Increased Risk of Subsequent Myocardial Infarction in Patients With Type 2 Diabetes: A Retrospective Cohort Study Using the U.K. General Practice Research Database

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OBJECTIVE

To compare the risk of subsequent myocardial infarction (MI) between patients with and without type 2 diabetes mellitus (T2DM) in a retrospective cohort study.

RESEARCH DESIGN AND METHODS

Patients with their first MI recorded in the U.K. General Practice Research Database in 1997–2008 were classified as T2DM, diagnosed before or within 28 days after the date of the first recorded MI (i.e., the index date), or non-T2DM. Patients diagnosed within 28 days after the index date were assumed to have developed T2DM at baseline (i.e., before the index date). The primary outcome was the first subsequent MI. The secondary outcomes were all-cause death and a composite of all-cause death or subsequent MI. Cox proportional hazards models were fit to obtain hazard ratios (HRs) for all outcomes.

RESULTS

A total of 7,411 T2DM (median age 72 years; men 63.4%) and 48,726 non-T2DM patients (median age 69 years; men 65.3%) were included. The crude incidences (per 1,000 patient-years) in T2DM vs. non-T2DM were 32.8 vs. 22.8 for subsequent MI, 83.7 vs. 52.1 for all-cause death, and 106.5 vs. 69.9 for the composite end point. The adjusted HRs for subsequent MI, all-cause death, and their combination were 1.41 (95% CI 1.27–1.56), 1.50 (1.41–1.60), and 1.42 (1.34–1.50), respectively, in women and 1.23 (1.14–1.34), 1.40 (1.33–1.47), and 1.33 (1.27–1.39) in men.

CONCLUSIONS

Compared with non-T2DM, T2DM was associated with an increased risk for subsequent MI, all-cause death, and their composite end point. The risk tends to be higher in women than in men.

Patients with recurrent myocardial infarction (MI), who account for ~35% of hospitalized patients with acute MI, are at an increased risk of complications and death (1). Diabetes mellitus, affecting 347 million people worldwide (2), increases heart disease mortality by approximately two to four times (3). To date, only a few studies have evaluated the association between diabetes mellitus and subsequent MI, and

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the results suggested an increased risk (4–6). Data in a nationally representative sample are lacking. Therefore, we assessed the risk of subsequent MI among patients with type 2 diabetes mellitus (T2DM) in the U.K. General Practice Research Database (GPRD), a nationally representative sample.

RESEARCH DESIGN AND METHODS

Study Design

A retrospective cohort study was conducted using the Clinical Practice Research Datalink (CPRD, formerly GPRD). As an electronic medical record database, the GPRD includes patient and practice information, medical events, prescribed therapies, and information on other areas of care such as tests, lifestyle factors, immunizations, and specialty consultation notes from referrals. It has been available since 1987 and represents >20% of the U.K. population as of 29 July 2013. Additionally, the U.K. Office for National Statistics (ONS) mortality data and the Hospital Episode Statistics (HES) data were requested from Clinical Practice Research Datalink, which contain cause of death (ONS) and ethnicity (HES) data from general practices willing to participate in the linkage at the time of the study.

Study Population

Patients with at least one MI recorded in the GPRD in 1997–2008 formed the study population. Potential patients were identified by using specific and nonspecific Read codes for the first recorded MI. A patient was defined as a definite case of MI if he or she had a specific Read code for diagnosis of MI or a nonspecific diagnosis code plus one of the following criteria within 7 days before or after the nonspecific diagnosis date: *1*) an electrocardiogram consistent with the diagnosis of MI, *2*) treatment with a thrombolytic agent, or *3*) hospital admission, with an arteriogram documenting a recent coronary occlusion, coronary reperfusion by percutaneous transluminal angioplasty, or coronary artery bypass grafting within 14 days before or after the nonspecific diagnosis (7–10). When a patient had a definite acute MI event based on both specific and nonspecific criteria, the earlier date was used to identify the date associated with the MI. We also conducted a sensitivity analysis limited to the first recorded MI with specific Read codes.

