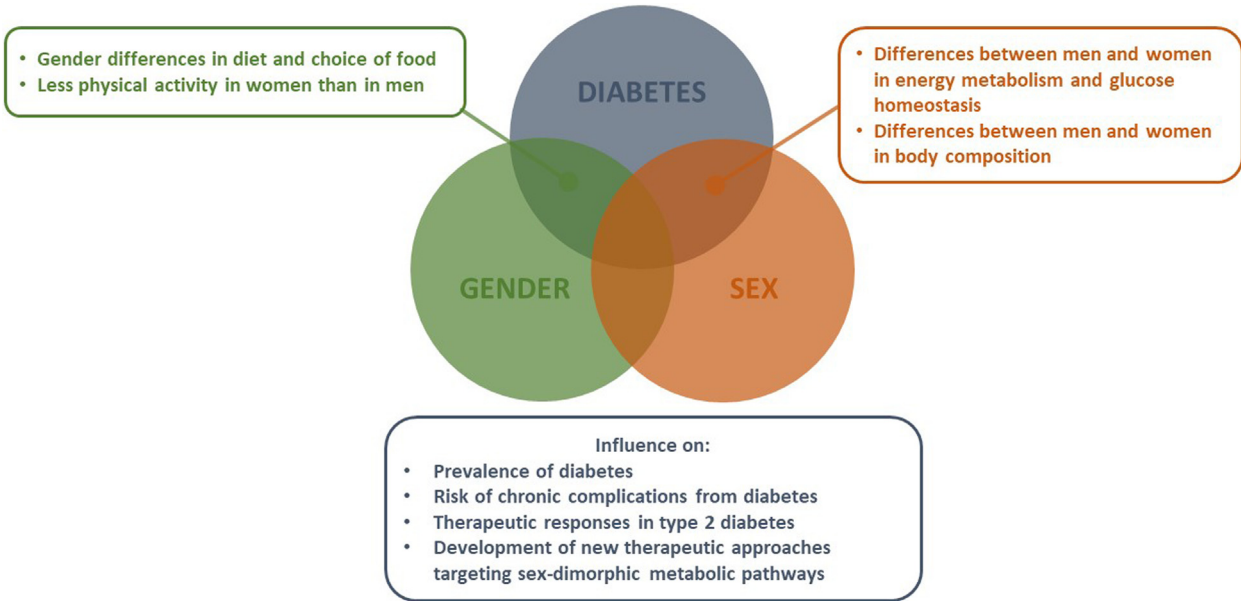


Figure 2. Sex and gender aspects in smoking and diabetes; a complex interplay: diabetes.

African (8 vs 2%, respectively) origin.²¹ A Centers for Disease Control and Prevention study conducted between 2001 and 2010 showed a decrease in smoking prevalence in all ethnic subgroups.²⁵ 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.²⁶ 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.^{26,27} In a recent Austrian study, an increase in smoking prevalence was observed among women between 2007 and 2014, whereas it remained stable among men.²⁸ 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.^{29,30} 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.³¹ 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.³² 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.³³ 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.³⁴ Studies in the general population have shown a greater negative health effect of smoking in women than in men for cardiovascular diseases.³⁵ 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^{1,36-40} (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.⁴¹ 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.³⁶ Similar results were reported for the risk of stroke in another study.⁴²

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.⁴³ 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

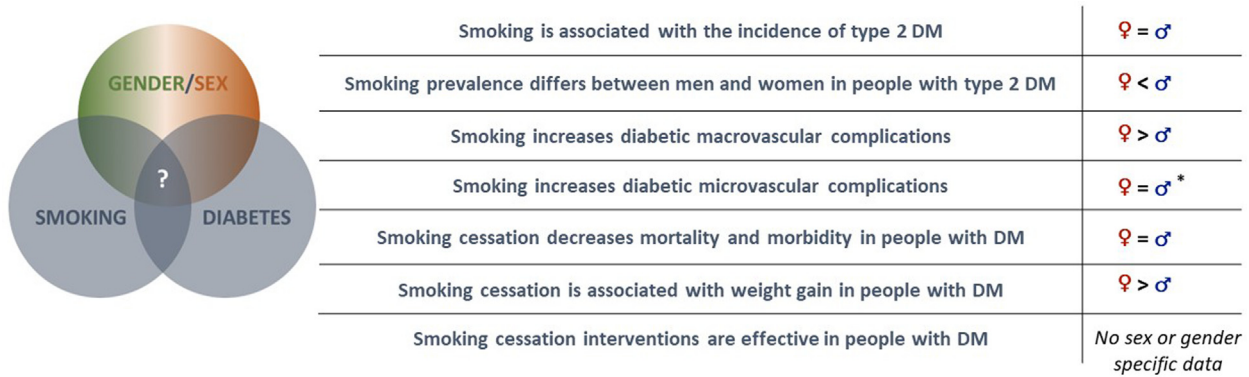


Figure 3. Sex and gender aspects in smoking and diabetes; a complex interplay: the association of smoking and diabetes. DM, diabetes mellitus.
* Except for microalbuminuria: ♀ > ♂.

