Diabetes, Glycated Hemoglobin, and the Risk of Myocardial Infarction in Women and Men: A Prospective Cohort Study of the UK Biobank

Marit de Jong,[1] Mark Woodward,[2,3,4] and Sanne A.E. Peters[1,2,3]

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OBJECTIVE

Diabetes has shown to be a stronger risk factor for myocardial infarction (MI) in women than men. Whether sex differences exist across the glycemic spectrum is unknown. We investigated sex differences in the associations of diabetes status and glycated hemoglobin (HbA_{1c}) with the risk of MI.

RESEARCH DESIGN AND METHODS

Data were used from 471,399 (56% women) individuals without cardiovascular disease (CVD) included in the UK Biobank. Sex-specific incidence rates were calculated by diabetes status and across levels of HbA_{1c} using Poisson regression. Cox proportional hazards analyses estimated sex-specific hazard ratios (HRs) and women-to-men ratios by diabetes status and HbA_{1c} for MI during a mean follow-up of 9 years.

RESULTS

Women had lower incidence rates of MI than men, regardless of diabetes status or HbA_{1c} level. Compared with individuals without diabetes, prediabetes, undiagnosed diabetes, and previously diagnosed diabetes were associated with an increased risk of MI in both sexes. Previously diagnosed diabetes was more strongly associated with MI in women (HR 2.33 [95% CI 1.96; 2.78]) than men (1.81 [1.63; 2.02]), with a women-to-men ratio of HRs of 1.29 (1.05; 1.58). Each 1% higher HbA_{1c}, independent of diabetes status, was associated with an 18% greater risk of MI in both women and men.

CONCLUSIONS

Although the incidence of MI was higher in men than women, the presence of diabetes is associated with a greater excess relative risk of MI in women. However, each 1% higher HbA_{1c} was associated with an 18% greater risk of MI in both women and men.

Despite significant improvements in prevention and treatment, coronary heart disease (CHD) remains the leading cause of death for both women and men worldwide (1). Diabetes is a key risk factor for CHD, and large studies and meta-analyses have provided convincing evidence that the magnitude of excess risk of CHD conferred by diabetes is stronger in women than men (2–6). For example,

[1]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands
[2]The George Institute for Global Health, University of Oxford, Oxford, U.K.
[3]The George Institute for Global Health, University of New South Wales, Sydney, New South Wales, Australia
[4]Department of Epidemiology, Johns Hopkins University, Baltimore, MD

Corresponding author: Sanne A.E. Peters, sanne.peters@georgeinstitute.ox.ac.uk

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previous analyses in the UK Biobank population demonstrated that the excess risk of myocardial infarction (MI) associated with diabetes is 47% greater in women than men (3).

Biological sex is known to affect the pathogenesis of metabolic disorders such as diabetes (7). The mechanisms underpinning the excess risk of CHD conferred by diabetes in women compared with men remain uncertain. However, previous studies have demonstrated that the differences in cardiovascular risk factors between people with and without diabetes are greater in women than men (8–12). Other studies have shown that women's greater excess risk of diabetes-related CHD is explained by greater cardiometabolic changes before the clinical diagnosis of diabetes (8). Diabetes is defined by an, arguably, arbitrary threshold of glycated hemoglobin (HbA_{1c}). However, previous large-scale studies have demonstrated that elevated HbA_{1c} levels are also associated with an increased risk of CHD below the clinical threshold of diabetes. If the sex difference in the cardiovascular complications of diabetes is present across the glucose intolerance continuum, both before and after the clinical diagnosis of diabetes, it could be hypothesized that the association of HbA_{1c} and the risk of CHD is stronger in women than men (13). Previous studies of sex differences in the association between HbA_{1c} levels and the risk of CHD are sparse and have been inconclusive (14–18). As such, it remains unclear whether sex differences in the risk of CHD exist across the glycemic spectrum. In this study, we used data from the UK Biobank to investigate the sex-specific association and the sex differences between various levels of diabetes status and levels of HbA_{1c} and the risk of MI.

RESEARCH DESIGN AND METHODS

Study Design and Participants

The UK Biobank is a large prospective cohort of >500,000 participants aged 40–69 years at study baseline between 2006 and 2010. Details of the study procedures for the UK Biobank have been described elsewhere (19). In short, individuals who lived near 1 of 22 assessment centers across the U.K. were invited to enter the cohort. Of these, 5.5% agreed to participate and attended the baseline assessment, which included questionnaires on lifestyle and medical history and physical and functional measurements (20,21). In addition, blood, urine, and saliva samples were taken. All participants provided written informed consent. Participants with a history of cardiovascular disease (CVD) (self-reported or hospital admission of MI, stroke, or angina pectoris, $n = 30{,}565$) at baseline were excluded from the current analyses. We also excluded those with missing data on both self-reported diabetes and HbA_{1c} ($n = 572$).

