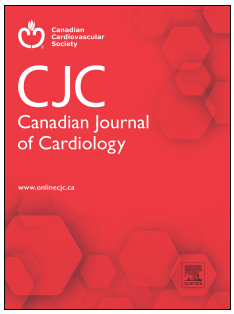

Smoking and diabetes: sex and gender aspects and their impact on vascular diseases

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Smoking and diabetes: sex and gender aspects and their impact on vascular diseases

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Abstract

Smoking and diabetes mellitus (DM) have been identified as two 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 healthcare. We reviewed the impact of sex or gender on the link between smoking and DM. The risk of type 2 DM (T2DM) 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 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 T2DM, the burden of smoking appears to be greater in women than in men for coronary heart disease morbidity, women having a 50% higher 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.

Brief Summary

There are differences between men and women regarding smoking, DM and their interaction. The prevalence of smoking is overall higher in men than in women with DM, although the recent decrease in smoking in men is less pronounced in women. The burden of smoking appears to be greater in women than in men. Women are more dependent to nicotine and cumulate psychosocial barriers to quitting smoking, which makes it more difficult for them to stop.

Introduction

Sex and gender dimensions have become a major concern in health and healthcare 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, behaviors, and expressions of women, men, and gender diverse people) influence the association between smoking and DM at different levels (**Figure 1abc**)[4, 5].

The prevalence of type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) differs between 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 behaviors (i.e. behaviors 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 between 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 behavior 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].

Regarding the association between smoking and DM, both sex and gender might have an influence (**Figure 1a**). Smoking and smoking cessation might have a differential action on

the risk of DM and its complications in men and women, related to both behavioral 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 between smoking and DM; we discuss the impact of smoking on the incidence of T2DM, the prevalence of smoking in people with DM, the impact 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 between smoking and gestational DM are not discussed.

Association between smoking and incident T2DM in men and women

An association between smoking and the incidence of T2DM has been demonstrated for several decades. Meta-analyses have found an increased risk of around 40% in developing T2DM in smokers[8, 13-15]. Moreover, some authors have reported differential effect of nicotine on beta-cell function according to sex[16]. Many studies have evaluated the association between smoking, sex, and the risk of developing T2DM.

Meta-analyses published in the last two decades support the link between smoking and T2DM in both 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, found an relative risk (RR) of T2DM in smokers compared with non-smokers of 1.42 (95% Confidence Interval [95% CI]: 1.34-1.50) and 1.33 (95% CI: 1.26-1.41) in men and women, respectively[14]. The authors estimated that, based on the assumption that the association

between smoking and 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, since 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]. Given the equivalent RR between men and women, it would seem that this risk is equivalent between the two sexes. More recently, Yuan et al. published a meta-analysis assessing 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 found a positive association between smoking and T2DM with an increased risk of 35% and 27% in male and female smokers, respectively, compared with that in non-smokers. The relative risk ratio (RRR) between 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 between active smoking and 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 both men and women[14, 18].

- **An association between 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 between men and women.**

Differences in the prevalence of smoking between men and women with DM

The prevalence of smoking among people with DM is 20-30%, similar to that observed in the general population[19]. A recent review shows that patients with T2DM are 26% less likely to smoke compared to those without T2DM[20]. Age, geographic region, and socio-economic 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 socio-cultural behaviors and norms, disparities in prevalence are observed by 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 socio-economic level is of interest. For example, in a population of 1,899 patients with DM (16% smokers, 31% ex-smokers, and 51% non-smokers) in London, Gulliford et al. observed[21] that smoking was more prevalent among people of Caucasian origin than it was among people of African or Afro-Caribbean origin. Few differences were observed between 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 African (8 vs 2%, respectively) origin[21]. A Centers for Disease Control and Prevention study conducted between 2001 and 2010 found 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 showing a male preponderance in the prevalence of smoking in people with DM, a Canadian study found that female sex was more frequently associated with the risk of being a smoker, regardless of type of DM[26]. One of the explanations put forward by the authors was the greater decline in

151 smoking prevalence among men than among women. Similarly, studies in young populations
152 with or without DM have shown that young girls were more exposed to tobacco than were
153 young boys[26, 27]. In a recent Austrian study, an increase in smoking prevalence was observed
154 among women between 2007 and 2014, whereas it remained stable among men[28].
155 Furthermore, in this study, analyses of people with DM revealed that the most notable
156 increase was observed in populations of women with DM, more specifically in women
157 between 30 and 64 years old and in those over 65 years old, with the prevalence increasing
158 from 9.9% to 16.9%.

