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Cardiovascular events in type 2 diabetes: comparison with nondiabetic individuals without and with prior cardiovascular disease

10-year follow-up of the Hoorn Study

Annemarie Becker[a], Griët Bos[b], Femmie de Vegt[b], Piet J. Kostense[b,c], Jacqueline M. Dekker[b], Giel Nijpels[b], Robert J. Heine[a,b], Lex M. Bouter[b], Coen D.A. Stehouwer[a,b]*

[a] *Department of Internal Medicine, VU University Medical Center, Amsterdam, Netherlands*
[b] *Institute for Research in Extramural Medicine, VU University Medical Center, Amsterdam, Netherlands*
[c] *Department of Clinical Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, Netherlands*

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Aims We questioned whether prior cardiovascular disease has the same impact on risk of cardiovascular events as type 2 diabetes, and whether this differed between men and women.

Methods and results To address these issues we compared the 10-year risk of cardiovascular events among 208 Caucasian individuals with diabetes to that of 2253 Caucasian individuals without diabetes, in a population-based cohort study. Gender significantly modified the association between type 2 diabetes and cardiovascular events (p=0.01). The hazard ratio of cardiovascular events associated with the presence of diabetes was higher in women (adjusted hazard ratio, 1.8; 95% CI, 1.2 to 2.7) than in men (adjusted hazard ratio, 1.3; 0.9 to 2). As compared to men without diabetes but with prior cardiovascular disease, risk of cardiovascular events was significantly lower in men with diabetes but without prior cardiovascular disease (adjusted hazard ratio, 0.5; 0.3 to 0.9). In contrast, this risk was equal in women with diabetes but without prior cardiovascular disease and women without diabetes but with prior cardiovascular disease (adjusted hazard ratio, 1.0; 0.6 to 1.7; P for interaction between gender and diabetes=0.05).

Conclusions Women with diabetes but without prior cardiovascular disease have a risk of cardiovascular events that is similar to that of women without diabetes but with prior cardiovascular disease, whereas in men the presence of prior cardiovascular disease conferred a higher risk. These data emphasise the necessity of aggressive treatment of cardiovascular risk factors in women with type 2 diabetes.

Introduction

Type 2 diabetes increases the risk of cardiovascular mortality by a factor of 1.5 to 4.[1–3] Patients with both diabetes and prior cardiovascular disease have a particularly poor prognosis.[4] According to Haffner et al., patients with diabetes but without prior myocardial infarction have a risk of fatal coronary heart disease that is similar to that of patients without diabetes who have survived a myocardial infarction.[5] Therefore, Haffner et al. conclude that, with regard to cardiovascular risk factors, all patients with diabetes could be treated as if they had prior coronary heart disease.

* Correspondence to: Professor Dr Coen D.A. Stehouwer, Department of Internal Medicine, VU University Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands. Tel: +31 20 444 0531; fax: +31 20 444 4313
E-mail address: cda.stehouwer@vumc.nl (C.D.A. Stehouwer).

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This concept is elegant and appealing. However, it is not clear whether Haffner et al.'s findings, which were obtained in Finnish individuals, can be generalised to other populations. First, studies do not concur quantitatively concerning the increased mortality risk associated with type 2 diabetes.[5–11] Relative mortality risks may vary substantially with ethnicity,[6,7] but even among ethnically similar populations different relative mortality risks have been reported.[8–11] Second, studies often have not distinguished between men and women, whereas diabetes is reported to have a greater impact on mortality risk in women than in men.[3,12,13] This specifically raises the question whether Haffner et al.'s findings[5] are valid in both men and women with type 2 diabetes. In fact, we have not been able to find reports in which relative mortality risks associated with type 2 diabetes have been analysed stratified for gender as well as for the presence of prior cardiovascular disease.

The aim of the present study, therefore, was to compare the risk of cardiovascular events among four subsets of participants: (1) individuals without diabetes or prior cardiovascular disease, (2) individuals without diabetes but with prior cardiovascular disease, (3) individuals with diabetes but without prior cardiovascular disease, and (4) individuals with both diabetes and cardiovascular disease. In addition, we assessed whether these comparisons were affected by gender.