HbA_{1c} and Diabetes Status

A medical history of diabetes, including age at first diagnosis of diabetes and the use of medications for diabetes regulation, were self-reported. In 438,259 (93%) of the included participants, HbA_{1c} was measured using high-performance liquid chromatography analysis on a Bio-Rad VARIANT II Turbo (22). We categorized diabetes status into four groups: *1*) no diabetes (i.e., no previous diagnosis of diabetes, HbA_{1c} level <5.7% [39 mmol/mol], no use of glucose-lowering medication), *2*) prediabetes (i.e., no previous diagnosis of diabetes, HbA_{1c} between ≥5.7% [39 mmol/mol] and <6.5% [48 mmol/mol] [23], no use of glucose-lowering medication), *3*) undiagnosed diabetes (no previous diagnosis of diabetes, HbA_{1c} ≥6.5% [48 mmol/mol], no use of glucose-lowering medication), and *4*) previously diagnosed diabetes (self-reported diagnosis of diabetes and/or the use of glucose-lowering medication). Participants with missing data on HbA_{1c} but without diabetes or glucose-lowering medication and participants with missing data on diabetes but with HbA_{1c} <5.7% (39 mmol/mol) and no use of glucose-lowering medication were classified as not having diabetes. Participants with missing data on diabetes but with HbA_{1c} ≥6.5% (48 mmol/mol) and no use of glucose-lowering medication were classified as having undiagnosed diabetes. Those with missing data on diabetes but with HbA_{1c} ≥5.7 to 6.5% (≥39 to 48 mmol/mol) and no use of glucose-lowering medication were classified as having prediabetes.

Study Outcomes

The study outcome was incident nonfatal or fatal MI, defined by ICD-10 codes I21–I21.4, I21.9, I22–I22.1, I22.8, I22.9, I23–I23.6, I23.8, I24.1, and I25.2. Outcome adjudication involved linkage with hospital admissions data from England, Scotland, and Wales and the national death register to identify the date of the first known MI after the date of baseline assessment (24). Follow-up started at inclusion in the UK Biobank and ended on 1 February 2018, date of death, or upon the first nonfatal or fatal MI, for all participants.

Statistical Analyses

Sex-specific baseline characteristics are presented by diabetes status. Although incidence rates are less likely to be translated to, and applied in, other populations because of the background variation in risks across populations, they should be considered when making clinical decisions. Therefore, we examined the sex-specific effects and sex differences in the association of diabetes status and HbA_{1c} with MI both on the absolute and on the relative scales.

Sex-specific incidence rates and women-minus-men differences-of-rate differences of MI were calculated by diabetes status and across levels of HbA_{1c} (in participants with previously diagnosed diabetes) using Poisson regression models (25). For diabetes status, the model was adjusted for age, smoking, BMI, systolic blood pressure, use of antihypertensive medication, total cholesterol, use of lipid-lowering medication, the Townsend social deprivation score, and interaction terms between each variable and sex. The model for levels of HbA_{1c} was additionally adjusted for the use of glucose-lowering medication, again with interaction terms between each variable and sex. The interaction terms of diabetes status and levels of HbA_{1c} with sex were used to obtain the sex-specific incidence rates and women-minus-men differences-of-rate differences. Interaction terms of the other variables with sex were included to adjust for sex-specific confounding, which is identical to stratification by sex, with the advantage of extracting sex-specific estimates and sex differences from one model (25).

Cox regression models were used to obtain the sex-specific hazard ratios (HRs) and the women-to-men ratio of HRs (RHRs) with 95% CIs of MI by diabetes status (25). In participants with previously diagnosed diabetes, we also estimated HRs and RHRs across levels of HbA_{1c}, using participants without previously diagnosed diabetes as the reference (including prediabetes and

