

ORIGINAL ARTICLE

WILEY

Sex-specific associations between cardiovascular risk factors and myocardial infarction in patients with type 2 diabetes: The ADVANCE-ON study

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Funding information

Servier; the National Health and Medical Research Council (NHMRC) of Australia

Peer Review

The peer review history for this article is available at <https://publons.com/publon/10.1111/dom.14103>.

Abstract

Aim: To examine possible sex differences in the excess risk of myocardial infarction (MI) consequent to a range of conventional risk factors in a large-scale international cohort of patients with diabetes, and to quantify these potential differences both on the relative and absolute scales.

Materials and methods: Eleven thousand and sixty-five participants (42% women) with type 2 diabetes in the ADVANCE trial and its post-trial follow-up study, ADVANCE-ON, were included. Cox regression models were used to estimate hazard ratios (HRs) for associations between risk factors and MI (fatal and non-fatal) by sex, and the women-to-men ratio of HRs (RHR).

Results: Over a median of 9.6 years of follow-up, 719 patients experienced MI. Smoking status, smoking intensity, higher systolic blood pressure (SBP), HbA1c, total and LDL cholesterol, duration of diabetes, triglycerides, body mass index (BMI) and lower HDL cholesterol were associated with an increased risk of MI in both sexes.

The ADVANCE trial was funded by the grants from the National Health and Medical Research Council (NHMRC) of Australia and Servier. TO is supported by the John Chalmers Clinical Research Fellowship of the George Institute. SAEP is supported by a UK Medical Research Council Skills Development Fellowship (MR/P014550/1). MJ is supported by a Scientia Fellowship from UNSW Sydney. MW is a NHMRC of Australia Principal Research Fellow (1080206).

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Furthermore, some variables were associated with a greater relative risk of MI in women than men: RHRs were 1.75 (95% CI: 1.05-2.91) for current smoking, 1.53 (1.00-2.32) for former smoking, 1.18 (1.02-1.37) for SBP, and 1.13 (95% CI, 1.003-1.26) for duration of diabetes. Although incidence rates of MI were higher in men (9.3 per 1000 person-years) compared with women (5.8 per 1000 person-years), rate differences associated with risk factors were greater in women than men, except for HDL cholesterol and BMI.

Conclusions: In patients with type 2 diabetes, smoking, higher SBP and longer duration of diabetes had a greater relative and absolute effect in women than men, highlighting the importance of routine sex-specific approaches and early interventions in women with diabetes.

KEYWORDS

cardiovascular disease, cohort study, macrovascular disease, type 2 diabetes

1 | INTRODUCTION

Atherosclerotic cardiovascular diseases (CVD), such as coronary heart disease (CHD), cerebrovascular disease and peripheral arterial disease, are the leading causes of morbidity and mortality among patients with diabetes.¹ More than 40% of first presentations of CVD in patients with diabetes are for CHD.² Furthermore, CHD is an important cause of heart failure in patients with type 2 diabetes,^{3,4} which also increases the risk of premature mortality.^{5,6} Therefore, efficient early prevention of CHD is crucial. Systematic assessment of CVD risk factors is currently recommended in patients with diabetes.¹

Recently, important sex differences in the associations between several risk factors and myocardial infarction (MI) have been found in general populations.⁷ In particular, systolic blood pressure (SBP), smoking and diabetes were more strongly associated with the incidence of MI in women than men in the UK Biobank,⁷ which highlights the importance of sex-specific management of risk factors in general populations. There is growing evidence for sex differences in the excess risk of CVD consequent to diabetes,⁷⁻¹¹ and this has become a topical issue from the perspective of both public health and clinical practice. Deterioration in atherosclerotic CVD risk factor levels in individuals with diabetes, in comparison with those without diabetes, has been found to be greater in women than in men,¹²⁻¹⁴ and thus the degree of sex differences in the hazardous effects of risk factors may differ between the general population and patients with diabetes. However, to date no study has assessed the issue of sex differences across a range of risk factors for MI in a cohort of patients with diabetes.

The objective of the current study was, thus, to examine possible sex differences in the excess risk of MI consequent to a range of conventional risk factors in a large-scale international cohort of patients with diabetes, and to quantify these potential differences both on the relative and absolute scales.