Methods

The Hoorn Study is a Dutch population-based cohort study of glucose intolerance and cardiovascular risk, which began in 1989. The study population and baseline measurements have been described in detail.[14,15] Briefly, a random sample of 3553 men and women aged 50–75 years was selected from the population register of the town of Hoorn; 2540 individuals (71%) agreed to participate. A total of 56 non-Caucasians and 23 participants with missing variables were excluded from the study, which resulted in a study population of 2461 participants. All participants gave their written informed consent. The ethics committee of the University Hospital Vrije Universiteit approved the study.

Baseline measurements

A fasting blood sample was taken from all participants and subsequently, a 75-g oral glucose tolerance test was administered. A glucose dehydrogenase method (Merck, Darmstadt, Germany) was used to determine fasting and 2-h postload plasma glucose levels. Participants were classified as having type 2 diabetes according to the 1985 World Health Organization criteria.[16] Serum lipids and lipoproteins were determined by means of enzymatic techniques (Boehringer-Mannheim, Mannheim, Germany) as described previously.[15]

Blood pressure was measured twice on the right arm with participants in the sitting position, by means of a random-zero sphygmomanometer (Hawksley-Gelman Ltd, Lancing, United Kingdom). Participants were classified as having hypertension if the mean systolic blood pressure was 160 mmHg or more, if the mean diastolic blood pressure was 95 mmHg or more, and/or if using anti-hypertensive medication. Body-mass index was calculated as body weight divided by the square of the height (kg/m^2). Smoking status was classified as nonsmoker, former smoker, or current smoker of cigarettes. Information about prior cardiovascular disease was obtained using a standardized questionnaire including a translated questionnaire from the London School of Hygiene.[17,18] Participants were regarded as having prior cardiovascular disease if they had a history of one or more of the following: acute myocardial infarction, coronary bypass surgery or angioplasty, angina pectoris, transient ischaemic attack or stroke, intermittent claudication, or the use of nitrates.

Follow-up

Data on the participants' vital status on 1 January 2000 were collected from the mortality register of the municipality of Hoorn. For all participants who died, the cause of death was extracted from the medical records of the general practitioner and the hospital of Hoorn. For participants who moved out of Hoorn, we obtained information on mortality from the new municipality. Information about nonfatal cardiovascular events was obtained from medical records of the hospital of Hoorn. The ninth edition of the International Classification of Diseases (ICD) was used to code the causes of death.[19] Cardiovascular mortality was defined as ICD codes 390-459 ('Diseases of the circulatory system') or 798 ('Sudden death, cause unknown'), because sudden death in general is of cardiovascular origin.[20] A customised and computerised classification system, based on existing systems, was used to classify cardiovascular events.[21–25] Cardiovascular events were defined as coronary heart disease (defined by the presence of prolonged typical chest pain, ECG changes, enzymes, and percutaneous transluminal angioplasty or coronary artery bypass grafting), congestive heart failure, transient ischaemic attack or stroke, or peripheral atherosclerotic disease.

Cardiovascular events (n=341) were defined as the first fatal or nonfatal cardiovascular event during follow-up. Seventeen participants (0.6%) were lost to follow-up. We did not receive information about nonfatal cardiovascular events from 612 (24.6%) participants, because they did not give permission or had moved out of Hoorn (185 participants, 7.4%). However, participants who were lost to follow-up did not differ importantly from the rest of the cohort with respect to cardiovascular risk factors at baseline (Table 1). Follow-up duration was defined as the period between the baseline examinations and the end-points death, first nonfatal cardiovascular event, or the date of leaving the area, loss to follow-up or 1 January 2000.