Table 1—Baseline characteristics by sex and diabetes status

	Women					Men				
	All (n = 263,024)	No diabetes (n = 221,592)	Prediabetes (n = 30,939)	Undiagnosed diabetes (n = 1,253)	Previously diagnosed diabetes (n = 9,240)	All (n = 208,375)	No diabetes (n = 170,672)	Prediabetes (n = 23,486)	Undiagnosed diabetes (n = 1,801)	Previously diagnosed diabetes (n = 12,416)
General characteristics										
Age (years)	56.2 (8.0)	55.6 (8.0)	59.8 (6.6)	58.9 (6.9)	58.3 (7.7)	56.3 (8.2)	55.7 (8.3)	58.6 (7.6)	57.3 (7.8)	59.4 (7.2)
Ethnicity										
White	247,983 (95)	211,266 (96)	27,885 (91)	1,003 (81)	7,829 (86)	195,940 (95)	162,750 (96)	20,864 (90)	1,519 (85)	10,807 (88)
Nonwhite/mixed	14,006 (5)	9,569 (4)	2,872 (9)	235 (19)	1,330 (15)	11,271 (5)	7,072 (4)	2,433 (10)	262 (15)	1,504 (12)
SES										
High	177,791 (68)	152,028 (69)	19,949 (65)	698 (56)	5,116 (55)	139,662 (67)	116,866 (69)	14,636 (62)	993 (55)	7,167 (58)
Low	84,921 (32)	69,310 (31)	10,950 (35)	553 (44)	4,108 (45)	68,441 (33)	53,594 (31)	8,813 (38)	803 (45)	5,231 (42)
Smoking										
Never	157,131 (60)	133,337 (60)	17,631 (57)	728 (59)	5,435 (59)	104,685 (50)	89,200 (52)	9,666 (42)	719 (40)	5,100 (41)
Past	81,592 (31)	69,100 (31)	9,184 (30)	378 (31)	2,930 (32)	76,900 (37)	61,270 (36)	9,175 (39)	755 (42)	5,700 (46)
Current	23,067 (9)	18,222 (8)	3,931 (13)	131 (11)	783 (9)	25,752 (12)	19,499 (11)	4,452 (19)	308 (17)	1,493 (12)
Diabetes characteristics										
Diabetes duration (years)	NA	NA	NA	NA	8.4 (10.0)	NA	NA	NA	NA	8.5 (10.1)
Median diabetes duration (years) (IQR)	NA	NA	NA	NA	5 (2–10)	NA	NA	NA	NA	5 (2–10)
Diabetes type 1^	NA	NA	NA	NA	500 (5)	NA	NA	NA	NA	531 (4)
HbA_{1c} (%)	5.4 (0.5)	5.3 (0.3)	5.9 (0.2)	7.4 (1.5)	6.9 (1.3)	5.5 (0.7)	5.3 (0.3)	5.9 (0.2)	7.7 (1.6)	7.0 (1.3)
Median HbA_{1c} (%) (IQR)	5.4 (5.1–5.6)	5.3 (5.1–5.5)	5.8 (5.8–6)	6.9 (6.7–7.5)	6.7 (6–7.5)	5.4 (5.1–5.6)	5.3 (5.1–5.5)	5.9 (5.8–6)	7.1 (6.7–8)	6.7 (6.1–7.6)
HbA_{1c} (mmol/mol)	35.7 (5.8)	34.0 (3.0)	41.0 (1.9)	58.0 (16.7)	51.8 (14.1)	36.2 (7.1)	33.9 (3.0)	41.1 (2.0)	60.8 (17.9)	52.8 (13.9)
Median HbA_{1c} (mmol/mol) (IQR)	35.1 (32.7–37.6)	34.4 (32.2–36.3)	40.4 (39.5–41.9)	51.8 (49.5–58.5)	49.4 (42.0–58.5)	35.1 (32.7–37.8)	34.3 (32.1–36.2)	40.5 (39.6–42.0)	53.6 (49.9–64.3)	50.1 (43.2–59.2)
Measurements										
BMI (kg/m^2)	27 (5.1)	26.5 (4.8)	28.8 (5.7)	32.7 (6.3)	31.8 (6.7)	27.7 (4.2)	27.3 (3.9)	28.9 (4.6)	31.4 (5.2)	30.7 (5.3)
Systolic BP (mmHg)	135.2 (19.2)	134.3 (19.1)	140.3 (19.1)	146.74 (19.4)	139.2 (17.7)	141.1 (17.4)	140.5 (17.3)	143.9 (17.8)	147.9 (18.1)	142.6 (16.6)
Diastolic BP (mmHg)	80.8 (10)	80.5 (10.0)	82.4 (9.9)	86.3 (10.2)	80.9 (9.7)	84.5 (9.9)	84.4 (9.9)	85.6 (9.9)	88.8 (10.2)	82.6 (9.4)
Cholesterol (mmol/L)	5.9 (1.1)	5.9 (1.1)	6.1 (1.2)	6.1 (1.3)	4.8 (1.1)	5.6 (1.1)	5.7 (1.0)	5.6 (1.1)	5.7 (1.2)	4.4 (1.0)

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Table 1—Continued

	Women					Men				
	All (n = 263,024)	No diabetes (n = 221,592)	Prediabetes (n = 30,939)	Undiagnosed diabetes (n = 1,253)	Previously diagnosed diabetes (n = 9,240)	All (n = 208,375)	No diabetes (n = 170,672)	Prediabetes (n = 23,486)	Undiagnosed diabetes (n = 1,801)	Previously diagnosed diabetes (n = 12,416)
Prescribed medication										
Antidiabetic medication										
Oral	NA	NA	NA	NA	4,109 (73)	NA	NA	NA	NA	6,045 (75)
Insulin	NA	NA	NA	NA	834 (15)	NA	NA	NA	NA	1,015 (13)
Oral + insulin	NA	NA	NA	NA	709 (13)	NA	NA	NA	NA	959 (12)
Antihypertensive medication	32,317 (12)	21,483 (10)	5,899 (19)	281 (22)	4,654 (50)	32,553 (16)	20,265 (12)	4,893 (21)	384 (21)	7,011 (57)
Lipid-lowering medication	23,057 (9)	12,680 (5.7)	4,583 (15)	227 (18)	5,567 (60)	29,535 (14)	16,204 (10)	4,664 (20)	315 (18)	8,352 (67)

Data are mean (SD) or n (%) unless otherwise indicated. BP, blood pressure; IQR, interquartile range; NA, not applicable. ^Participants with self-reported diabetes onset before the age of 30 years and using insulin were considered to have type 1 diabetes. Because of missing data, not all variables included add up to n = 208,375 for men and n = 263,024 for women.