2 | MATERIALS AND METHODS

2.1 | Study design and population

ADVANCE was a 2 × 2 factorial randomized controlled trial evaluating the effects of intensive blood glucose-lowering and blood pressure (BP)-lowering treatment on vascular outcomes in patients with type 2 diabetes. A detailed description of the design has previously been published.¹⁵⁻¹⁷ In brief, 11 140 participants with type 2 diabetes aged 55 years or older at high risk of cardiovascular events were recruited from 215 centres in 20 countries. Importantly, for the current study, it included a greater percentage (42.5%) of women than any comparable trial in diabetes,¹⁸ including recent trials of sodium-glucose co-transporter-2 inhibitors.¹⁹ Participants were randomly assigned to either a gliclazide (modified release)-based intensive glucose control regimen aiming for an HbA1c ≤6.5%, or standard glucose control, based on local guidelines, and also to a fixed-dose combination of perindopril and indapamide (2/0.625 mg) or matching placebo, after a 6-week active run-in period. The dose of randomized perindopril and indapamide treatment was doubled to 4 and 1.25 mg, respectively, 3 months after randomization. ADVANCE-ON (trial registration clinicaltrials.gov identifier: NCT00949286) was a post-trial follow-up study of ADVANCE, which enrolled 8494 participants out of a total of 10 082 surviving participants at the end of the randomized treatment phase of the ADVANCE trial (84%).²⁰ All participants discontinued the randomized treatments and returned to usual care determined by their physician(s). In the final year of ADVANCE-ON, 5131 (70%) out of the 7279 surviving participants completed a follow-up visit. This study was a post hoc analysis consisting of the ADVANCE trial and the ADVANCE-ON study,²⁰ taking the null hypothesis that there would be no difference in the effects of risk factors by sex. Ethical approval of the study was obtained from the institutional review board of each centre, and all participants provided written informed consent.

2.2 | Measurement of risk factors

Ten prespecified cardiovascular risk factors, both general and diabetes specific, were examined: smoking, SBP, diastolic blood pressure, HDL-, LDL- and total cholesterol, triglycerides, body mass index (BMI), HbA1c and duration of diabetes. Smoking status and intensity were self-reported and categorized into current, former and never smoking. SBP was recorded as the mean of two measurements, after at least 5 minutes of rest in the seated position, by using a standardized automated sphygmomanometer (Omron HEM-705CP, Tokyo, Japan). All laboratory measurements were performed in local laboratories, and HbA1c measurements were standardized. BMI was calculated as weight (kg) divided by the square of height (m). Information on history of diabetes, major macrovascular disease and major microvascular disease was obtained by the study staff.^{16,17} Duration of diabetes was calculated as baseline age minus self-reported age at diagnosis.

2.3 | Study outcome

The study outcome was MI (either fatal or non-fatal). Information on occurrence of MI was collected at study visits, reviewed and validated by an independent end-point adjudication committee only during the trial period (approximately half of the total follow-up). Events occurring during the postrandomization observational period were collected at annual visits using a questionnaire, and were reported by the study centres using the standardized definitions adopted during the trial, without adjudication.²⁰

2.4 | Statistical analysis

Baseline characteristics of the study participants by sex are presented as means (SD) for continuous variables that were approximately symmetrically distributed, and number (percentage) for categorical variables. Differences in baseline characteristics between women and men were tested by an unpaired *t*-test or chi-square test, as appropriate. Triglycerides were summarized as median (interquartile interval) because of a skewed distribution, and were log-transformed before testing.

Cox regression models were used to estimate hazard ratios (HRs) for associations between risk factors and MI, according to sex, in complete-case analyses. The proportional hazards assumption was explored through Schoenfeld residuals and log cumulative hazards plots, and found no apparent violations. HRs for continuous variables were computed per 10 cigarettes per day for smoking intensity,⁷ per 20 and 10 mmHg higher for SBP and diastolic BP,⁷ per 1 mmol/L higher for lipids,²¹ per 5 kg/m² higher for BMI,⁷ and per 5 years longer for duration of diabetes.²² Sex differences on the absolute scale were also evaluated. Incidence rates per 1000 person-years by sex and their women-to-men difference of rate differences were calculated by using Poisson regression models.²³ Models were adjusted for baseline age, region of residence, duration of diabetes, currently treated

hypertension, history of MI, smoking status, alcohol drinking habits, BMI, HbA1c, total cholesterol (not for models for LDL-C and HDL-C), log-transformed triglycerides, SBP, and randomized treatment allocations. The women-to-men ratio of HRs (RHR) for MI for each risk factor was estimated by adding interaction terms to the Cox model.²³ Log-transformed RHRs were provided from the models and were exponentially transformed to obtain RHRs.²³ For each variable that showed a significant sex difference, subgroup analyses were performed by baseline age, region of residence (Asia/not), history of MI, macrovascular disease (MI, stroke, hospital admission for transient ischaemic attack, hospital admission for unstable angina, coronary revascularization, peripheral revascularization, or amputation secondary to vascular disease) and microvascular disease (macroalbuminuria [urinary albumin-to-creatinine ratio {UACR} > 300 µg/mg], proliferative diabetic retinopathy, retinal photocoagulation therapy, macular oedema, or blindness in one eye thought to be caused by diabetes). Post hoc, we also conducted additional analyses which examined sex differences in the association between the kidney markers (estimated glomerular filtration rate [eGFR]²⁴ and UACR) and MI.

