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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

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ABSTRACT

Objectives: In general populations, the adverse effects of smoking on coronary risk have been demonstrated to be greater in women than in men; whether this is true for individuals with diabetes is unclear.

Design: Cohort study.

Setting: 20 countries worldwide participating in the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron modified release Controlled Evaluation) trial.

Participants: 11 140 patients with type 2 diabetes aged ≥55 years and in cardiovascular risk at the time of randomisation.

Primary and secondary outcome measures: Major cardiovascular events (death from cardiovascular disease, non-fatal stroke or non-fatal myocardial infarction (MI)), all cardiovascular events (major cardiovascular event or peripheral arterial disease or transient ischaemic attack), and all-cause mortality. Secondary outcome measures were major coronary events (fatal and non-fatal MI), major cerebrovascular events (fatal and non-fatal stroke), nephropathy (new or worsening renal disease), and all cancer.

Results: At baseline, 6466 (56% women) participants were never-smokers, 1550 (28% women) were daily smokers and 3124 (21% women) were former smokers. Median follow-up time was 5 years. In Cox regression models after multiple adjustments, compared with never smoking, daily smoking was associated with increased risk of all primary and secondary outcomes with the exception of major cerebrovascular disease. Only for major coronary events was there any evidence of a stronger effect in women than in men (ratio of the adjusted HRs women:men; 1.64 (0.83 to 3.26) p=0.08). For all other outcomes considered, the hazards of smoking were similar in men and women. Quitting smoking was associated with a 30% reduction in all-cause mortality (p=0.001) in both sexes.

Conclusions: In individuals with diabetes, the effects of smoking on all major forms of cardiovascular disease are equally as hazardous in women and men with the possible exception of major coronary events where there was some evidence of a greater hazard in women.

Trial registration number: NCT00145925.

Strengths and limitations of this study

- The ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron modified release Controlled Evaluation) trial was a randomised, factorial controlled trial conducted in 20 countries providing detailed and well-documented data throughout the trial.
- This study includes a broad variety of cardiovascular and other outcomes associated with smoking that all have been adjudicated providing solid evidence of the risks associated with smoking.
- The issue of generalisability is a concern when using data from a clinical trial to inform on risk in the general population.
- There is a potential for misclassification of some individuals who were 'occasional' smokers (ie, not daily smokers) as never-smokers, resulting in an attenuation of the strength of the associations between smoking and vascular outcomes.

INTRODUCTION

In recent years, there has been a greater appreciation of the possible existence of important and clinically meaningful sex differences in the impact of risk factors on selected health outcomes.[1–3] Type 2 diabetes has unequivocally been demonstrated to be a more potent risk factor for coronary heart disease (CHD) and stroke in women than in men.[1 3] Similarly, cigarette smoking has also been shown to confer an excess risk of CHD in women than in men in otherwise healthy populations. For example, compared with never-smokers, women who smoke have a 25% greater relative risk of CHD than men independent of sex differences in the levels of other cardiovascular risk factors.[2 4] Despite the almost universal acceptance of cigarette smoking as a major hazard for cardiovascular disease (CVD) in individuals with and without diabetes, the prevalence of smoking in those with diabetes (in whom the risk for CVD is already substantially elevated), in the USA and the UK is high and comparable to that of the general population at 20–25%.[5 6] According to a recent multicentre cohort study in Europe, the current smoking prevalence among individuals with type 2 diabetes is similar to that of the general population where current smokers are 25% vs 28% and never-smokers 39% vs 42%, respectively.[7]

In a recent meta-analysis that examined the effects of smoking on vascular risk among individuals with type 1 and/or 2 diabetes, although not formally tested, there was some evidence that women with diabetes who smoke are at increased risk of CHD (but not other vascular outcomes) compared with their male counterparts.[8] Since this subgroup analysis was based on data from only two small studies, it precludes any definitive conclusions being drawn about the sex-specific nature of the association, and thus it remains to be determined whether smoking exerts a differential effect on vascular outcomes in women and men with diabetes.