Statistical analyses

Our aim was to compare the risk of cardiovascular events in individuals with type 2 diabetes to that of individuals without diabetes with and without prior cardiovascular disease, and to assess whether these comparisons were affected by gender. Hazard ratios and 95% confidence intervals were calculated by means of Cox proportional hazards model. Individuals with missing values for morbidity were omitted from analyses with nonfatal events as an endpoint. If a participant developed a cardiovascular event and died after the next event, we used the follow-up time until the first event, except in the separate analyses of fatal cardiovascular events. In initial analyses we considered the following possible determinants of cardiovascular events: age, diabetes, prior cardiovascular disease, gender and the interaction term of the variables gender and diabetes. Analyses were done with adjustment for age and without (model 1) and with (model 2) adjustment for other potentially confounding variables, namely low-density lipoprotein and high-density lipoprotein cholesterol concentration, triglyceride

Table 1 Baseline characteristics of the participants and the participants who were lost to follow-up

	Participants	Participants lost to follow-up	*p*-value of difference between the groups
Gender (% men)	47.7	40.2	0.001
Age (year)	61.7±7.3	61.8±7.5	0.8
Diabetes (%)	8.5	8.1	0.7
Newly diagnosed diabetes (% of participants with diabetes)	54.1	65.3	0.2
Diabetes duration (year)[a]	6.4 (2.8–13.5)	5.9 (2.4–15.8)	1.0
HbA1c (%)	5.5±0.9	5.5±0.8	0.5
Prior cardiovascular disease (%)	16.2	14.6	0.4
Body-mass index	26.5±3.4	26.9±4.1	0.03
Systolic blood pressure (mmHg)	135.5±20.4	135.1±19.9	0.7
Diastolic blood pressure (mmHg)	82.2±10.3	81.2±10.5	0.4
Hypertension (%)	32.2	30.2	0.5
Total cholesterol (mmol/l)	6.6±1.2	6.7±1.3	0.04
HDL cholesterol (mmol/l)	1.3±0.4	1.3±0.4	0.7
LDL cholesterol (mmol/l)[b]	4.6±1.1	4.7±1.2	0.03
Triglycerides (mmol/l)	1.4 (1.0–1.9)	1.4 (1.0–2.0)	0.6
Smoking status (%)			
Never/former/current	34.0/30.2/35.8	35.5/35.0/29.5	0.05

Data are presented as mean±standard deviation, median (interquartile range) or number (percentage). HDL=high-density lipoprotein, LDL=low-density lipoprotein.

[a] Among those with a prior diagnosis of diabetes.
[b] The Friedewald formula was used to calculate low-density lipoprotein if triglyceride level was <4.5 mmol/l.

concentration, presence of hypertension, and smoking status. All analyses were performed with SPSS 10.1 for Windows 95. Variables measured on a continuous scale were used as such in the regression models.

Results

At baseline, the cohort consisted of 90 men with and 1044 men without diabetes, and of 118 women with and 1209 women without diabetes. Three hundred eighty-nine individuals had prior cardiovascular disease (205 men and 184 women): myocardial infarction (*n*=135); coronary surgery or angioplasty (*n*=79); angina pectoris (*n*=134); transient ischaemic attack or stroke (*n*=110); intermittent claudication (*n*=25); and/or use of nitrates (*n*=92). (Twelve individuals had nitrate use as their only criterion.) Table 2 shows gender-specific clinical characteristics of the individuals according to their diabetic status and history of cardiovascular disease. After up to 10.2 years of follow-up (median, 8.8; range, 9 days to 10.2 years), the cardiovascular death rate was 1.8 per 100 person years (*n*=12) for men with and 0.9 (*n*=79) for men without diabetes, versus 2.4 (*n*=22) for women with and 0.4 (*n*=37) for women without diabetes. The rate of cardiovascular events (fatal or nonfatal) was 5.1 per 100 person years (*n*=30) for men with and 2.8 (*n*=225) for men without diabetes, versus 4.8 (*n*=38) for women with and 1.3 (*n*=134) for women without diabetes. Among women with diabetes, the first event during follow-up was nonfatal in 28 and fatal in 10 of 38; 12 fatal events were preceded by a nonfatal event. Among men with diabetes, the first event during follow-up was nonfatal in 23 and fatal in seven of 30; five fatal events were preceded by a nonfatal event.