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. ⁴¹	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. ⁴²	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. ⁶⁰	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.⁴¹ 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.⁴⁴ Second, hormones such as estrogens have an influence on the metabolism of nicotine, increasing its clearance.⁴⁵ As a consequence women might smoke more intensely to compensate, leading to an increase in toxicity.⁴⁶ Third, women are more exposed to secondhand smoke than are men.⁴⁷ 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.⁴⁸⁻⁵⁰ 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.⁵¹ 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.⁵² 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.⁵³ 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.⁵³ 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).⁵⁴ 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. ⁴³	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. ⁵⁴	T2DM	Fatal/nonfatal MI	HR, 2.17 (1.69-2.79)*	HR, 1.45 (1.19-1.77)*	—
Barengo et al. ⁵⁵	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. ⁵⁶	T2DM	Major coronary events	—	—	1.64 (0.83-3.26) ^{†,§}
Microvascular complications					
Blomster et al. ⁵⁶	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.⁵⁵

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.⁵⁶ 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.⁵⁷⁻⁵⁹ 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]).⁵⁶ 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.⁵⁶ 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]).⁶⁰ 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.^{14,38,61-64} 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.⁶³⁻⁶⁵ 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.⁵⁶ Notably, however, in that study, only the benefit for all-cause mortality after smoking cessation was significant (30% risk reduction) in both sexes.⁵⁶ 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

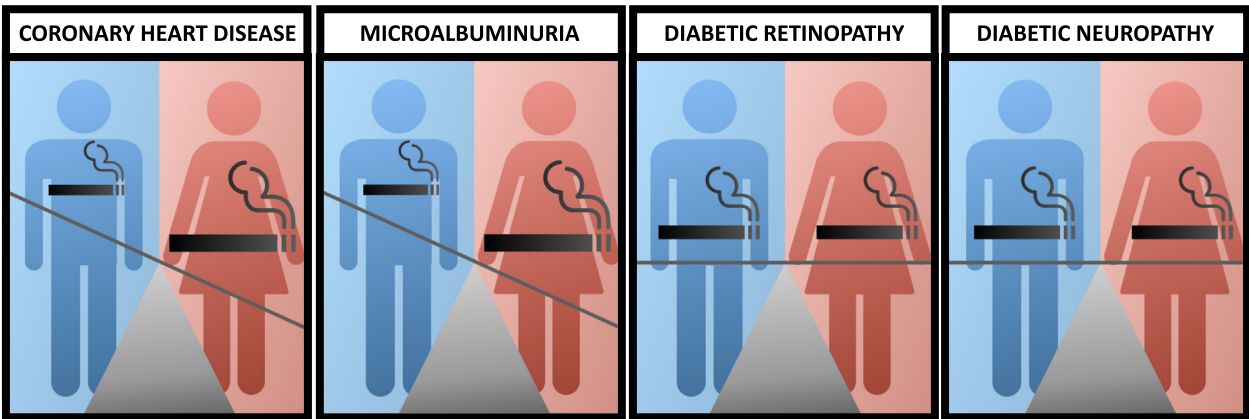


Figure 4. Effect of smoking on chronic complications of type 2 diabetes mellitus according to sex.

smokers with DM, and this was comparable for men and women.⁵⁵ 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.⁵⁵ 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.⁶⁶ 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.^{61,66,67}

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.⁶⁸ 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.^{67,69} The observations concerning the gender difference in weight gain secondary to cessation might sometimes be contradictory.^{70,71} 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.⁷² Significant weight gain (> 13 kg) was observed in 9.8% of men and in 13.4% of women.⁷² 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.⁷³ 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.⁷⁴ 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.⁷⁵ 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.⁷⁶ 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.⁷⁷ 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.⁷⁷ 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.⁷⁸ 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.⁷⁹ In patients with T1DM, weight concern was more prevalent in women than in men, as well as in patients with poor glycemic control.⁷⁹ 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.⁷⁸ 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.⁷⁸ 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.^{78,80} 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.⁸¹ 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.⁸²⁻⁸⁶ These differences are linked to pharmacogenetic factors.⁸⁷ 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*.^{87,88} 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.⁸⁸ 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.⁸⁹ 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.^{90,91} 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.⁹² 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.¹⁸ 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.⁹³ This includes interventions that address emotions and stress in women⁹⁴ or an implementation design to reach specific populations of men.⁹³

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.^{95,96} 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.⁹⁷⁻⁹⁹ 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).⁹⁹ Animal studies suggest that glycerol contained in ENDS liquids can affect glucose homeostasis in men and women.¹⁰⁰ 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.¹⁰¹

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.

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