In general populations, the adverse effects of smoking on coronary risk have been demonstrated to be greater in women than in men; whether this is true for individuals with diabetes is unclear. We sought to investigate smoking-associated risks in men and women with type 2 diabetes from 20 countries worldwide participating in the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron modified release Controlled Evaluation) trial.

METHODS

We analysed the 11 140 patients enrolled on the ADVANCE study (ClinicalTrials.gov number NCT00145925). The ADVANCE study was a randomised, factorial, controlled trial conducted in 20 countries including participants aged at least 55 years who had been diagnosed with type 2 diabetes after the age of 30 years. All participants had a history of major macrovascular or microvascular disease or at least one additional cardiovascular risk factor. The study consisted of two treatment arms, one comparing intensive with standard glycaemic control and another comparing active with standard antihypertensive treatment.

All analysed outcomes in the study were adjudicated. The primary outcomes consisted of major cardiovascular events (death from CVD, non-fatal stroke or non-fatal myocardial infarction (MI)), all cardiovascular events (major cardiovascular event or peripheral arterial disease or transient ischaemic attack) and all-cause mortality.[9–11] The secondary outcomes comprised major coronary events (fatal and non-fatal MI), major cerebrovascular events (fatal and non-fatal stroke), nephropathy (new or worsening renal disease) and all cancer.[9–11] Smoking was categorised, by self-report, into three groups including daily smoking, former smoking and never smoking. Daily smoking was defined by daily cigarette smoking (at least one). 'Previous smoking of at least one cigarette daily or nearly daily for at least a year' was used to classify 'former smoking'. Time since smoking cessation in former smokers at randomisation was recorded in years. Written informed consents were obtained from all study participants. The study eligibility criteria and study methods,[9] as well as the main results,[10 11] have been published previously.

Statistical analyses

The main analyses included assessing daily smoking versus never smoking and former smoking versus daily smoking. Besides sex as the factor of interest, the HRs from Cox models were adjusted for age, body mass index, randomised treatment groups, glycated haemoglobin, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, creatinine clearance, systolic blood pressure (SBP), heart rate, duration of diabetes, history of CVD, any blood pressure medication, any lipid-lowering medication and use of acetyl salicylic acid or thienopyridines, exercise times per week (minimum 15 min/time), habit of weekly use of alcohol and higher education (age at the time of finishing highest level of education >15 years). Interactions between sex and smoking habit were tested for each studied outcome, and the ratio of the HRs (women: men) were calculated. Incidence rates per 1000 person years for primary and secondary outcomes were calculated by sex and smoking status at baseline. Sensitivity analyses were conducted comparing the outcomes in former versus never-smokers and in those smokers who had quit smoking more than 10 years and less than 10 years since study baseline. Analyses were performed using SAS V.9.3 (SAS Institute Inc, Cary, North Carolina).

RESULTS

At baseline, of the 11 140 study participants, 14% were daily smokers (17% men and 9% women) and 28% were former smokers (38% men and 14% women). Table 1 describes the general characteristics of the study

Table 1 Patient characteristics by smoking status: mean (SD) unless otherwise stated