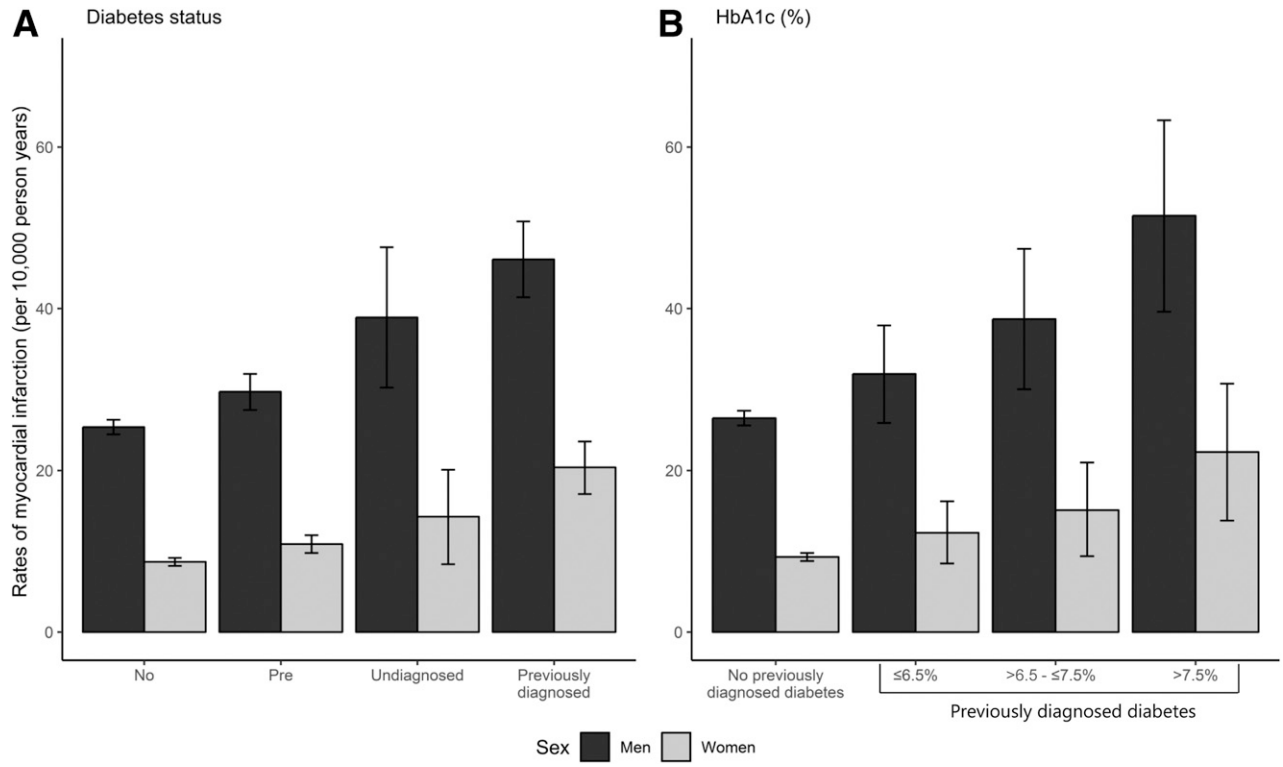

Figure 1—Multiple-adjusted rates of MI (per 10,000 person-years) by sex for diabetes status (*A*) and levels of HbA_{1c} (*B*). Analyses on diabetes status were adjusted for age, smoking, BMI, systolic blood pressure, use of antihypertensive medication, total cholesterol, use of lipid-lowering medication, and the Townsend social deprivation score, with interaction terms between each variable and sex. Analyses for levels of HbA_{1c} were additionally adjusted for the use of glucose-lowering medication, again with interaction terms between each variable and sex. No previously diagnosed diabetes includes no diabetes, prediabetes, and undiagnosed diabetes. HbA_{1c} 6.5% = 48 mmol/mol; HbA_{1c} 7.5% = 58 mmol/mol. Pre, prediabetes.

undiagnosed diabetes). Three levels of adjustments were used. For diabetes status, the first model was adjusted for age. The second model was additionally adjusted for smoking, BMI, systolic blood pressure, use of antihypertensive medication, total cholesterol, use of lipid-lowering medication, and the Townsend social deprivation score. The third model included the interaction terms between each variable in the second model and sex. Models for levels of HbA_{1c} were additionally adjusted for the use of glucose-lowering medication, again with sex interactions in the third model. For all three models, an interaction term between the determinant of interest (diabetes status or levels of HbA_{1c}) and sex was used to obtain the sex-specific HRs and women-to-men RHRs. The third model included interaction terms between each variable in the second model and sex to additionally adjust for sex-specific confounding.

Penalized spline models with 4 df were used to examine the sex-specific association between baseline HbA_{1c} and MI. Adjustments were as in the second model for levels of HbA_{1c}, with additional adjustment for history of diabetes. The sex-specific penalized spline models were obtained using stratification by sex. Therefore, additional adjustments for each variable in the model and sex were not included.

Cox analyses estimated the HRs and RHRs between a 1% increase in baseline HbA_{1c} and MI. In prespecified subgroup analyses, results were stratified for age (<60 years and ≥60 years), BMI (<25 kg/m^2 and ≥25 kg/m^2), socioeconomic status (SES) on the basis of the Townsend deprivation index (> −0.56 [lower SES] and ≤ −0.56 [higher SES]), and use of glucose-lowering medication. Two levels of adjustments were used. The first model was adjusted for age, smoking, BMI, systolic blood pressure, use of antihypertensive medication, total cholesterol, use of lipid-lowering medication, the Townsend social deprivation score, use of glucose-lowering medication, and history of diabetes. The second model included the interaction terms between each variable in the first model and sex. Again, interaction terms between 1% increase in baseline HbA_{1c} and sex in both models were used to obtain the sex-specific HRs and women-to-men RHRs.

To ensure that the association between 1% increase in baseline HbA_{1c} and MI was not explained by diabetes status, the analysis was adjusted for history of diabetes. However, by adjusting for history of diabetes, we may have adjusted away some of the effects of higher HbA_{1c} levels. Therefore, a sensitivity analysis was performed without adjusting for history of diabetes. Furthermore, sensitivity analyses were performed in which analyses were additionally adjusted for depression and sleep characteristics, again with interaction terms between each variable in the model and sex. Moreover, sex-specific subgroups for depression and sleep characteristics were included in the analyses of 1% increase in HbA_{1c} and MI. Analyses were conducted using Stata SE 13 and RStudio version 1.1.456.