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

- **As observed in the general population, the prevalence of smoking varies between 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, developing macrovascular and microvascular complications in the population with DM has been demonstrated 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 impact 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[36-41] (**Table 1**). In a meta-analysis of 37 prospective studies that included people with and without T2DM, Huxley et al. found a higher RR of fatal coronary events in women than in men with DM compared to women and men without DM[42]. The RRR between women and men with DM was 1.46 (95% CI: 1.14-1.88), indicating that women with DM had about a 50% higher risk of a fatal coronary event than did men with DM. For T1DM, the same authors found an excess risk of all-cause mortality of about 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 found for the risk of stroke in another study[43].

Regarding the sex-specific impact of smoking on cardiovascular and some microvascular complications in populations with DM, the deleterious impact of smoking is higher among women than men (summarized in **Table 2** and **Figure 2**). 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[44]. In this cohort, smoking was an independent risk factor of mortality in women but not in men. The excess mortality in women with DM could be explained by the higher occurrence of coronary heart disease (CHD) and mediated by higher contribution of cardiovascular risk factors such as high blood pressure and higher plasma lipids in women with DM than in men with DM[42]. Several mechanisms may explain the higher toxicity of smoking in women, but they are not fully understood. First, women have on average a smaller body surface than men do and so they may extract more carcinogens and toxic substances from tobacco smoke than men do[45]. Second, hormones such as estrogens have an influence on the metabolism of nicotine, increasing its clearance[46]. As a consequence women might smoke more intensely to compensate, leading to an increase in toxicity[47]. Third, women are more exposed to second hand smoke than men[48]. Thus, women who smoke are more likely to be doubly exposed to second hand smoke and to their own consumption, leading to higher total exposure than occurs for men. Nevertheless, this excess risk is not found in all studies; for example, in several studies that report 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[49-51]. Furthermore, in the 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[52]. In the Finnish Diabetic Nephropathy (FinnDiane) study, which included 4,506 individuals with T1DM, no interaction was found between smoking and sex in cardiovascular disease risk with the exception of stroke[53]. This risk was higher in both 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 morbi-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 to women of the same age without DM[54]. The 5-year incidence rate of cardiovascular disease was 4.6 per 100 non-smoking 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[54]. In a Swedish cohort of T2DM, the hazard ratio (HR) for the risk of heart attack (fatal or not) attributable to smoking was higher in women than in men (HR=2.17 [95% CI:1.69-2.79] vs 1.45 [95% CI:1.19-1.77], respectively)[55]. In a Finnish cohort of people with and without T2DM that included 28,712 men and 30,700 women aged 25-64 years, smokers with DM had higher all-cause and CHD mortality than non-smokers with DM did, 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[56].

In the ADVANCE study (Action in Diabetes and Vascular Disease: Preterax and Diamicron modified release Controlled Evaluation), 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[57]. 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 non-smokers 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 favor 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 report a greater incidence in men than in women, whereas others find no difference[58-60]. These studies mainly concern patients with T2DM. Nevertheless, only a few studies evaluated the role of smoking in order to explain such differences. In the previously mentioned ADVANCE study, a similar impact was observed for active smoking on the risk of diabetic nephropathy between men and women (HR between women and men: 1.04 [95% CI: 0.57-1.89])[57]. The authors acknowledged the lack of statistical power to detect a sex-differentiated impact of smoking. Indeed, the number of women smokers or ex-smokers was 434 and 658, respectively, compared with 1,116 and 2,466 male smokers or ex-smokers, respectively[57]. In a Dutch prospective cohort of 1,886 patients with T2DM with a mean follow-up of about 7 years, the incidence of microalbuminuria was significantly higher in men than in women (HR = 1.64 [95% CI: 1.21-2.24])[61]. No sex difference was found in the incidence of diabetic retinopathy or diabetic neuropathy. When assessing the effect of smoking on microvascular complications, 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.