	Men			Women		
	Never	Daily	Former	Never	Daily	Former
Number of individuals	2825	1116	2466	3641	434	658
Age (years)	66.4 (6.1)	62.3 (5.9)	66.9 (6.5)	65.7 (6.2)	62.9 (5.8)	67.1 (6.7)
Body mass index (kg/m^2)	27.3 (4.6)	27.7 (4.9)	28.9 (4.6)	28.2 (5.5)	29.8 (5.8)	31.3 (5.9)
Current weekly alcohol use (%)	32.3	46.4	55.4	9.0	20.0	27.1
History of macrovascular disease (%)	34.3	30.7	43.0	25.2	17.7	33.4
History of microvascular disease (%)	11.1	8.7	10.6	11.0	7.8	7.6
History of stroke (%)	11.1	8.0	8.8	9.2	4.6	7.4
Age at completion of highest level of education (years)	20.0 (7.3)	19.3 (6.9)	18.7 (7.4)	17.1 (7.1)	17.6 (6.6)	17.3 (7.1)
Systolic blood pressure (mm Hg)	144.1 (20.8)	141.0 (20.8)	147.3 (21.0)	145.3 (2.2)	142.5 (20.9)	147.5 (22.9)
Diastolic blood pressure (mm Hg)	81.0 (11.0)	81.1 (10.9)	81.7 (10.7)	75.7 (11.5)	79.7 (11.0)	80.0 (11.3)
Heart rate (bpm)	74 (12)	75 (12)	72 (13)	76 (12)	75 (11)	74 (11)
Total cholesterol (mmol/L)	4.92 (1.14)	5.10 (1.10)	4.87 (1.05)	5.60 (1.22)	5.51 (1.23)	5.35 (1.17)
HDL cholesterol (mmol/L)	1.21 (0.34)	1.18 (0.30)	1.17 (0.31)	1.35 (0.37)	1.30 (0.37)	1.32 (0.36)
LDL cholesterol (mmol/L)	2.96 (0.96)	3.07 (1.02)	2.87 (0.98)	3.38 (1.05)	3.31 (1.09)	3.13 (1.03)
Triglycerides (mmol/L)	1.77 (1.21)	2.06 (1.30)	1.94 (1.29)	2.04 (1.33)	2.11 (1.30)	2.04 (1.23)
HbA1c (%)	7.45 (1.52)	7.67 (1.59)	7.35 (1.38)	7.65 (1.70)	7.45 (1.49)	7.40 (1.38)
Exercise times per week, (minimum 15 min/time)	9.0 (10.8)	9.3 (12.2)	8.6 (9.9)	9.0 (11.5)	7.8 (7.7)	7.5 (8.1)
Creatinine clearance (mL/min)	81.9 (27.0)	93.5 (30.3)	85.9 (28.2)	76.7 (28.3)	83.7 (27.2)	81.1 (28.3)
ACE/ARB medication (%)	46.7	43.7	54.2	43.6	50.2	55.2
β-blocker (%)	24.6	20.2	28.0	22.3	26.5	29.6
Any blood pressure medications (%)	74.8	67.3	75.3	77.0	72.4	80.2
Lipid-lowering medication (%)	32.0	36.0	45.5	27.4	41.7	49.5
Aspirin or thienopyridines (%)	48.8	47.9	54.7	39.7	40.1	49.8
Duration of diabetes (years)	8.6 (6.7)	6.4 (5.6)	7.9 (6.4)	8.2 (6.2)	6.4 (5.8)	7.2 (6.2)

ARB, angiotensin receptor blocker; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

population by sex, whereas the corresponding figures of the entire population have been published previously.[12] Daily smokers were younger, which may account in part for the shorter duration of diabetes and lower SBP in this subgroup compared with the other two subgroups (p<0.01 in all).

The median duration of follow-up was 5 years, during which time 1147 (10%) participants experienced a major cardiovascular event and 1031 (9%) patients died. From the 11 140 participants in the ADVANCE study, 15 were lost to follow-up. In the entire cohort, the risk for all-cause mortality associated with daily smoking was increased (HR 1.52, 95% CI 1.27 to 1.83, <0.0001), and in the analyses by sex the risk was higher in women (men; HR 1.45, 95% CI 1.18 to 1.80, p=0.0006, women; HR 1.78, 95% CI 1.23 to 2.59, p=0.0025). In the subgroup of daily and never-smokers, major cardiovascular events were experienced by 772 participants (57% men; 43% women) and 664 patients (59% men; 41% women) died. The corresponding numbers in former and daily smokers were 526 (85% men; 15% women) and 513 patients (84% men; 16% women), respectively. Detailed numbers for each outcome are reported in figures 1 and 2.

Web table 1 shows the incidence rates for each outcome by sex and smoking status; there are higher incidence rates among former compared with daily smokers in men and women, whereas never-smokers tend to have lower incidences in studied outcomes with the exception of major cerebrovascular events.