MI patients were eligible if they met the following criteria: *1*) Patients were continuously active and free of MIs for at least 12 months before the index date, defined as the date of the first recorded MI in 1997–2008. Any diagnosis or procedure codes for MI within 90 days of the index date were considered to correspond to the index MI. *2*) Patients were continuously with a general practice for at least 90 days after the index date. And *3*) patients were at least 40 years old on the index date. The rationale of this age restriction was to minimize the possibility of patients with type 1 diabetes mellitus being included in the study.

Eligible MI patients were classified into T2DM and non-T2DM cohorts, where the T2DM cohort included anyone diagnosed with T2DM before the index date or within 28 days after the index date. Patients diagnosed with T2DM within 28 days after the index date were considered to be diabetic at baseline (i.e., before the index date), under the assumption that patients developed T2DM before the index date. Patients who did not have a T2DM diagnosis at baseline but were diagnosed with T2DM at least 90 days after the index date were censored on the date of T2DM diagnosis. Patients who did not have a T2DM diagnosis at baseline but were diagnosed with T2DM between 29 and 90 days after the index date were excluded to minimize misclassification bias and ensure that T2DM diagnosis preceded the outcome.

Patients who had a diagnosis of type 1 diabetes mellitus, gestational diabetes mellitus, diabetes insipidus, or renal glycosuria before the index date were excluded. Those who had a history of MI before the baseline period were not excluded but marked with an indicator variable. (See EXPOSURE, OUTCOMES, AND COVARIATES.)

All information for the study population was de-identified, and no patient enrollment or medical chart review was involved. This study protocol was approved by the GPRD Independent Scientific Advisory Committee.

Exposure, Outcomes, and Covariates

The exposure of interest was T2DM at baseline, defined as either one diagnosis code for T2DM or two prescriptions for any antidiabetes agents except insulin. The earlier date of the medical diagnosis or the first prescription date was defined as the diagnosis date of T2DM.

The primary outcome was subsequent MI, defined as the first MI at least 90 days after the index date. The procedure used for identifying a subsequent MI was the same as that for identifying the first recorded MI in the database, as described in STUDY POPULATION. Patients without a subsequent MI were censored at the earliest occurrence of patient death, transfer out of the general practice, or the end of the study (29 July 2013). Non-T2DM patients were also censored when they were diagnosed with T2DM at least 90 days after the index date and before the end of follow-up. Patients were followed from the index date (the first recorded date of MI) to the occurrence of a censoring event or the date of subsequent MI—whichever occurred first. The secondary outcomes were all-cause death and a composite end point of all-cause death or subsequent MI. The date for all-cause death was defined based on the algorithm recommended by the GPRD research team, which used information from the patient, clinical/referral, and additional files. Compared with the ONS mortality data, 99.2% of deaths in the ONS were identified in the GPRD, and the mean and median death date differences were 3.65 and 0 days, respectively (unpublished data). The end of follow-up was the same for the secondary outcomes, except that death was identified as an event. As a sensitivity analysis, cardiovascular death (Supplementary Data) was determined based on the underlying cause of death on the death certificate.

Covariates consisted of demographics (age at index date, sex), smoking status, obesity (defined as Read code or BMI $\geq$30 kg/m^2 if available, both using data at 15 months before the index date), dyslipidemia, hypertension (defined as a systolic blood pressure $\geq$140 mmHg, a diastolic blood pressure $\geq$90 mmHg, taking antihypertensive medication [11], or Read code diagnosis), unstable angina, history of MI, statin use, and family history of MI. In a secondary analysis, obesity was replaced with BMI (measured as weight in kilograms divided by the square of height in meters) as a categorical

variable using the World Health Organization obesity classifications: underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2, reference), overweight (25.0–29.9 kg/m^2), class I obesity (30–34.9 kg/m^2), and class II and up obesity (≥35 kg/m^2) (12). Class II and class III obesity were combined to increase the sample size in that group. All other covariates were captured using data any time before the index date. Read codes and product codes were used to define exposure, outcomes, and covariates.

Statistical Analysis

Baseline characteristics (age, sex, and disease comorbidities) were expressed as means and SDs for continuous variables and frequencies for categorical variables. Continuous variables were compared using the Student *t* test and categorical variables by the χ^2 test. Age-groups were categorized into 40–64, 65–74, and ≥75 years. The crude incidence rate was determined by the number of patients experiencing an outcome divided by person-time at risk.