- **In people with DM, smoking is an independent risk factor for all-cause mortality and macrovascular and microvascular complications in both women and men.**
- **In T2DM, the burden of smoking appears to be greater in women than in men in terms of coronary morbidity.**

- **In T1DM, it is difficult to conclude whether smoking has a different impact on men or women due to 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, both macrovascular and microvascular[14, 38, 62-65]. 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[64-66]. 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[57]. Notably, however, in that study, only the benefit for all-cause mortality after smoking cessation was found to be significant (30% risk reduction) in both sexes[57]. 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 smokers with DM, and this was comparable between men and women[56]. However, in both sexes, an excess risk persisted in comparison with non-smoking people with DM. On the other hand, in terms of the incidence of CHD, the benefit of quitting smoking compared with continuing to smoke was greater in women than in men[56]. 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[67]. Thus, even if the data are tenuous, it seems that smoking cessation is beneficial in the population with DM in a comparable manner between 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[62, 66, 68].

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[69]. In this context, the question of a difference in weight gain between men and women may 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[68, 70]. The observations concerning the gender difference in weight gain secondary to cessation may sometimes be contradictory[71, 72]. Some authors observe a greater average weight gain in women than in men. Thus, Williamson et al. found 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[73]. Significant weight gain (>13 kg) was observed in 9.8% of men and in 13.4% of women[73]. In another study evaluating weight change in the 5 years following 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[74]. Conversely, some authors have found a higher 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[75]. Another study found an interaction between weight gain after quitting, sex, and pre-quitting smoking status. Specifically, men with a low level of smoking (about 10 cigarettes/day) gained more weight at

1 year after quitting than women did, whereas with a higher level of smoking (25 cigarettes/day), the opposite was observed[76]. 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[77]. Men reported a weight gain of 4.9 kg (±3.5 kg), whereas women reported a weight gain of 2.3 kg (±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 psycho-social (emotion and stress) among women, but more related to environmental factors among men[78]. 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[78]. Nevertheless, such findings are not necessarily transposable to people with DM. In this specific population, barriers to quitting smoking between men and women might differ, and specificities inherent to diabetic status are observed[79]. In people with DM, apprehension about weight gain could be exacerbated because of its possible impact on glycemic control. Furthermore, health professionals may also be more likely to focus on the weight objective after smoking cessation[80]. In patients with T1DM, weight concern was more prevalent in women than in men, as well as in patients with poor glycemic control[80]. 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 by gender, weight gain did not emerge as a major

326 concern[79]. Moreover, in this study, DM significantly modulated the barriers to smoking
327 cessation compared with that in the general population, making it difficult to generalize to
328 people with DM[79]. Studies specifically targeting people with DM are needed. Furthermore, in
329 T2DM, several studies report a lack of knowledge concerning the links between smoking and
330 T2DM[79, 81]. Thus, smoking cessation strategies must take into account gender differences to
331 improve the success and long-term maintenance of abstinence.
332
333 *Smoking cessation interventions in people with DM*
334 Regarding non-pharmacological smoking cessation strategies, some authors found sex and
335 gender differences in their effectiveness. However, no data are available to date for people
336 with DM. This is the objective of the DISCGO-RCT study, which evaluates the effectiveness of
337 smoking cessation interventions in the T2DM population by also integrating gender
338 specificities[82]. Concerning pharmacological strategies, in the general population, the literature
339 shows differences according to sex or gender. Nicotine replacement therapies or bupropion
340 are more effective in men, whereas varenicline is more efficient in women[83-87]. These
341 differences are linked to pharmacogenetic factors[88]. As reviewed in this paper, sex affects
342 enzymes that metabolize drugs such as CYP2B6, or genes that influence dopamine
343 concentrations such as *DRD2* or *COMT*[89,88]. Such observations have not been tested
344 specifically in people with DM. Differences between men and women in barriers or responses
345 to smoking cessation strategies have an impact on the success of smoking cessation. In the
346 general population, data are divergent between studies, but it seems that there is no
347 difference in the proportion of women initiating cessation compared with men, nor in the
348 success of cessation. On the other hand, a difference in the ability to maintain abstinence over
349 the long term has been observed[89]. Another study has found 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[90]. 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 T2DM or T1DM[91, 92]. However, these data mainly concern the management of dyslipidemia or hypertension on the basis of prescription data for lipid-lowering and anti-hypertensive medications. In these studies, the occurrence of smoking cessation advice by 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 between men and women[93]. 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 behavioral 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[94]. This includes interventions that address emotions and stress in women[95] or an implementation design to reach specific populations of men[94].