RESULTS

Overall, 471,399 participants were included (56% women). At baseline, 6.0% of men and 3.5% of women were previously diagnosed with diabetes, with a median HbA_{1c} of 6.7% (50 mmol/mol) in both sexes (Table 1). Over a mean

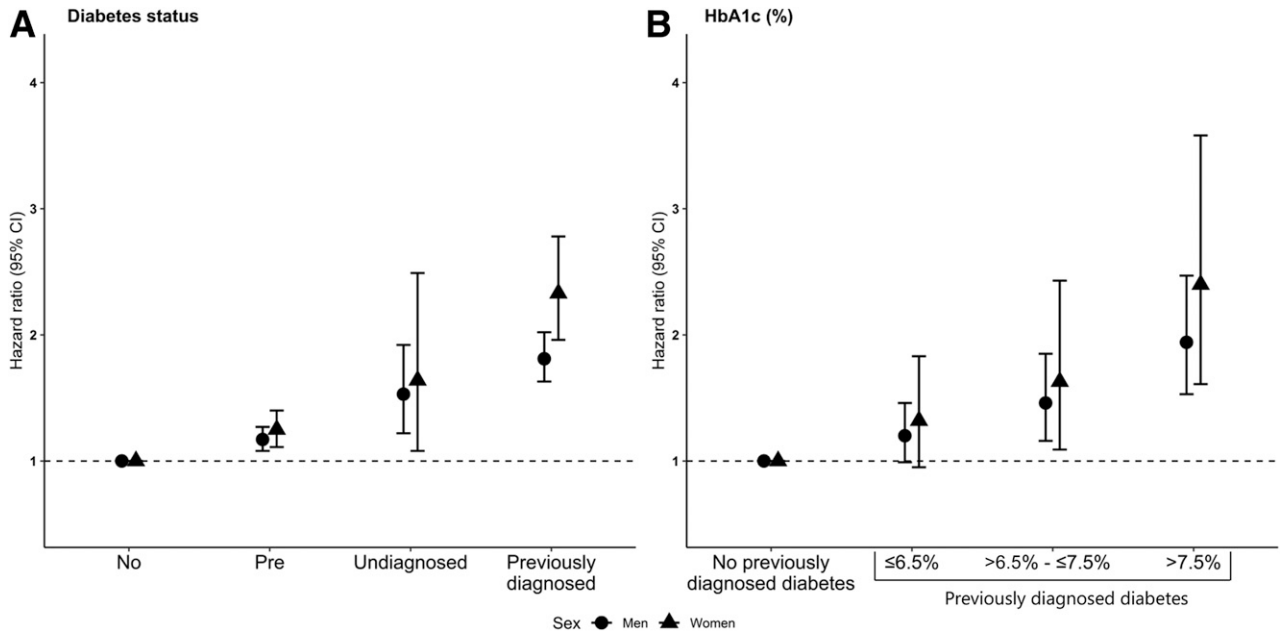

Figure 2—Multiple-adjusted sex-specific HRs for MI by diabetes status (reference = no diabetes) (*A*) and levels of HbA_{1c} (reference = no previously diagnosed diabetes) (*B*). Analyses on diabetes status were adjusted for age, smoking, BMI, systolic blood pressure, use of antihypertensive medication, total cholesterol, use of lipid-lowering medication, and the Townsend social deprivation score, with interaction terms between each variable and sex. Analyses for levels of HbA_{1c} were additionally adjusted for the use of glucose-lowering medication. No previously diagnosed diabetes includes participants categorized as having no diabetes, prediabetes, and undiagnosed diabetes. HbA_{1c} 6.5% = 48 mmol/mol; HbA_{1c} 7.5% = 58 mmol/mol. Pre, prediabetes.

follow-up of 8.9 years, 7,316 MI events (30% in women) were documented. The incidence of MI per 10,000 person-years was 9.3 (95% CI 8.9; 9.7) for women and 27.6 (26.8; 28.3) for men.

Sex-Specific Rates of MI According to Diabetes Status

Following multiple adjustments, women had lower incidence rates of MI per 10,000 person-years than men for no diabetes (8.7 [95% CI 8.2; 9.2] vs. 25.4 [24.5; 26.3]), prediabetes (10.9 [9.8; 12.0] vs. 29.7 [27.5; 31.9]), undiagnosed diabetes (14.3 [8.4; 20.1] vs. 38.9 [30.2; 47.6]), and previously diagnosed diabetes (20.4 [17.1; 23.6] vs. 46.1 [41.4; 50.8]) (Fig. 1*A* and Supplementary Table 1). Similar results were found for individuals without previously diagnosed diabetes and those with previously diagnosed diabetes at different levels of HbA_{1c} (Fig. 1*B* and Supplementary Table 2**)**.

Diabetes Status and the Risk of MI

Compared with no diabetes, prediabetes, undiagnosed diabetes, and previously diagnosed diabetes were each associated with an increased risk of MI in both sexes in each of the models (Fig.