Statistical analyses were performed using SAS 7.11 (SAS Institute, Cary, NC, USA) and Stata software release 13 (StataCorp, College Station, TX, USA). A two-sided *P*-value of <.05 was considered to be statistically significant.

3 | RESULTS

Of the 11 140 participants in the ADVANCE trial, 11 065 participants (99.3%) were included in the present analysis consisting of the in-trial and post-trial period; the few excluded had missing values of covariates. Baseline characteristics of the study participants are shown in Table 1. The mean age of the included participants was 66 years (SD 6) and 42% were women. Women were less probable to have a past history of MI, macrovascular disease or current alcohol drinking habits and were more probable to have never smoked. On average, women had higher levels of lipids and BMI.

Over a median of 9.6 years of follow-up, 719 patients experienced an MI (232 [32%] in women), among whom 209 (29%) experienced fatal events. Smoking status, smoking intensity, higher SBP, HbA1c, total and LDL cholesterol, triglycerides, BMI, duration of diabetes and lower HDL cholesterol level were all associated with an increased risk of MI both in women and men, after multiple adjustment, although not all associations were statistically significant. The observed associations were generally stronger in women than in men (Figure 1).

Former and current smoking were associated with a 53% (95% CI, 0%-132%) and 75% (95% CI, 5%-191%) greater excess risk of MI in women compared with men (Figure 2). Also, a higher SBP conferred an 18% (95% CI, 2%-37%) greater risk of MI in women than men. A longer duration of diabetes was associated with a 13% (95% CI 0%-26%) higher risk of MI in women than men. The analyses for kidney markers showed that both eGFR and UACR were associated with an increased risk of MI both in women and men, but no sex differences were observed (Figure S1).

TABLE 1 Baseline characteristics of women and men included in ADVANCE-ON

Variable	Women (n = 4697)	Men (n = 6368)
Age (y)	66 (6)	66 (6)
Residence in Asia (%)	40.6	34.5
Duration of diabetes (y)	7.9 (6.2)	8.0 (6.5)
History of myocardial infarction	6.9	15.7
History of macrovascular disease (%)	25.7	37.1
History of microvascular disease (%)	10.3	10.5
Current alcohol drinking (%)	12.5	43.7
Smoking status		
Never smoked (%)	76.8	44.1
Former smoker (%)	14.0	38.6
Current smoker (%)	9.2	17.4
Smoking intensity (for current smokers)		
1-9 cigarettes per day (%)	33.1	26.1
10-19 cigarettes per day (%)	38.7	32.9
≥20 cigarettes per day (%)	28.2	41.1
SBP (mm Hg)	145 (22)	145 (21)
Diastolic BP (mm Hg)	80 (11)	81 (11)
Currently treated hypertension (%)	73.1	65.7
HbA1c (%)	7.6 (1.6)	7.5 (1.5)
Oral hypoglycaemic agents use (%)	90.5	91.2
Insulin use (%)	1.9	1.0
Total cholesterol (mmol/L)	5.5 (1.2)	4.9 (1.1)
LDL cholesterol (mmol/L)	3.3 (1.1)	2.9 (1.0)
HDL cholesterol (mmol/L)	1.3 (0.4)	1.2 (0.3)
Triglycerides (mmol/L)	1.7 (1.2, 2.4)	1.6 (1.1, 2.2)
Body mass index (kg/m ²)	28.8 (5.7)	28.0 (4.7)
Randomized treatments		
Perindopril-indapamide (%)	50.0	49.9
Intensive blood glucose control (%)	50.2	49.8

Abbreviations: BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.

Patients with missing values in covariates were excluded. Values shown are means (SDs) for continuous variables, except for triglycerides, where medians (interquartile intervals) are given, and percentages for categorical variables.

Subgroup comparisons showed broadly consistent estimates of RHRs for longer duration of diabetes (Figure 3), smoking (Figures S2 and S3) and higher SBP (Figure S4) by age, study region, history of MI, history of macrovascular disease and history of microvascular disease. The only significant heterogeneity ($.01 < P < .05$) was found in the RHRs for former smokers stratified by age and region of residence, although even then the HRs were greater for women than men in all subgroups.