For comparison of T2DM with non-T2DM, Cox proportional hazards models were fitted to estimate adjusted hazard ratios (HRs) and 95% CIs for the risk of subsequent MI. We also carried out secondary analyses using Cox models for all-cause death and a composite end point of all-cause death or subsequent MI. From all available covariates, the final list of fitted covariates was based on a stepwise regression with *P* value <0.2 to enter the model and $P < 0.05$ to remain. The primary comparison was based on the HR of the indicator variable that identified patients with T2DM, applying a two-sided test with a significance level of $\alpha = 0.05$. The assumption of proportional hazards was empirically tested with a graph of log(cumulative hazard) vs. log (time). Four sensitivity analyses were performed: *1*) we included patients with specific Read codes only (see STUDY POPULATION) in the analysis; *2*) we added BMI as a covariate to the model so that patients who did not have a baseline BMI measurement were excluded; *3*) we assessed cardiovascular mortality as an outcome, as cause of death data were only available for a subset of patients; and *4*) we required a minimum of 28 days instead of 90 days of registration with a general practice. Therefore, patients who were diagnosed with T2DM between 29 days and 90 days after the index date were not excluded. All data were managed and analyzed using SAS software, version 9.2 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

A total of 478,208 patients had at least one specific or nonspecific MI code in the database after applying the inclusion and exclusion criteria; 13% of these patients (*n* = 56,137) were eligible for the study. The detailed patient flow diagram is presented in Fig. 1.

Baseline characteristics of eligible patients used in the primary analysis are shown in Table 1. Overall, the study included 7,411 (13.2%) T2DM and 48,726 (86.8%) non-T2DM patients: an approximate ratio of 1:7. Due to the large sample size, relatively small differences between the T2DM and non-T2DM groups achieved significance, such as sex and smoking. Compared with non-T2DM subjects, patients with T2DM were slightly older (median 72 vs. 69 years), more likely to have hypertension (97.2 vs. 87.4%), use statins (52.4 vs. 24.4%), have obesity (34.0 vs. 10.6%), have dyslipidemia (21.4 vs. 11.9%), and have history of MI (14.0 vs. 10.2%). The percentages of patients who had a family history of MI were small and practically identical between the two groups. Only 39.2% of all patients (77.0% among T2DM vs. 33.4% among non-T2DM) had BMI information within 15 months before the index date. Compared with

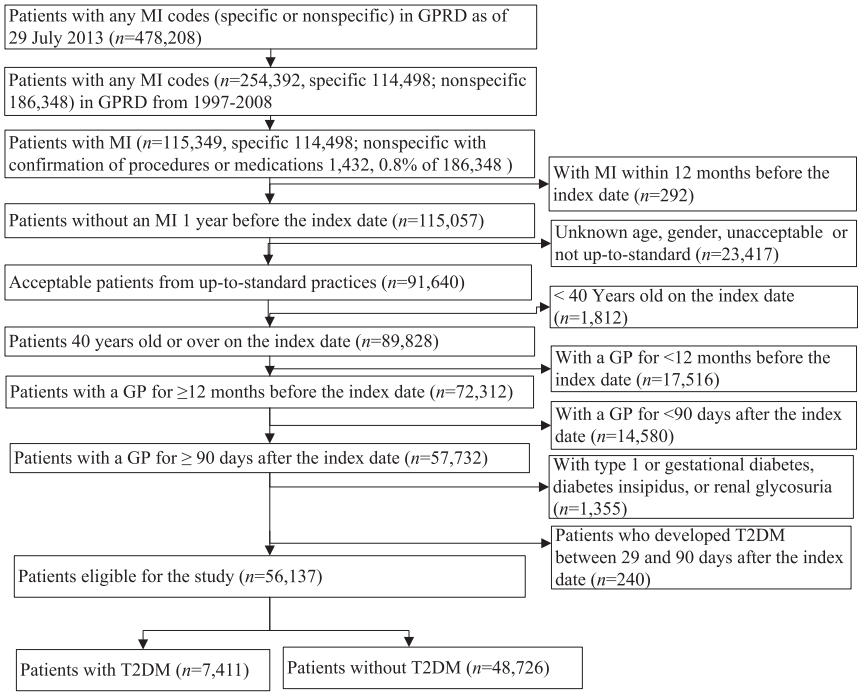

Figure 1—Patient flow diagram in this study.