As shown in figure 2, cigarette smoking was associated with a significantly increased risk for all of the primary and most of the secondary outcomes in individuals with type 2 diabetes: the risk of all-cause mortality and all cancer was increased by about 60% in smokers compared with never-smokers. For all other outcomes, smoking increased the relative risk by between one-quarter to one-third compared with never-smokers. There was no obvious association with major cerebrovascular events (HR 1.04 (95% CI 0.77 to 1.41)). In the analysis comparing the sex-specific HRs, the effects of smoking were broadly comparable in women and men for each of the outcomes with the exception of major coronary events: compared with never-smokers, women who smoked had an approximately 60% greater risk (ratio of HRs 1.64 (95% CI 0.83 to 3.26; p=0.081) compared with men in figure 1).

Smoking cessation was associated with a reduced risk of all-cause mortality (HR 0.70 (95% CI 0.57 to 0.87) for former vs daily smoking; p=0.0012) with non-significant reductions in all other outcomes (figure 3). The improvements in outcomes associated with quitting were consistent in women and men as shown in figure 4. Compared with never-smokers, the effect of quitting smoking on most outcomes diminished but did not fully

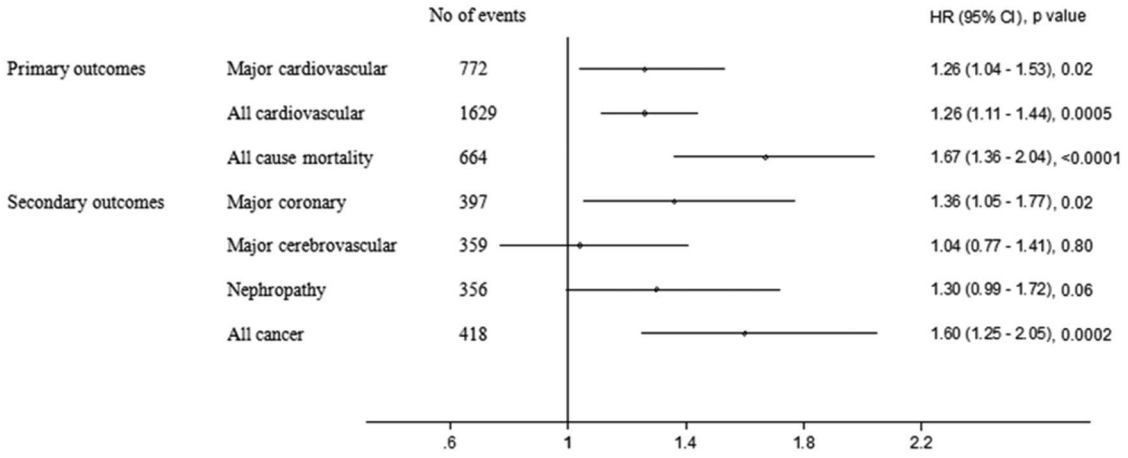

Figure 1 HR and 95% CIs for daily smoking versus never smoking. The total number of individuals is 8016. Cox models adjusted for age, sex, body mass index, randomised treatment groups, glycated haemoglobin, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, creatinine clearance, systolic blood pressure, heart rate, duration of diabetes, history of cardiovascular disease, any blood pressure medication, any lipid-lowering medication, use of acetyl salicylic acid or thienopyridines, exercise times per week, alcohol use and level of education.

negate the risks associated with past smoking habits (see web table 2). The benefits of quitting smoking, however, were, in general, greater in those individuals who had quit smoking for more than 10 years since study enrolment than in those who had quit less than 10 years before study initiation (see web table 3).