- **The benefit of smoking cessation appears to be similar between men and women with DM.**
- **As in the general population, weight change following 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 impact 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[96, 97]. 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 non-users[98-100]. 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 non-smoking 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)[100]. Animal studies suggest that glycerol contained in ENDS liquids can

affect glucose homeostasis in both males and females[101]. Finally, regarding the effects of ENDS use on diabetic complications few studies exists and none with sex or gender specific data. One Chinese study found 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[102].

- Few data exist on the use and health impact of ENDS in men and women with DM.
- ENDS use aiming at smoking cessation should be of limited duration, once 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 both men and women and the risk conferred by smoking appears to be comparable between them. As observed in the general population, the prevalence of smoking varies between 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 a specific attention on women who might be especially exposed to tobacco industry's marketing strategies.

Smoking is an independent risk factor for all-cause mortality, macrovascular and microvascular complications in both women and men with DM. However in 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 higher 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 following smoking cessation also appears to be greater in women than in men. These factors may hinder smoking cessation and should be addressed when managing smokers with DM. People with DM should be offered the same first-line therapies smoking cessation treatment as the general population, including behavioral 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 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 in order to better reach people with DM on the basis of their sex or gender specificities.

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718 **Figure legends**

719 **Figure 1. Sex and gender aspects in smoking and diabetes: a complex interplay**
720 **1a: Sex and gender aspects in smoking**
721 **1b: Sex and gender aspects in diabetes**
722 **1c: Sex and gender aspects in the association between smoking and diabetes**
723
724 **Figure 2. Impact of smoking on chronic complications of type 2 diabetes mellitus according to sex**
725

726 **Table 1:** Sex-stratified impact of diabetes on chronic macro- and microvascular complications

Study	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.* 2006[38]	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.* 2014[39]	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.* 2020[57]	T2DM	Microalbuminuria			1.64 (1.21–2.24)	
		Retinopathy			1.27 (0.93–1.74)[$]	
		Neuropathy			1.35 (0.99–1.83)[$]	

727 RR: Relative Risk; HR: Hazard Ratio; 95% CI: 95% Confidence Interval; CHD: coronary heart disease; T2DM: Type 2 Diabetes Mellitus.
728 * People without diabetes are the reference group
729 ** Women are the reference group
730 [$] Not significant