On the absolute scale, men (9.3 per 1000 person-years) had a higher risk of MI compared with women (5.8 per 1000 person-years). However, rate differences associated with risk factors were generally greater in women than men; the only exceptions were LDL and HDL cholesterol and BMI (Table 2). These tendencies were broadly similar in unadjusted rates (Table S1).

4 | DISCUSSION

The present analysis, using data from one of the largest clinical trials of type 2 diabetes, with a greater proportion of women than in previous comparable trials, and a particularly wide geographical coverage, showed that the excess risk of MI associated with several traditional risk factors is significantly proportionally greater in women than men. Current and former smoking, and higher SBP levels were associated, respectively, with a 75%, 53% and 18% greater proportional excess risk of MI in women than men. Longer duration of diabetes was also 13% more strongly associated with the risk of MI in women with type 2 diabetes compared with their male counterparts. The observed sex differences between duration of diabetes and MI were consistent across a range of subgroups. While the risk of MI among people with diabetes was greater in men than women, these sex differences were attenuated in the presence of most of the risk factors investigated.

In order to provide a context for our results, necessarily restricted to patients with diabetes, we compared them to a previous study of ours that used data from the general population of the UK Biobank of primarily middle-aged people (mean age: 56 years). In that study we used the same basic methodology as in the current study. There, we found that the risk of MI in women was less than half of that in men.⁷ However, women with certain risk factors tended to 'catch up' with men, in terms of the risk of MI. Indeed, while these UK Biobank analyses showed that current smoking, hypertension and diabetes were risk factors for MI in both sexes, there was a significantly greater effect in women than men.⁷ The current study, in type 2 diabetes, found broadly consistent results to those found in the UK Biobank,⁷ as illustrated by Table S2, which compares the sex-specific HRs, and their ratio, between ADVANCE-ON (mean age of 66 years) and a similar age group (≥60 years) in the UK Biobank. Greater relative effects of smoking in women than men might be explained by sex differences in the susceptibility for smoking²⁵ or extraction of a greater amount of toxic agents from the same number of cigarettes in women than men.²⁶ For the sex differences in the relative effects of SBP, women may be less probable to receive and be adherent to BP-lowering agents,²⁷ and less probable to have their BP controlled.^{28,29} In addition, women may have a longer period with hypertension, including before starting treatment.⁷ Taken together, the current results provide additional support for sex-specific prevention and treatment policies and emphasize the importance of early detection followed by intensive and comprehensive management of type 2 diabetes in both women and men. Clinical practitioners should be particularly aware of the heightened risk of MI in female patients who have diabetes, smoke, and have high BP.