DISCUSSION

In this trial population of more than 11 000 patients with type 2 diabetes, cigarette smoking was associated with a significantly increased risk of all cancer, CVD and all-cause mortality, consistent with what we know about the harms of prolonged smoking from observational studies. Importantly, in this population, which is already at substantially greater risk of premature mortality, smoking cessation was associated with a significant 30% reduction in all-cause mortality. The hazards of smoking, and conversely the benefits of smoking cessation, were broadly comparable in women and men, with the possible exception of major coronary events where there was some suggestion of a greater adverse effect of smoking in women compared with men. With respect to all other outcomes, the effects of quitting smoking in comparison to daily smoking were less pronounced; this may have been due to a relatively short period of follow-up combined with a lack of efficacy of smoking cessation (subsequent to a history of prolonged smoking) to negate the risk for some of the outcomes (especially cancer) under investigation. There was, however, some evidence that the longer the period of smoking cessation prior to study baseline, the greater the benefits (>10 years), a finding consistent with the literature. Alternatively, since a higher proportion of former (43% in men and 33% in women) compared

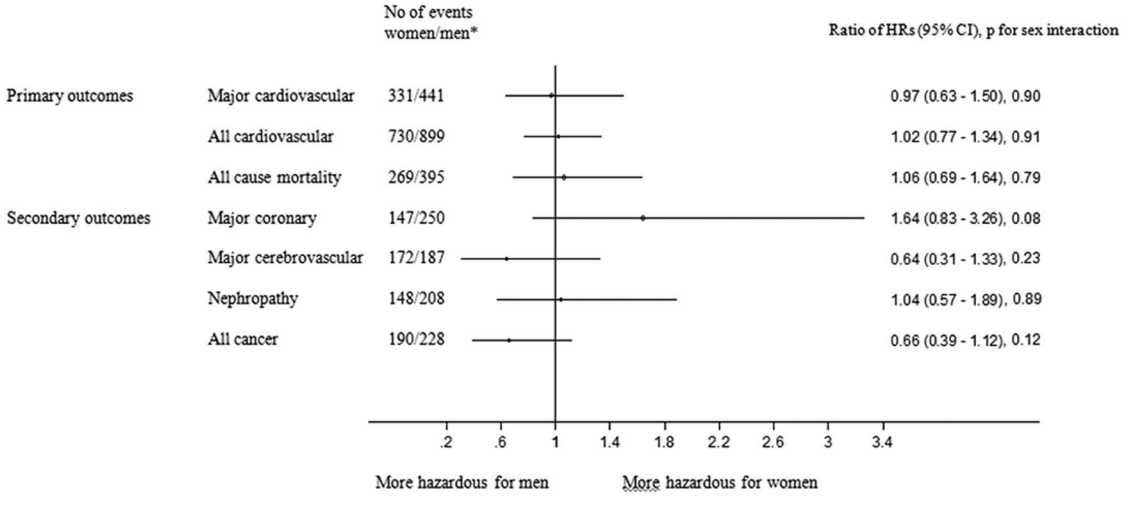

Figure 2 Ratio of the HRs (women:men) for daily smoking versus never smoking. *Total number of women is 4075 and men is 3941. Cox model adjustments are as in figure 1.