In Cox regression analyses, gender modified the association between diabetes and cardiovascular events (P for interaction among gender and diabetes=0.01). Therefore, we performed all analyses for men and women separately. Fig. 1 shows the Kaplan–Meier estimates of the proportion of participants without cardiovascular events during follow-up. The proportion of participants with a cardiovascular event was highest among men and women with both diabetes and prior cardiovascular disease and lowest among individuals with no diabetes or prior cardiovascular disease. Men with diabetes but without prior cardiovascular disease, however, had a lesser risk of cardiovascular events than did men without diabetes but with prior cardiovascular disease. In contrast, women with diabetes but without prior cardiovascular disease had a risk of cardiovascular events that was similar to that of women without diabetes but with prior cardiovascular disease.

The age-adjusted hazard ratio of cardiovascular events associated with the presence of diabetes, regardless of the presence of prior cardiovascular disease, was 1.5 (95% CI, 1.1 to 2.3) in men and 2.6 (95% CI, 1.9 to 3.8) in women. After adjustment for low-density lipoprotein and high-density lipoprotein cholesterol concentration, triglyceride concentration, presence of hypertension and smoking status, these hazard ratios were 1.3 (95% CI, 0.9 to 2) and 1.8 (95% CI, 1.2 to 2.7). Table 3 shows the hazard ratios of cardiovascular events associated with diabetes and prior cardiovascular disease for men and women, with individuals with no diabetes or cardiovascular disease as the reference group. Among both men and women, prior cardiovascular disease, regardless of the presence of diabetes, was associated with an increased risk of cardiovascular events (adjusted hazard ratios for

Table 2 Baseline characteristics stratified for gender, history of cardiovascular disease and presence of type 2 diabetes

	Non-diabetic men		Men with Type 2 diabetes		Non-diabetic women		Women with type 2 diabetes	
	No prior CVD (*n*=866)	Prior CVD (*n*=178)	No prior CVD (*n*=63)	Prior CVD (*n*=27)	No prior CVD (*n*=1053)	Prior CVD (*n*=156)	No prior CVD (*n*=90)	Prior CVD (*n*=28)
Age (year)	60.6±7.2	63.4±7.1	63.8±6.9	65.0±7.1	61.2±7.3	64.1±7.1	66.0±6.6	69.0±4.9
Body-mass index	26.0±3.0	26.2±2.6	27.4±3.3	27.5±3.3	26.5±3.8	27.2±3.9	29.1±5.0	31.2±5.1
Systolic blood pressure (mmHg)	134.1±18.7	136.9±20.3	146.0±20.2	142.1±20.1	133.9±20.7	136.5±21.3	145.9±20.5	148.1±19.9
Diastolic blood pressure (mmHg)	83.4±9.9	83.6±9.8	87.3±10.8	81.5±10.8	80.7±10.7	80.6±10.4	82.8±9.4	80.6±10.5
Hypertension (%)	22.2	57.6	46.0	77.8	26.4	54.5	60.0	78.6
Antihypertensive medication (%)	9.5	48.9	20.6	63.0	15.5	50.6	37.8	75.0
Hypo-lipidaemic medication (%)	0.7	4.5	0	3.7	0.7	6.4	2.2	0
Total cholesterol (mmol/l)	6.4±1.1	6.7±1.0	6.2±1.2	6.4±1.1	6.9±1.2	7.0±1.2	6.9±1.5	6.8±1.0
HDL cholesterol (mmol/l)	1.2±0.3	1.1±0.3	1.1±0.3	1.1±0.2	1.5±0.4	1.4±0.4	1.2±0.3	1.1±0.2
LDL cholesterol (mmol/l)[a]	4.5±1.0	4.7±1.0	4.1±1.2	4.3±1.0	4.7±1.2	4.8±1.2	4.6±1.2	4.7±0.9
Triglycerides (mmol/l)	1.4 (1.0–1.9)	1.6 (1.2–2.2)	1.6 (1.2–2.5)	2.5 (1.8–3.1)	1.3 (1.0–1.7)	1.4 (1.1-2.0)	1.9 (1.4-2.8)	2.3 (1.7-3.1)
HbA1c (%)	5.4±0.5	5.5±0.5	6.9±1.7	7.2±1.6	5.3±0.5	5.5±0.5	7.2±1.9	7.5±1.9
Smoking status (%)								
Never/former/current	17.5/45.6/36.9	8.4/56.2/35.4	17.7/59.7/22.6	11.5/46.2/42.3	48.6/22.5/28.9	51.3/25.6/23.1	61.4/18.2/20.5	53.6/17.9/28.6
Newly diagnosed diabetes (%)	–	–	65	52	–	–	58	40
Diabetes duration (year)[b]	–	–	7.0 (4.6–11.3)	6.7 (2.6–14.5)	–	–	5.6 (2.2–14.2)	6.5 (2.6–13.5)