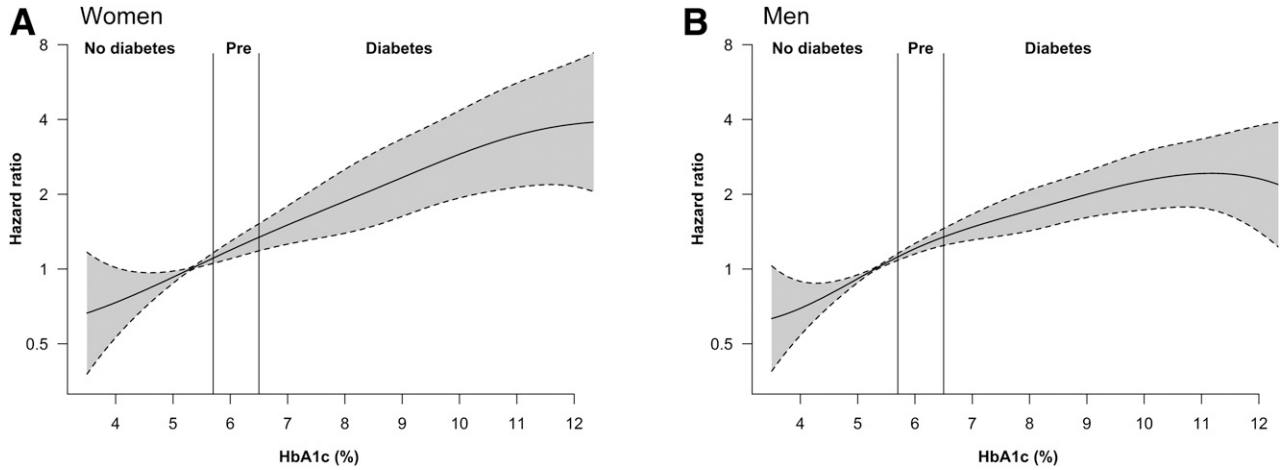

Figure 3—Multiple-adjusted HRs for MI according to baseline HbA_{1c}, stratified by women (*A*) and men (*B*). Penalized spline models with 4 df and reference HbA_{1c} set at 5.3% (34 mmol/mol). Analyses were adjusted for age, smoking, BMI, systolic blood pressure, antihypertensive medication, total cholesterol, use of lipid-lowering medication, Townsend social deprivation score, history of diabetes (no previously diagnosed diabetes, including prediabetes and undiagnosed diabetes), and the use of glucose-lowering medication. Shaded lines show 95% CIs. Vertical lines at HbA_{1c} 5.7% (39 mmol/mol) and 6.5% (48 mmol/mol) show the threshold for prediabetes (Pre) and diabetes, respectively.

2*A* and Supplementary Table 3). Prediabetes was more strongly associated with MI in women than men in the age-adjusted and multiple-adjusted model without, but not with, sex ∗ confounder interaction terms. In the full interaction model, compared with no diabetes, previously diagnosed diabetes was associated with a greater increased risk of MI in women (2.33 [95% CI 1.96; 2.78]) than men (1.81 [1.63; 2.02]), with a corresponding RHR of 1.29 (1.05; 1.58).

Levels of HbA_{1c} Among People With Diabetes and the Risk of MI

In the multiple-adjusted model without sex ∗ confounder interactions, compared with those without previously diagnosed diabetes (including prediabetes and undiagnosed diabetes), the risk of MI among people with previously diagnosed diabetes was higher in both women and men at different HbA_{1c} levels, except for men with an HbA_{1c} ≤6.5% (48 mmol/mol). Different HbA_{1c} levels were found to be more strongly associated with MI in women with previously diagnosed diabetes than men. These sex differences were no longer statistically significant in the full interaction model. The women-to-men RHRs were 1.39 (95% CI 1.03; 1.88) for ≤6.5% (48 mmol/mol), 1.50 (1.10; 2.05) for >6.5 to ≤7.5% (>48 to ≤58 mmol/mol), and 1.69 (1.28; 2.23) for >7.5% (58 mmol/mol) in the multiple-adjusted model with main effects for confounders only but were 1.09 (0.75; 1.60), 1.11 (0.70; 1.77), and 1.24 (0.78; 1.97), respectively, in the full interaction model (Fig. 2*B* and Supplementary Table 4).

HbA_{1c} Among All Individuals and the Risk of MI

Independent of diabetes status, there was an approximately log-linear association between levels of HbA_{1c} and MI in both sexes (Fig. 3*A* and *B*). In the multiple-adjusted model without sex ∗ confounder interactions, a 1% increase in HbA_{1c} was more strongly associated with MI in women than men: the HRs were 1.24 (95% CI 1.20; 1.28) in women and 1.14 (1.10; 1.19) in men, and the women-to-men RHR was 1.09 (1.03; 1.14). After including the sex ∗ confounder interactions, the HRs were 1.18 (1.13; 1.24) in women and 1.18 (1.13; 1.23) in men. The corresponding RHR was 1.00 (0.94; 1.07).

There was no evidence for differences in the multiple-adjusted association between HbA_{1c} and MI across sex-specific subgroups in the multiple-adjusted models with sex ∗ confounder interactions. Similarly, no significant differences in women-to-men RHRs by age, BMI, SES, and use of glucose-lowering medication were found (Fig. 4 and Supplementary Table 5).