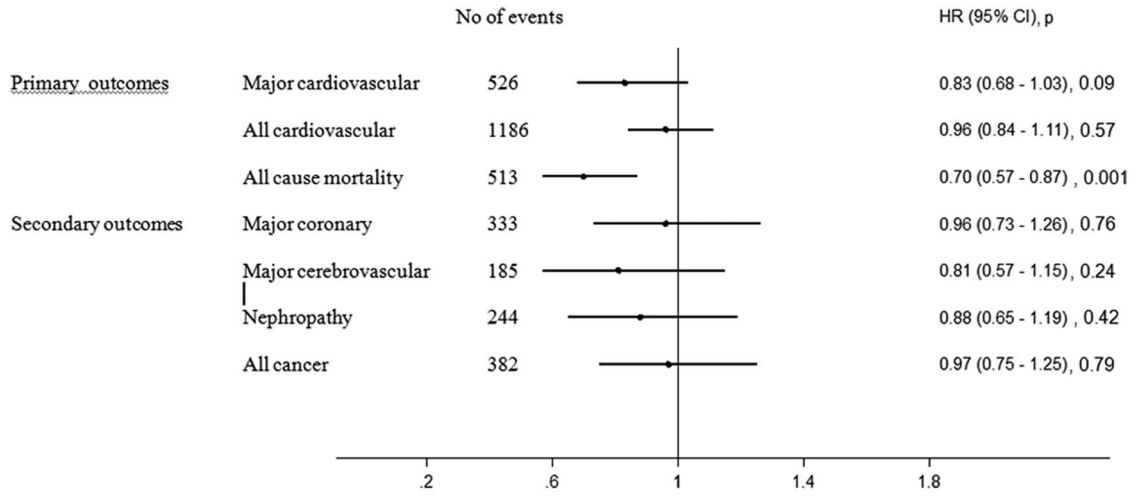

Figure 3 HR and 95% CIs for former versus daily smoking. The total number of individuals is 4674. Cox model adjustments are as in figure 1.

with daily smokers (31% in men and 20% in women) already had a history of macrovascular disease (which may have been the reason for quitting) at baseline, former smokers would therefore have had an increased susceptibility towards an adverse CVD outcome compared with daily smokers, a risk that is not sufficiently ameliorated by quitting smoking.

Previously, a large-scale meta-analysis of 75 cohort studies combining information on more than 4 million individuals (predominantly free from CVD at study baseline) and more than 67 000 CHD events suggested that the coronary hazards of smoking are stronger in women than in men, even after consideration of sex differences in other major cardiovascular risk factors that may confound the association.[2] Similarly, in the current study, on the basis of about 400 coronary events, there was some weak evidence that among individuals with diabetes, the effects of smoking on coronary outcomes are more hazardous in women than in men, although the test for interaction was of borderline statistical significance (p=0.081). The potential mechanism responsible for the greater adverse effects of smoking on CHD risk in women than in men remains speculative. Historically, women have been more likely to be undertreated with respect to their cardiovascular risk, but more contemporary studies have indicated that the sex disparity in treatment is diminishing. Since all of the participants in this study were recruited into the ADVANCE trial, women and men were treated and monitored according to the trial protocol. We therefore consider it unlikely that women were undertreated relative to men. Rather, the tendency for women who smoke to be at greater coronary hazard compared with men may be due to behavioural or physiological sex differences in smokers; for

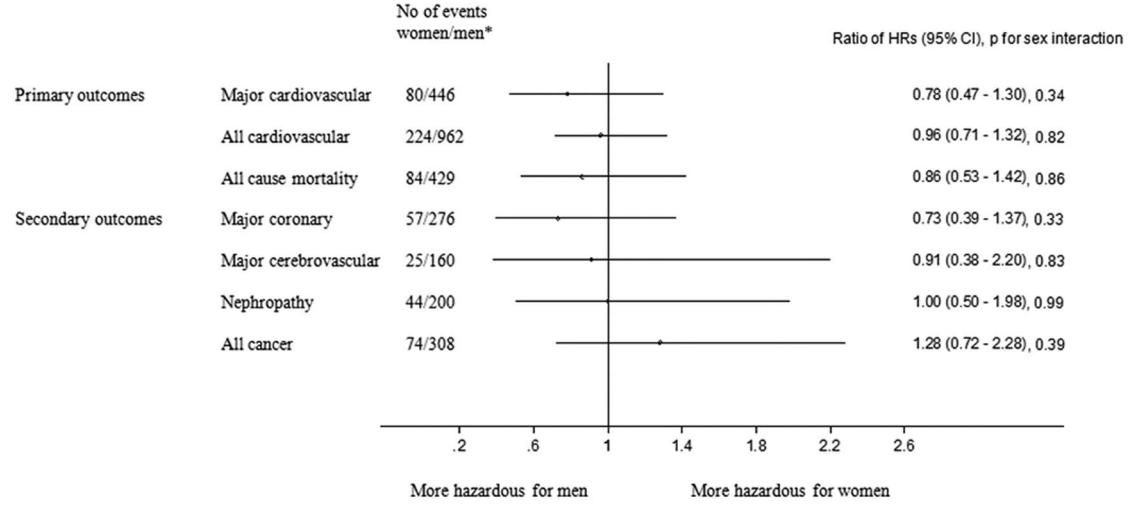

Figure 4 Ratio of the HRs (women:men) for former versus daily smoking. *Total number of women is 1092 and men is 3582. Cox model adjustments are as in figure 1.