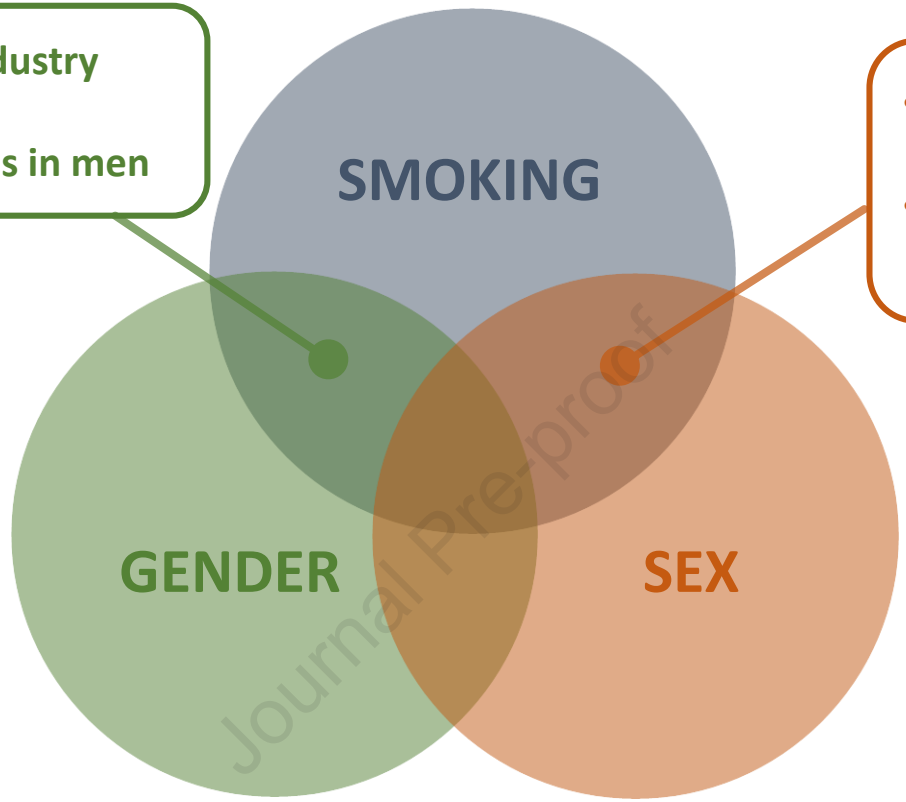
731 **Table 2:** Sex-stratified impact of smoking on chronic macro- and microvascular complications in people with diabetes

Study	Type of diabetes	Outcome	Women RR or HR (95% CI)	Men RR or HR (95% CI)	Women:Men Ratio of HR (95% CI)
Macrovacular complications					
Moy et *al.* 1990[40]	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.* 2009[51]	T2DM	Fatal/non-fatal myocardial infarction	HR 2.17 (1.69–2.79)*	HR 1.45 (1.19–1.77)*	
Barengo et *al.* 2017[52]	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.* 2016[53]	T2DM	Major coronary events			1.64 (0.83-3.26)$,***
Microvascular complications					
Blomster et *al.* 2016[53]	T2DM	Nephropathy			1.04 (0.57-1.89)$,***

732 RR: Relative Risk; HR: Hazard Ratio; 95% CI: 95% Confidence Interval; CHD: coronary heart disease; T1DM: Type 1 Diabetes Mellitus ; T2DM: Type 2 Diabetes
733 Mellitus.
734 * Cox regression analysis
735 ** 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
736 women with T2DM and non-smokers, HRs (95%CI) were 2.11 (1.71-2.59), 4.06 (2.83-5.82), 2.60 (2.02-3.35) for all-cause mortality, CHD mortality and CHD
737 incidence, respectively. In men with T2DM and non-smokers, HRs (95%CI) were 2.03 (1.51-2.74), 2.62 (1.60-4.29), 1.56 (1.08-2.24) for all-cause mortality, CHD
738 mortality and CHD incidence, respectively.

739 ***Ratio of the HRs (women:men) for daily smoking versus never smoking
740 $ Not significant
741

- Influences of gender norms by tobacco industry
- Higher risk of relapse in women
- Less use of nicotine replacement therapies in men