Data are presented as mean±standard deviation, median (interquartile) or number (percentage). CVD=cardiovascular disease, HDL=high-density lipoprotein, and LDL=low-density lipoprotein.

[a] The Friedewald formula was used to calculate low-density lipoprotein if triglyceride level was <4.5 mmol/l.

[b] Among those with a prior diagnosis of diabetes.

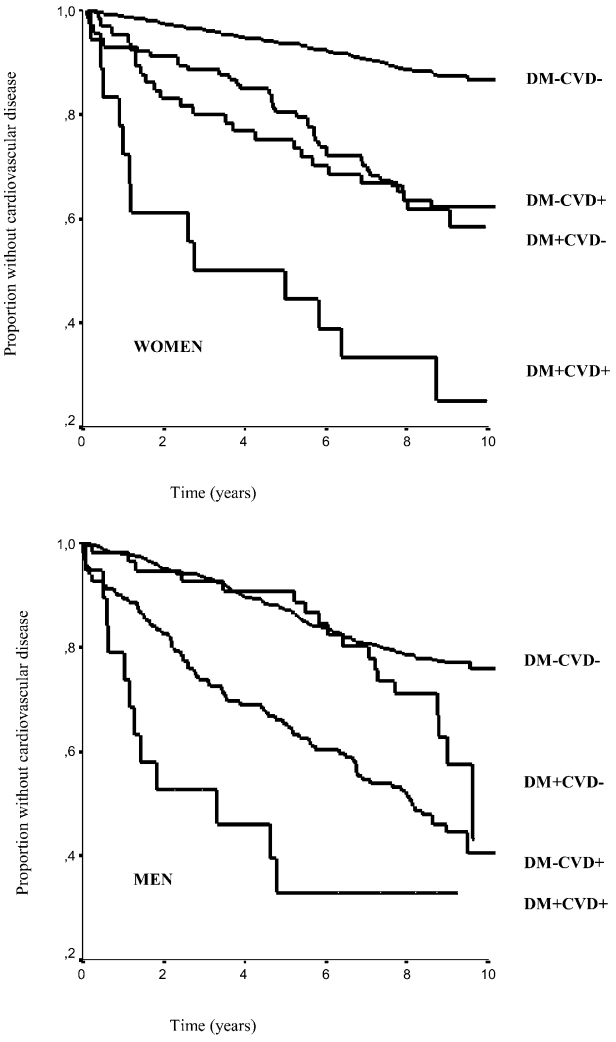

Fig. 1 Kaplan–Meier estimates of the proportion of individuals without cardiovascular events, stratified for diabetes and prior cardiovascular disease. DM– or + denotes the absence or presence of type 2 diabetes mellitus and CVD– or + the absence or presence of prior cardiovascular disease at baseline.

men and women without diabetes, 2.2 and 2.0; for men and women with diabetes, 4.3 and 3.8). In contrast, among individuals without prior cardiovascular disease, the presence of diabetes was strongly associated with cardiovascular events among women (adjusted hazard ratio, 2.0), but less so among men (adjusted hazard ratio, 1.3; Table 3).