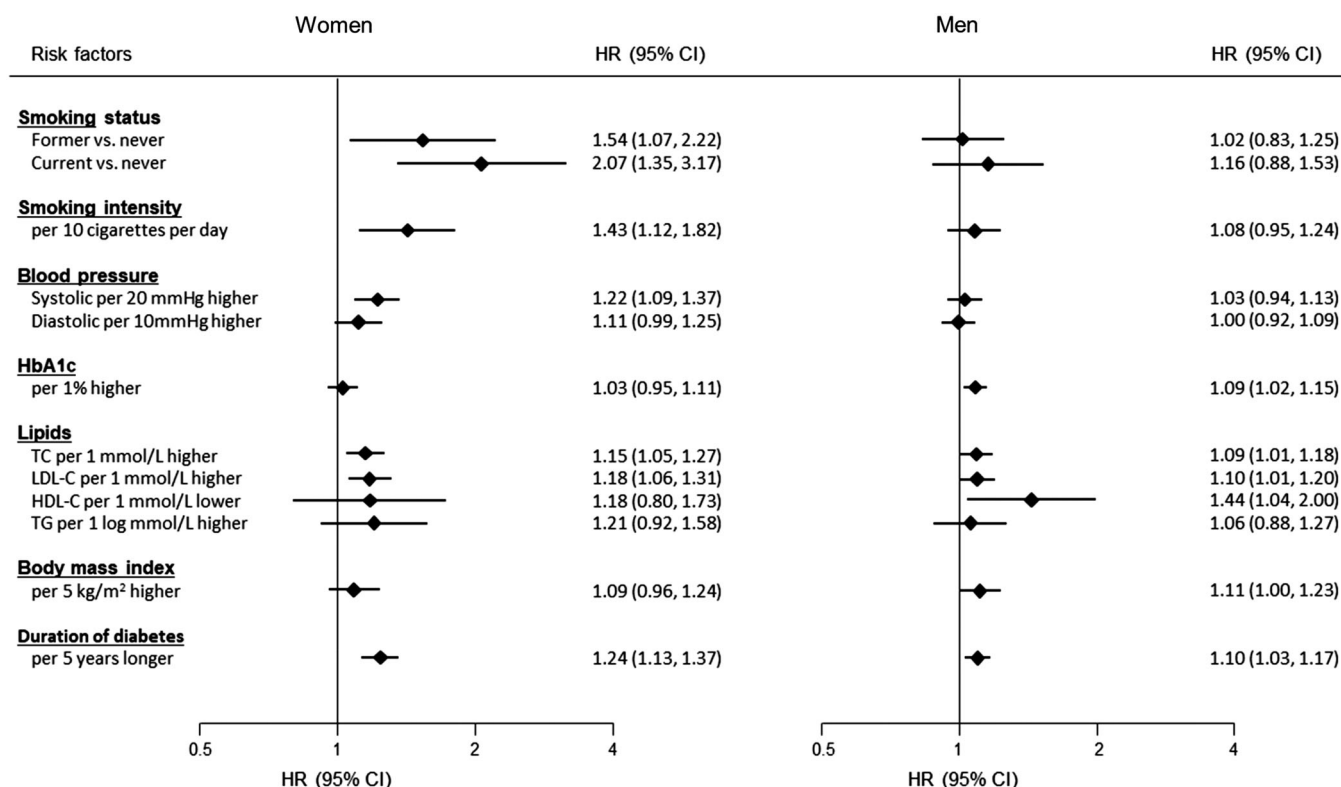


FIGURE 1 Adjusted hazard ratios (HRs) for association between risk factors and myocardial infarction by sex. Models were adjusted for age, sex, region of residence, duration of diabetes, currently treated hypertension, history of myocardial infarction, smoking status, alcohol drinking habits, body mass index, HbA1c, total cholesterol, log-transformed triglycerides (TG), systolic blood pressure, and randomized blood pressure-lowering intervention, and randomized glucose control intervention. Models for low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) were not adjusted for total cholesterol (TC). Former smokers were excluded from the analysis of smoking intensity

As far as is known, the UK Biobank study⁷ is the only large study to have assessed sex differences on the absolute scale across a range of risk factors for MI. Although additive risks, as opposed to relative risks, are generally not reported, they may be more relevant to decision-making in clinical practice as they indicate the expected number that will experience the outcome over a fixed time period, which is essential for planning purposes.²³ The UK Biobank analyses found that diabetes, especially type 1, conferred a greater excess additive risk of MI in women than men. Unlike the current study, among patients with type 2 diabetes, in the general population of the UK Biobank the additive effects of other risk factors on the rate of MI was greater among men than women, despite SBP and smoking showing significantly higher relative risks of MI for women than men.⁷ These differences will inevitably be affected by the higher risk of MI in diabetes than in general populations.

Duration of diabetes has previously been shown to be associated with an increased risk of macrovascular complications, including MI and stroke²² and death because of coronary heart disease.³⁰ A US population-based cohort study found that longer duration of diabetes was more strongly associated with the risk of fatal CHD in women than men.³¹ Current findings are consistent with this previous study, and extend it to all MI (including non-fatal events), different

subpopulations, and the impact on the absolute scale. A previous study has suggested that the development of diabetes may take longer in women than men,³² which may explain why the deteriorations in the metabolic profile associated with diabetes are greater in women than men.¹¹ The greater change in metabolic profile in women than in men may be explained by sex differences in body fat distribution, specifically the greater subcutaneous fat storage capacity in women, which may delay the diagnosis of diabetes in women, and result in a greater excess risk of the vascular consequences of diabetes once subcutaneous fat storage has reached its full capacity and excess adipose tissue is deposited in abdominal regions.³³ Several studies have shown that women tend to develop diabetes at higher levels of BMI^{34,35} and present with worse risk factor profiles at the time of, as well as after, diagnosis with diabetes than men.^{35,36} Thus, the excess risk of a longer duration of diabetes on the risk of MI in women than men may reflect greater accumulation of the hazardous effects of risk factors in women than men.

The strengths of this study are the large number, and diverse backgrounds, of study participants enrolled from 20 countries from Europe, Asia, Australasia and North America, a long duration of follow-up, and a comprehensive assessment of sex differences in the effects of traditional risk factors within the same cohort, taking the

FIGURE 2 Adjusted women-to-men ratios of hazard ratios (HRs) for association between risk factors and myocardial infarction. Models were adjusted for age, sex, region of residence, duration of diabetes, currently treated hypertension, history of myocardial infarction, smoking status, alcohol drinking habits, body mass index, HbA1c, total cholesterol, log-transformed triglycerides (TG), systolic blood pressure and randomized blood pressure-lowering intervention, and randomized glucose control intervention. Models for low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) were not adjusted for total cholesterol (TC). Former smokers were excluded from the analysis of smoking intensity