Sensitivity Analyses

There was no evidence of a difference in the multiple-adjusted association between HbA_{1c} and MI after excluding history of diabetes from the main analysis (Supplementary Table 6). Furthermore, the results of the multiple-adjusted analyses on diabetes status, levels of HbA_{1c}, and 1% HbA_{1c} increase with MI were virtually identical to the main analyses after adjusting for depression and sleep characteristics (Supplementary Tables 7–10). Moreover, there was no evidence for

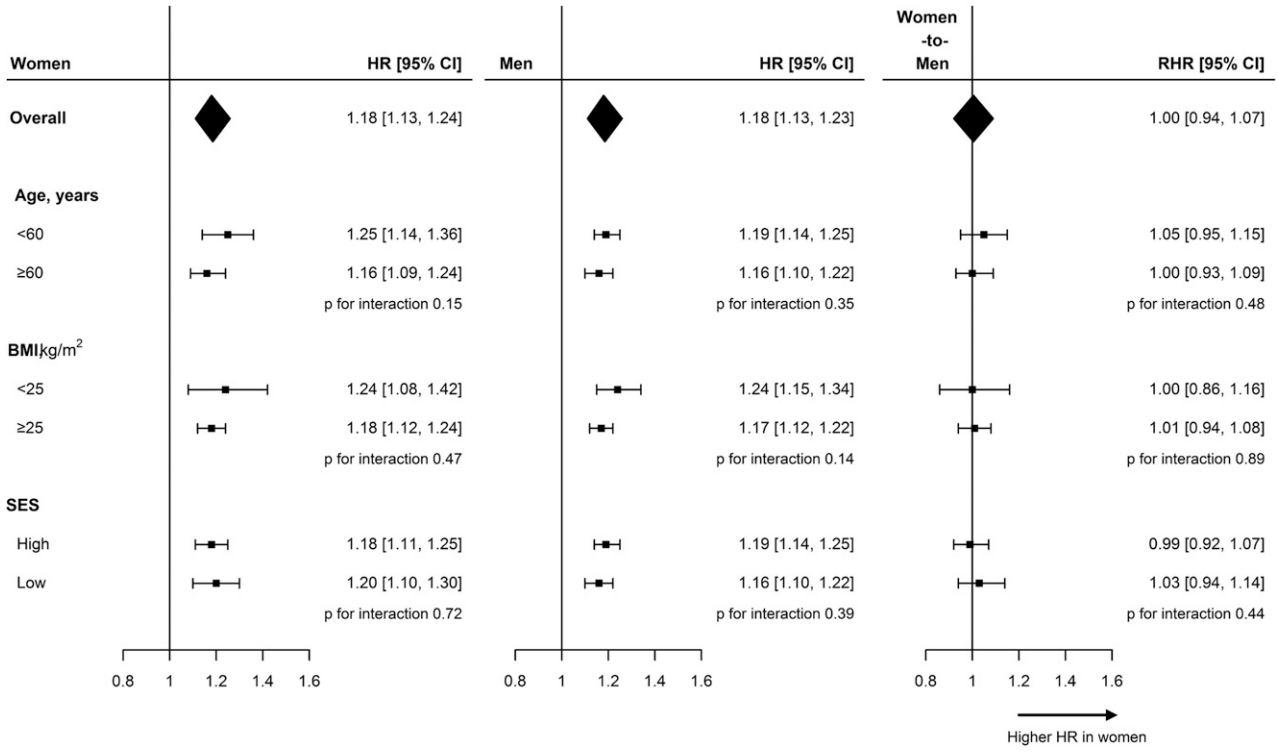

Figure 4—Multiple-adjusted sex-specific HRs and women-to-men RHRs for MI per 1% HbA_{1c} change overall and in subgroups. Analyses were adjusted for age, smoking, BMI, systolic blood pressure, antihypertensive medication, total cholesterol, use of lipid-lowering medication, the Townsend social deprivation score, history of diabetes (no previously diagnosed diabetes, including prediabetes and undiagnosed diabetes), and the use of glucose-lowering medication, with interaction terms between each variable and sex. *P* values for the sex-specific HRs represent the two-way interaction terms, including HbA_{1c} and the variable that was stratified for. *P* values for the women-to-men RHRs represent the three-way interaction terms, including sex, HbA_{1c}, and the variable that was stratified for.

sex differences in the multiple-adjusted association between 1% HbA_{1c} increase and MI across sex-specific subgroups for depression and sleep characteristics because there was no evidence of significant differences in women-to-men RHRs by depression and sleep characteristics (Supplementary Table 11).

CONCLUSIONS

This study, which included 471,399 UK Biobank participants without prevalent CVD, showed that although the incidence of MI was considerably higher in men than women for diabetes status and across levels of HbA_{1c}, the presence of previously diagnosed diabetes was associated with a greater excess relative risk of MI in women than in men. Each 1% higher HbA_{1c}, independent of diabetes status, was associated with an 18% greater risk of MI in both women and men.

This study adds to the growing body of evidence on sex differences in the risk of MI, and other CVD phenotypes, associated with diabetes (2–6,26,27). Studies assessing sex-specific effects and sex differences in the association between diabetes status by HbA_{1c} thresholds, including prediabetes and/or undiagnosed diabetes, and major cardiovascular events are limited and have provided mixed results (14–18). A large cohort study in >140,000 Mexican adults showed that both undiagnosed and previously diagnosed diabetes were associated with a higher risk of CVD-related mortality, with higher risks among individuals with poorer glycemic control (14). No sex differences in the risk of mortality of vascular, renal, and infectious causes according to diabetes status were found (14). The Atherosclerosis Risk in Communities (ARIC) study, which included 10,844 participants in the U.S. without previously diagnosed diabetes, showed that both men and women with HbA_{1c}-defined prediabetes or undiagnosed diabetes had a higher CVD risk (15). Although sex-stratified analyses provided some evidence for a stronger association of prediabetes and undiagnosed diabetes with peripheral artery disease in women than men, no statistically significant sex differences were present for CHD and/or ischemic stroke (15). A cohort study among 22,106 participants in the U.K. showed that undiagnosed, controlled (HbA_{1c} <5.7% [<39 mmol/mol]), and uncontrolled (HbA_{1c} ≥6.5% [≥48 mmol/mol]) diabetes and diabetes with moderately raised HbA_{1c} (5.7 to <6.5% [39 to <48 mmol/mol]), but not prediabetes, were associated with an increased risk of cardiovascular mortality. After stratification by sex, mixed results were found regarding the presence and magnitude for the association between diabetes status and CVD mortality (17). Our study also showed that prediabetes was associated with an increased risk of MI in both sexes, with evidence for stronger effects in women than men. However, this sex difference attenuated to unity and was no longer statistically significant in analyses that also accounted for sex-specific confounding effects. Similarly, while our analyses that did not account for sex-specific confounding showed that the relationship between HbA_{1c} and the risk of MI was stronger in women than men, accounting for sex-specific confounding demonstrated that a 1% increase in HbA_{1c} was associated with an 18% greater risk of MI in both sexes.