When analyses were performed for fatal and nonfatal cardiovascular disease separately, the results for men were similar (adjusted hazard ratios, 1.2 and 1.2; Table 3). However, for women with diabetes the hazard ratio for fatal cardiovascular events was markedly higher than that for nonfatal events (adjusted hazard ratios, 5.1 and 1.7; Table 3).

Table 4 illustrates that, as compared to individuals without diabetes but with prior cardiovascular disease, the hazard ratio for a cardiovascular event was lower in men with diabetes but without prior cardiovascular disease (adjusted hazard ratio, 0.5; 95% CI, 0.3 to 0.9), but equal in women with diabetes but without prior cardiovascular disease (adjusted hazard ratio, 1.0; 95% CI, 0.6 to 1.7; P for interaction between gender and diabetes=0.05).

When analyses were performed for fatal and nonfatal cardiovascular events separately, the results for men were again similar (adjusted hazard ratios, 0.4 and 0.5; Table 4). Again, for women with diabetes the hazard ratio for fatal cardiovascular events was higher than that for nonfatal events (adjusted hazard ratios, 1.7 and 0.9; Table 4).

Additional analyses

Analyses with prior myocardial infarction instead of prior cardiovascular disease did not clearly change the results. Among men, fully adjusted hazard ratios for cardiovascular events were 1.9 (1.3–2.7) among DM–CVD+ (abbreviations are explained in the legend to Table 3) versus 1.2 (0.7–1.9) among DM+CVD– and 6.7 (3.0–14.9) among DM+CVD+ (p-value for the difference between DM–CVD+ and DM+CVD–=0.01). Among women these hazard ratios were 3.2 (1.8–5.6) among DM–CVD+ versus 2.1 (1.4–3.2) among DM+CVD- and 2.1 (0.5–8.8) among DM+CVD+ (p-value for the difference between DM–CVD+ and DM+CVD–=0.14). The following additional analyses also did not materially alter our results (data not shown): analyses with myocardial infarction as outcome variable instead of cardiovascular events; analyses that excluded angina as sole cause of prior cardiovascular disease (because angina may be a poor marker of coronary heart disease among women); analyses that excluded participants with newly detected diabetes; and analyses with additional adjustment for duration of diabetes.

Discussion

This study is the first to compare the risk of cardiovascular events in individuals with type 2 diabetes to that of nondiabetic individuals with and without prior cardiovascular disease, and to assess whether these comparisons were affected by gender. Our results suggest that the concept of Haffner et al., that individuals with diabetes but *without* prior myocardial infarction have a cardiovascular mortality risk that is of similar magnitude as that of individuals without diabetes but *with* prior myocardial infarction,[5] cannot be generalised to all populations. We found that gender strongly modified the associations between diabetes and cardiovascular events. In analyses stratified for gender, the hazard ratio of cardiovascular disease of women with diabetes but without prior cardiovascular disease was indeed similar to that of women without diabetes but with prior cardiovascular disease. However, for fatal cardiovascular disease, this risk was actually higher among women with diabetes but without prior cardiovascular disease than among women without diabetes but with prior cardiovascular disease. In contrast, the risk of cardiovascular disease among men with diabetes but without prior cardiovascular disease was

Table 3 Hazard ratios for fatal and nonfatal cardiovascular events associated with type 2 diabetes and/or prior cardiovascular disease