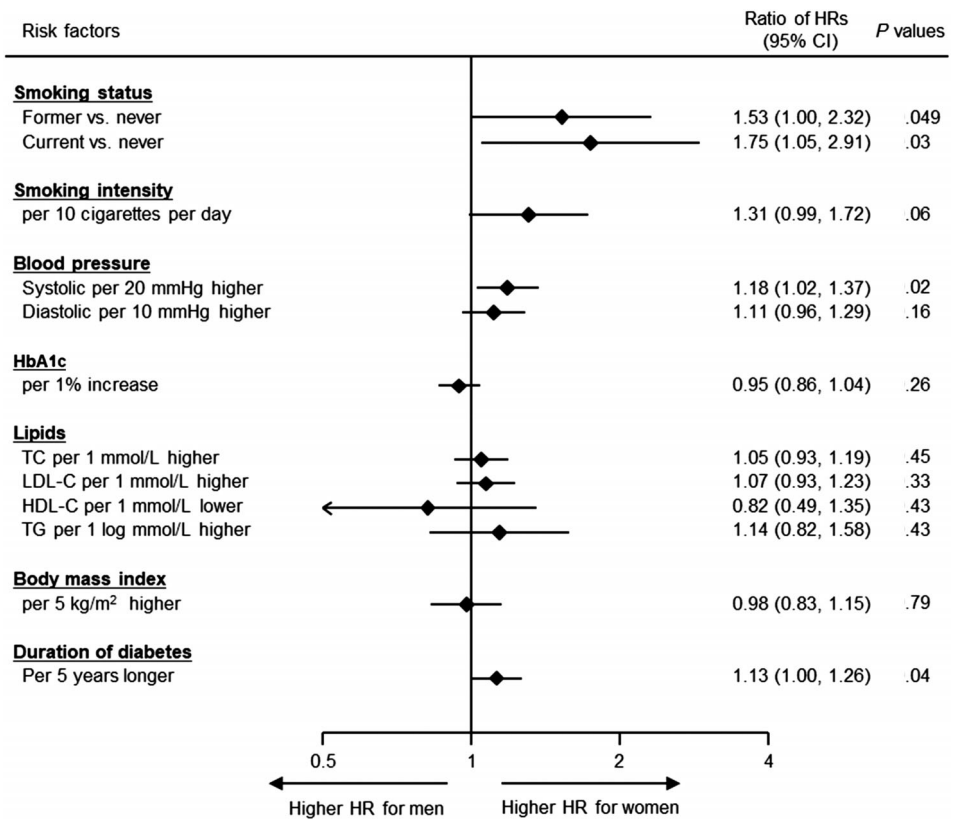


FIGURE 3 Adjusted women-to-men ratios of hazard ratios (HRs) for myocardial infarction (MI), associated with a 5-year increase in the duration of diabetes. Models were adjusted for age, sex, region of residence, currently treated hypertension, history of MI, smoking status, alcohol drinking habits, body mass index, HbA1c, total cholesterol, log-transformed triglycerides, systolic blood pressure and randomized blood pressure-lowering intervention, and randomized glucose control intervention. Age was not adjusted for the subgroup analyses by age. Region of residence was not adjusted for the subgroups analyses by region of residence. History of MI was not adjusted for the subgroup analyses by history of MI or history of macrovascular diseases