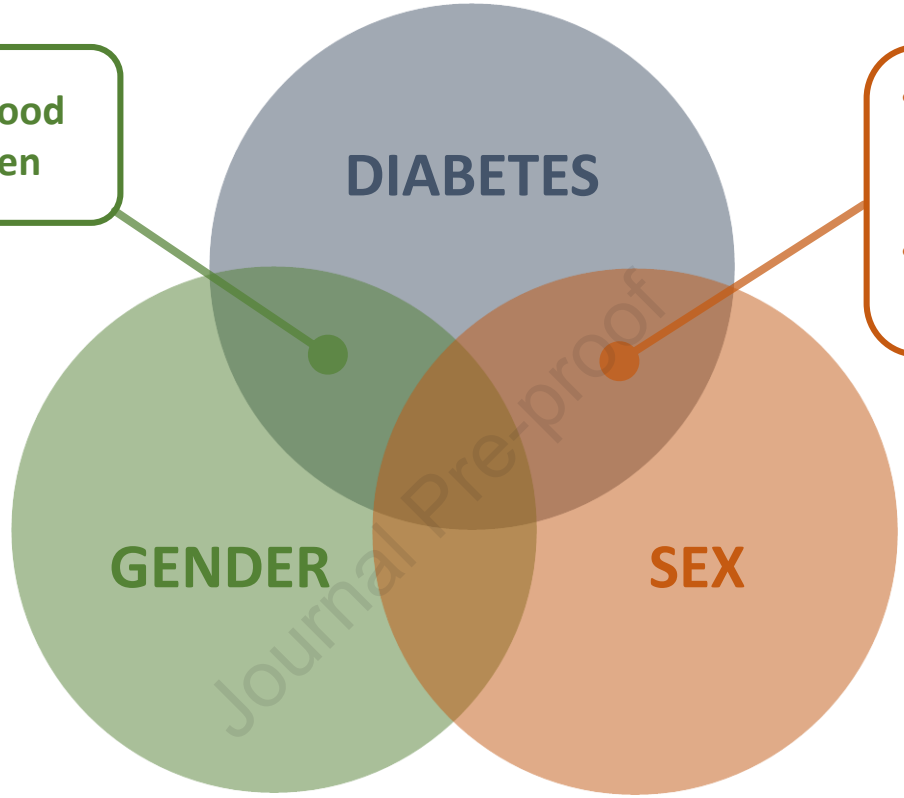


- Increased risk of nicotine dependence in women
- Lower efficacy of smoking cessation interventions or treatments in women

Influence on:

- Prevalence of smoking
- Weight gain after smoking cessation
- Access to smoking cessation interventions
- Efficacy of smoking cessation interventions

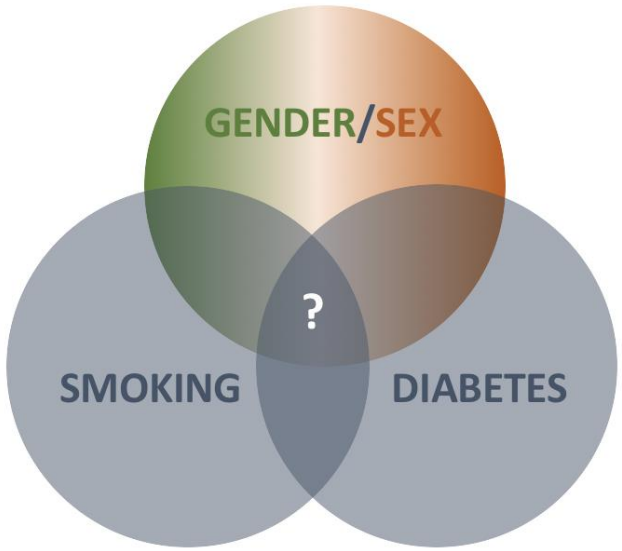
- Gender differences in diet and choice of food
- Less physical activity in women than in men



- Differences between men and women in energy metabolism and glucose homeostasis
- Differences between men and women in body composition

Influence on:

- Prevalence of diabetes
- Risk of chronic complications from diabetes
- Therapeutic responses in type 2 diabetes
- Development of new therapeutic approaches targeting sex-dimorphic metabolic pathways



Smoking is associated with the incidence of type 2 DM	♀ = ♂
Smoking prevalence differs between men and women in people with type 2 DM	♀ < ♂
Smoking increases diabetic macrovascular complications	♀ > ♂
Smoking increases diabetic microvascular complications	♀ = ♂ *
Smoking cessation decreases mortality and morbidity in people with DM	♀ = ♂
Smoking cessation is associated with weight gain in people with DM	♀ > ♂
Smoking cessation interventions are effective in people with DM	*No sex or gender specific data*

DM= diabetes mellitus

* *except for microalbuminuria :* ♀ > ♂