MEN	DM−CVD−	DM-CVD+	DM+CVD−	DM+CVD+
First cardiovascular event	145	79	18	12
Event rate[a]	2.1	7.1	4.0	9.0
Cases (n)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Model 1	1.0	2.8 (2.1–3.7)[b]	1.4 (0.9–2.3)	5.7 (3.1–10.3)[b]
Model 2	1.0	2.2 (1.7–3.0)[b]	1.3 (0.7–2.1)	4.3 (1.4–8.3)[b]
Fatal events[c]	1.0	2.4 (1.5–3.8)[b]	1.2 (0.5–3.1)	2.3 (0.9–6.2)
Nonfatal events[c]	1.0	2.3 (1.7–3.2)[b]	1.2 (0.7–.2)	4.8 (2.4–9.7)[b]
WOMEN	DM−CVD+	DM−CVD+	DM+CVD−	DM+CVD+
First cardiovascular event	93	41	25	13
Event rate[a]	1.1	3.5	4.0	7.8
Cases (n)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Model 1	1.0	2.7 (1.9–4.0)[b]	2.7 (1.8–4.3)[b]	6.0 (3.3–11.0)[b]
Model 2	1.0	2.0 (1.2–3.2)[b]	2.0 (1.2–3.2)[a]	3.8 (2.0–7.0)[a]
Fatal events[c]	1.0	2.6 (1.3–5.2)[a]	5.1 (2.6–9.9)[b]	6.8 (3.0–15.3)[b]
Nonfatal events[c]	1.0	2.0 (1.3–3.1)[a]	1.7 (1.0–3.0)	3.4 (1.7–7.0)[b]

DM+ or DM− denotes the presence or absence of type 2 diabetes; CVD+ or CVD−, the presence or absence of prior cardiovascular disease; HR=hazard ratio; 95% CI, the 95% confidence intervals; DM−CVD− is used as reference group; *per 100 person years.

Model 1: hazard ratios of cardiovascular events adjusted to age.

Model 2: hazard ratios of cardiovascular events adjusted for age, smoking status, hypertension, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides.

[a] *p*-value <0.01.
[b] *p*-value <0.001.
[c] Model 2.

Table 4 Hazard ratios for fatal and nonfatal cardiovascular events (as a composite variable and separately) in individuals with type 2 diabetes without prior cardiovascular disease compared to those in nondiabetic individuals with prior cardiovascular disease

First cardiovascular event	Hazard ratio for diabetic men and women (95% CI)	*p* value	Hazard ratio for diabetic men (95% CI)	*p* value	Hazard ratio for diabetic women (95% CI)	*p* value
Model 1	0.7 (0.5–1.0)	0.08	0.5 (0.3–0.9)	0.01	1.0 (0.6–1.7)	0.91
Model 2	0.7 (0.5–1.0)	0.06	0.5 (0.3–0.9)	0.01	1.0 (0.6–1.7)	0.99
Fatal events[a]	1.0 (1.6–1.7)	0.97	0.4 (0.2–1.1)	0.07	1.7 (0.8–3.9)	0.17
Nonfatal events[a]	0.6 (0.4–1.0)	0.03	0.5 (0.2–0.9)	0.02	0.9 (0.5–1.7)	0.73

95% CI denotes the 95 percent confidence intervals,

Model 1: hazard ratios of cardiovascular events adjusted for age.

Model 2: hazard ratios of cardiovascular events adjusted for age, smoking status, hypertension, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides.

[a] Model 2.

substantially lower than that of men without diabetes but with prior cardiovascular disease. Although the confidence intervals around some of these hazard ratios were rather wide, they clearly and significantly differed between men and women. Adjustment for potential confounders did not alter these results.

Haffner et al. found a similar risk for mortality from coronary heart disease for individuals with diabetes but *without* prior myocardial infarction as for individuals without diabetes but *with* prior myocardial infarction. Their study did not report analyses for men and women separately, but if we assume that results in their study were not affected by gender, then our results differ markedly from theirs. We used a different definition of prior cardiovascular disease than did Haffner et al., but this is unlikely to explain the differences in results. When we analysed our results according to the presence of prior myocardial infarction instead of prior cardiovascular disease, the hazard ratios were not importantly altered, although the confidence intervals became wider (data not shown). Another possible explanation for the observed differences between our study and Haffner et al.'s study may be that we included participants with newly detected diabetes. However, exclusion of these participants from the analyses did not materially alter our results (data not shown). Taken together, the differences in the participants' clinical characteristics and in the definition of prior cardiovascular disease between