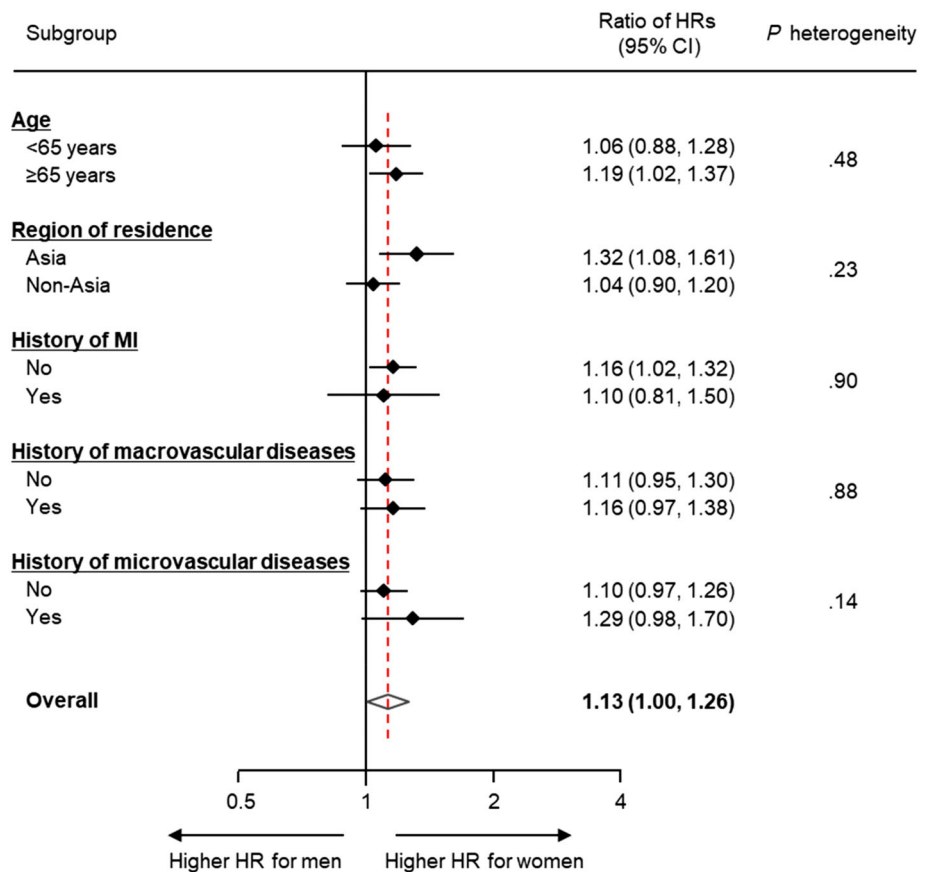


TABLE 2 Multiple adjusted incidence rates of myocardial infarction (per 1000 person-years) by sex, and women-to-men difference of rate differences for each risk factor

	Rates (per 1000 person-years)		Difference of rate difference
	Women	Men	
	(n = 4697)	(n = 6368)	
Smoking status			
Never smoked	4.9 (4.0, 5.8)	10.2 (8.7, 11.6)	
Former smoker	7.6 (5.2, 10.1)	10.4 (8.8, 11.9)	2.5 (−0.8, 5.9)
Current smoker	9.7 (5.9, 13.6)	11.7 (8.8, 14.5)	3.3 (−1.7, 8.4)
Systolic BP (mm Hg)			
<140	4.7 (3.5, 5.9)	10.5 (8.9, 12.2)	
≥140	7.1 (5.7, 8.4)	10.3 (9.0, 11.6)	2.6 (0.1, 5.2)
Diastolic BP (mm Hg)			
<90	5.9 (4.9, 6.9)	10.6 (9.4, 11.8)	
≥90	7.3 (5.0, 9.5)	9.6 (7.6, 11.6)	2.4 (−0.8, 5.6)
HbA1c (%)			
<7	5.2 (3.9, 6.5)	9.8 (8.3, 11.3)	
7-<8	6.7 (5.0, 8.4)	8.8 (7.2, 10.5)	2.4 (−0.5, 5.3)
≥8	6.9 (5.2, 8.6)	12.6 (10.6, 14.7)	−1.1 (−4.3, 2.0)
Total cholesterol (mmol/L)			
<5.2	5.2 (3.9, 6.5)	9.5 (8.4, 10.7)	
≥5.2	7.3 (5.9, 8.7)	11.2 (9.5, 12.9)	0.4 (−2.2, 3.1)
LDL cholesterol (mmol/L)			
<4.1	6.0 (4.9, 7.1)	10.0 (9.0, 11.0)	
≥4.1	7.7 (5.6, 9.9)	11.8 (8.6, 15.0)	−0.1 (−4.1, 3.9)
HDL cholesterol (mmol/L)			
W ≥ 1.3, M ≥ 1.0	6.5 (5.1, 7.8)	9.6 (8.5, 10.7)	
W < 1.3, M < 1.0	6.3 (4.9, 7.6)	11.4 (9.5, 13.3)	−2.0 (−4.8, 0.8)
Triglycerides (mmol/L)			
<1.7	5.6 (4.3, 6.9)	10.5 (9.0, 12.0)	
≥1.7	6.6 (5.3, 8.0)	10.3 (8.9, 11.7)	1.2 (−1.4, 3.8)
Body mass index (kg/m ²)			
Normal (<25)	6.1 (4.3, 7.8)	8.5 (6.7, 10.3)	
Overweight (25-<30)	5.9 (4.5, 7.4)	10.3 (8.9, 11.8)	−2.0 (−5.0, 1.1)
Obese (≥30)	6.6 (5.0, 8.3)	11.7 (9.7, 13.8)	−2.7 (−6.4, 1.0)
Duration of diabetes (y)			
<5	5.1 (3.2, 7.1)	9.6 (7.3, 11.9)	
5-9	6.8 (4.9, 8.7)	11.0 (9.0, 13.0)	0.2 (−3.2, 3.7)
≥10	6.5 (4.6, 8.4)	10.7 (8.3, 13.0)	0.3 (−4.8, 5.4)

Abbreviations: BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; M, men; SBP, systolic blood pressure; W, women.