Sex differences in the uptake and provision of health care for diabetes or differences in underlying biological mechanisms of diabetes may explain the greater excess risk of MI conferred by diabetes in women. The National Diabetes Audit among 2 million individuals with diabetes in England and Wales showed that women were 15% less likely to receive assessment of critical care processes as recommended by the guidelines compared with men (28). In addition, only 30% of women and 33% of men attained all treatment targets for HbA_{1c}, cholesterol, and blood pressure (28). A population-based study in Italy also showed that women were less likely to receive recommended care and to attain treatment targets for HbA_{1c} and LDL cholesterol (29). In contrast, a large cohort study performed in the U.S. among 18,000 individuals with diabetes demonstrated that women were more likely to receive recommended care than men (30). Overall, previous studies on sex differences in the provision of health care for diabetes have reported mixed results regarding the presence, magnitude, and direction of sex differences in health care provision, and no final conclusions about the impact of differences in health care provision on sex disparities related to cardiovascular complications can be drawn. Notably, sex differences in health care provision are also seen in populations without diabetes, suggesting that sex differences in care alone are unlikely to be the only cause of the excess cardiovascular risk in women with diabetes (31,32).

Biological differences between the sexes may therefore play a key role in explaining these sex differences. Previous studies suggested that the cardiovascular risk profile needs to deteriorate further in women than in men before they develop overt diabetes (9–12). Consequently, women may be exposed to adverse cardiovascular risk factors over a longer time period. This hypothesis is in line with findings of a study that showed that the average duration of prediabetes was 10.3 years in women and 8.5 years in men (33). The Asia Pacific Cohort Studies Collaboration, including 161,214 individuals from the Asia-Pacific region, showed that differences in blood pressure, lipids, and BMI among individuals with and without diabetes were larger in women than men (34). A recent study among 3,400 Dutch individuals showed that several cardiovascular risk factors were already more elevated in women with prediabetes than men, and these difference were even more pronounced in individuals with type 2 diabetes compared with individuals with a normal glucose metabolism (8). In addition, increases in HbA_{1c} among individuals without type 2 diabetes was more strongly associated with systolic and diastolic blood pressure, HDL cholesterol, and LDL cholesterol in women than men (8). In our study, we found no evidence of a sex difference in the association between increases in HbA_{1c} and the risk of MI. Instead, the notion that the sex-specific effects attenuated after adjustment for sex-specific confounders suggest that other sex-specific pathways may be involved. A recent Mendelian randomization study showed that higher BMI led to higher risk of type 2 diabetes in women than in men (35). Hence, it may be that the sex differences in the association between diabetes and MI occur before the onset of diabetes.

Another possible explanation for the greater relative risk of MI found in women with diabetes compared with men is that this may simply be a mathematical artifact as a result of the lower cardiovascular risk in women. However, meta-analyses of sex differences in the association between blood pressure and

high BMI with CVD showed no sex difference in the relative risks. In addition, for total cholesterol associated with CVD, there is some indication of higher relative risks in men. Thus, it seems unlikely that the finding of a greater relative risk of MI associated with diabetes in women compared with men is an inevitable consequence of women's lower absolute rates compared with men (9,36).

It is surprising that while diabetes was associated with a greater relative risk of MI in women than men, increases in HbA_{1c} levels did not show any sex differences. Reasons for this apparent discrepancy warrant further investigation, ideally in studies with repeated HbA_{1c} measurements so as to assess the potential impact of sex differences in glycemic control post baseline assessment.

The strengths of this study include its prospective design, large sample size, and extensive phenotypic detail available on all participants. This study also has some limitations. First, people with a higher SES and of Caucasian background are overrepresented in the UK Biobank, which may have limited the generalizability of our results. Second, diagnosis of diabetes, CVD, and the use of diabetes medications were self-reported, which may have resulted in some misclassification in both sexes. However, there is no reason to assume that women and men reported differently on these aspects. Third, participants with missing data on self-reported diabetes or HbA_{1c} measurements were allocated to the best-fitting diabetes status category by using the available information; this may have resulted in some additional misclassification, most likely resulting in underestimation of the sex-specific effects that were found in this study. Finally, although we adjusted for several major confounding factors, including sex-specific confounding, residual confounding may be present.

In conclusion, the presence of diabetes is associated with a greater excess relative risk of MI in women than men. However, each 1% higher HbA_{1c}, independent of diabetes status, was associated with an 18% greater risk of MI in both women and men.

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