the study of Haffner et al. and the present study are unlikely to account for the observed differences in cardiovascular risks of diabetic individuals without prior cardiovascular disease. A recent Scottish study on this issue suggested that patients with type 2 diabetes are at lower risk of (cardiovascular) death or hospital admission for myocardial infarction than patients with established coronary heart disease.[26] In our population this hypothesis was confirmed among men, but not among women with regard to cardiovascular events. Unfortunately, this study did not compare risks conferred by diabetes or myocardial infarction for men and women separately. One potential explanation for the discrepancies between the findings in these studies is that there may be true heterogeneity among populations, that is, gender may modify the associations between type 2 diabetes and cardiovascular mortality in some populations but not in others.

The finding that, for men, the presence of diabetes did not notably increase the hazard ratio of cardiovascular events is remarkable, but has been reported before in two large studies,[9,27] although other studies did find a higher risk.[6,11,28] Our finding that the hazard ratio of cardiovascular mortality associated with the presence of diabetes was higher among women than men is consistent with previous observations.[3,12,13] Other cardiovascular risk factors did not explain the greater vulnerability of women than men with type 2 diabetes in the present study. We considered several other possible explanations. First, myocardial infarction has a higher case fatality rate in patients with than in patients without diabetes,[29] so if myocardial infarctions would have a higher case fatality rate in women with diabetes than in men with diabetes, this could explain the difference in cardiovascular mortality risk between the sexes. Previous studies do not support this hypothesis, [30–33] but, on the basis of our data, we can neither reject nor confirm this possibility. Second, a better treatment for men than for women with diabetes, especially after a first cardiovascular event, could to some extent explain the worse cardiovascular survival for women than for men. At first glance, this is not likely in our population because, among individuals with known diabetes at baseline, the frequency of medical treatment for diabetes, hypertension and/or dyslipidaemia was similar for men and women (91.4% vs 92.7%), but this issue requires further study, because we were unable to analyse whether treatment differed during follow-up. Third, Barrett-Connor et al.[12] and others[34] have suggested that the higher relative cardiovascular mortality risk of women with diabetes is largely a function of their superior survival in the absence of diabetes. This is also evident in our study: women without diabetes had a lower cardiovascular mortality risk compared to men without diabetes. In addition, the absolute cardiovascular mortality risk among women with diabetes was higher than that in men with diabetes. Therefore, the higher hazard ratio of cardiovascular mortality among women than men with diabetes in our study was a function of both the low absolute risk among women without diabetes and the high absolute risk among women with diabetes.

The biological basis for our findings remains to be clarified. We speculate that one or more cardiovascular risk factors associated with type 2 diabetes interact with female gender to increase the risk of atherothrombotic disease. For example, it has been shown that insulin resistance is more strongly associated with arterial stiffness in women than in men.[35,36]

There are several potential limitations to our study. We studied a Caucasian population, so the question remains whether our conclusions can be generalised to other ethnic groups. Furthermore, we studied individuals aged 50 to 75 at baseline and we cannot exclude the possibility that men with diabetes had already died before the age of 50, thus potentially underestimating the mortality risk of men with diabetes. However, this is improbable because the prevalence of diabetes is relatively low among individuals under 50.[37] A third shortcoming may be that information about prior cardiovascular disease was self-reported. Therefore, some misclassification might exist. However, such misclassification is likely to be nondifferential and therefore cannot explain the gender differences we observed. Finally, men and women may report symptoms differently. However, since men and women were analysed separately, bias is most likely limited and only occurs when men and women are compared. The prevalence of angina pectoris was 5.0% among men and 5.7% among women. These percentages do not differ significantly (p-value of the difference=0.4).

In conclusion, we compared, among individuals with and without prior cardiovascular disease, the risk of cardiovascular events associated with type 2 diabetes. The risk varied substantially between the sexes: it was considerably higher in women than in men. These data emphasise the necessity of aggressive treatment of cardiovascular risk factors in women with type 2 diabetes.

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