Numbers in parentheses represent 95% confidence intervals. Models were adjusted for age, sex, region of residence, currently treated hypertension, history of myocardial infarction, smoking status, alcohol drinking habits, body mass index, HbA1c, total cholesterol, log-transformed triglycerides, SBP and randomized BP-lowering intervention, and randomized glucose control intervention. Models for LDL cholesterol and HDL cholesterol were not adjusted for total cholesterol.

sexes on an equal basis. Furthermore, this study is the first to examine the sex differences in both additive and relative excess risk of MI associated with a range of traditional risk factors, as well as duration of diabetes, within the same diabetes cohort. The findings highlight the importance of a sex-specific approach in patients with diabetes,

who could obtain greater benefits than the general population. However, some limitations of this study are notable. First, participants in the current study were recruited for a clinical trial,¹⁸ which may limit the generalizability of the findings to broader, unselected, diabetes populations. On the other hand, a previous study found close

similarities between the ADVANCE study population and community diabetes studies in Europe and Australia.³⁷ Second, MI events occurring during the post-trial follow-up were reported by the local site investigators using prespecified criteria, but were not centrally adjudicated. However, the endpoint adjudication process had no discernible effect on the results in the ADVANCE trial.³⁸ Third, we could not evaluate the difference in sex differences between diabetes and non-diabetes participants on an equal footing, as this study was restricted to patients with diabetes. However, we were able to make direct comparisons between our patients with diabetes and the general population of the UK Biobank. Finally, there may be residual confounding factors other than those adjusted for in the current study.

In conclusion, in this population of patients with diabetes, the excess risk of MI associated with several traditional risk factors, such as smoking, SBP and longer duration of diabetes, was greater in women than men. These findings underscore the importance of routinely applying a sex-specific approach in the management plan of patients with type 2 diabetes.

ACKNOWLEDGMENTS

The ADVANCE trial was funded by the grants from the National Health and Medical Research Council (NHMRC) of Australia and Servier. TO is supported by the John Chalmers Clinical Research Fellowship of the George Institute. SAEP is supported by a UK Medical Research Council Skills Development Fellowship (MR/P014550/1). MJ is supported by a Scientia Fellowship from UNSW Sydney. MW is a NHMRC of Australia Principal Research Fellow (1080206).

CONFLICT OF INTEREST

TO reports no conflicts of interest. SAEP reports no conflicts of interest. MJ reports receiving grant support from the National Health and Medical Research Council of Australia (Project Grant: 1148060) and unrestricted grant support from VentureWise (a wholly owned commercial subsidiary of NPS MedicineWise) to conduct a commissioned project funded by AstraZeneca. SH reports grants from the George Institute for Global Health during the conduct of the study; and from Servier, outside the submitted work. MC reports grants from Novo Nordisk, grants and personal fees from Boehringer Ingelheim, and personal fees from Servier, AstraZeneca, Novartis, Merck and Bayer, outside the submitted work. PH reports consulting fees from Servier, and grant support from Quebec CQDM and Servier. NP received honoraria and personal fees from Servier Laboratories, Takeda Pharmaceutical Company, Menarini Group and Pfizer, and grant support from Servier Laboratories and Pfizer. JC received research grants from the National Health and Medical Research Council of Australia and from Servier for the ADVANCE trial and ADVANCE-ON post-trial follow-up, and honoraria for speaking about these studies at scientific meetings, and reports grant support from Program Grant APP1149987 from the National Health and Medical Research Council of Australia. MW reports consultancy fees from Amgen and Kirin and is supported by an Australian National Health and Medical Research Council fellowship (APP1080206) and Program Grant (APP1149987).

AUTHOR CONTRIBUTIONS

TO had the initial idea for this study, conducted statistical analysis with advice from MW, and drafted the manuscript. SP, MJ, JC and MW helped design the study and drafted the manuscript. TO conducted statistical analysis with advice from MW. All authors contributed to discussion and reviewed and edited the manuscript. MW is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Ohkuma T, Peters SAE, Jun M, et al. Sex-specific associations between cardiovascular risk factors and myocardial infarction in patients with type 2 diabetes: The ADVANCE-ON study. *Diabetes Obes Metab*. 2020;22:1818-1826. <https://doi.org/10.1111/dom.14103>