example, absorption of nicotine has been reported to be greater among women than men.[13]

For major cerebrovascular disease, there was no evidence of a sex difference in the impact of smoking on subsequent cerebrovascular risk, which again is consistent with findings from a large meta-analysis.[4] The lack of any clear evidence of a sex difference in smoking-related risk of stroke (in contrast to CHD) is an interesting finding, which potentially suggests that the sex difference in smoking-related risk of CHD is unlikely to be mediated by differences in smoking-related behaviour (such as a greater degree of smoke inhalation by women) because the sex effect would also be shown for stroke. Instead, it is plausible that some of the pathways mediating the relationship between smoking and coronary risk are more susceptible to the antioestrogenic effect of smoking than those governing the relationship between smoking and stroke risk. For example, reduced oestrogen levels in smokers are considered to impact negatively on components of the lipid profile (a major risk factor for CHD and, to a lesser extent, for stroke) causing elevations in total cholesterol and triglycerides while lowering levels of high-density lipoprotein cholesterol.[14]

The lack of power to reliably examine sex differences in the effects of smoking is a limitation of this study; specifically, the proportion of women who were current and former smokers was substantially less than in men, which is likely to have limited the ability to detect sex-specific effects and any small but real sex differences in the associations between smoking and outcomes. However, to the best of our knowledge, this is the first study in a trial population of individuals with diabetes that has explored the sex-specific effects of smoking on major disease outcomes. The issue of generalisability is also a concern when using data from a clinical trial to inform on risk in the general population. We further acknowledge the potential for misclassification of some individuals who were 'occasional' smokers (ie, not daily smokers) as never-smokers resulting in an attenuation of the strength of the associations between smoking and vascular outcomes. However, this limitation is also true of the vast majority of previous studies that have reported on the sex-specific association between smoking and health outcomes. Most studies largely defined smoking in one of two ways: smoking (yes/no) or as current, never and former, either of which have the potential for misclassification of an individual's smoking status at baseline as well as during follow-up.[2] Similarly, a lack of information of change in smoking status over the duration of the trial may have resulted in some former smokers being misclassified as current smokers, which would be expected to diminish the effects of smoking on outcomes. However, in both instances, any misclassification is likely to have been non-differential between women and men, and thus the validity of the internal sex comparisons is unlikely to have been materially affected. There was also no information on smoking intensity, which is likely to have been higher in men than in women. Moreover, these current data are not without precedent and are in agreement with a subgroup analysis of a meta-analysis that showed a greater adverse effect for CHD due to smoking among women with diabetes compared with men.[8]

In summary, the effects of smoking and quitting are broadly consistent between the sexes, although the possibility of a greater adverse effect of smoking on coronary outcomes in women as compared with men could not be precluded.

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Contributors JIB, RH and MW contributed to the conception, design, acquisition of data, analysis and interpretation of data. GSH, SZ, SH, BN, NP, GM and JC contributed to the acquisition of data, analysis and interpretation of data. JIB and RH drafted the manuscript and MW, GSH, SZ, SH, BN, NP, GM and JC revised it critically for important intellectual content. All the authors gave final approval of the version to be published. JIB is the guarantor.

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Competing interests JIB has a financial relationship with AstraZeneca and is employed by AstraZeneca. GM reports personal fees from BOEHRINGER INGELHEIM, BAYER AG, DAIICHI SANKYO, FERRER, MEDTRONIC, MENARINI INT, MERCK SERONO and NOVARTIS PHARMA, all outside the submitted work. BN reports grants from Janssen, Abbvie, Dr Reddy's Laboratories, Merck Schering Plough, Roche and other from Abbott, Novartis, Pfizer, Servier, Roche and Janssen, all outside the submitted work. JC, MW and SZ have received honoraria from Servier for speaking at scientific meetings.

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Notes