Table 1—Patient characteristics at baseline

	T2DM			Non-T2DM			
	Both	Men	Women	Both	Men	Women	*P**
n	7,411	4,695	2,716	48,726	31,826	16,901	NA
Age-group (years)							
40–64	28.6	34.7	17.9	38.3	46.1	23.4	
65–74	31.3	32.4	29.5	26.7	27.0	26.1	
≥75	40.1	32.9	52.6	35.1	26.9	50.5	<0.0001
Age (years), mean ± SD	71 ± 11	69 ± 11	74 ± 11	68 ± 12	66 ± 12	73 ± 12	<0.0001
Age (years), median	72	70	75	69	66	75	<0.0001
Sex	100.0	63.4	36.6	100.0	65.3	34.7	0.0009
Smoking	69.3	73.5	62.2	61.6	65.1	55.1	<0.0001
Obesity	34.0	32.3	37.0	10.6	10.1	11.4	<0.0001
Dyslipidemia	21.4	20.1	23.5	11.9	11.7	12.1	<0.0001
Hypertension	97.2	96.6	98.4	87.4	84.5	93.0	<0.0001
Unstable angina	5.9	5.7	6.2	3.5	3.5	3.4	<0.0001
History of MI	14.0	16.3	9.9	10.2	11.4	7.7	<0.0001
Family history of MI	2.3	2.6	1.7	2.2	2.4	2.0	0.79
Statin use	52.4	51.3	54.3	24.4	24.3	24.7	<0.0001
BMI (kg/m^2)							
Nonmissing	77.0	78.1	75.1	33.4	33.6	33.0	<0.0001
Mean ± SD	29.2 ± 5.4	29.0 ± 4.9	29.5 ± 6.1	27.3 ± 5.0	27.5 ± 4.6	26.8 ± 5.8	<0.0001
Median	28.4	28.3	28.7	26.8	27.1	26.1	<0.0001

Data are % unless otherwise indicated. *N* patients = 56,137. NA, not applicable. *All *P* values were for comparison between overall patients with T2DM and those without T2DM.

those without BMI, a higher percentage of patients with BMI had a smoking history (77.3 vs. 55.8%), used statins (41.7 vs. 19.4%), had obesity (30.3 vs. 2.9%), had dyslipidemia (18.4 vs. 9.7%), and had hypertension (94.4 vs. 85.0%) (Supplementary Table 1).

In the primary analysis, patients with T2DM had a crude recurrence rate of MI of 32.8 cases per 1,000 person-years, which was 44% higher than that of the non-T2DM patients (22.8 cases per 1,000 person-years) (Table 2). Average follow-up was 4.9 years for patients with T2DM and 5.5 years for non-T2DM subjects. Patients with T2DM totaled 36,499 patient-years, compared with 268,137 patient-years for non-T2DM subjects. Patients with T2DM experienced 1,198 subsequent MIs, while non-T2DM subjects accumulated 6,114 events during the follow-up period. The crude recurrence rate of the composite end point was 106.5 per 1,000 patient-years in T2DM and 69.9 per 1,000 patient-years—approximately three times higher than that of subsequent MI. The unadjusted rate ratio for the composite end point comparing T2DM versus non-T2DM was 1.52 (95% CI 1.47–1.58). Women appeared to have a higher crude rate of subsequent MI than men. The trend was the same for all-cause death, with women having a higher rate than men in both T2DM and non-T2DM.

The corresponding rates in the sensitivity analysis, which included only events identified with specific MI diagnosis codes, were very similar to those in the primary cohort (Table 2). Hence, the crude recurrence rate ratio and its 95% CI for the sensitivity cohort were almost identical to the results for the primary cohort. Including only specific MI Read codes excluded 95 patients (a decrease of 1.3%) in the T2DM group and 562 patients (1.2%) in the non-T2DM group.

The graphical check on the proportional hazards assumption (Supplementary Figs. 1 and 2) produced a pair of parallel logs of the fitted cumulative hazard when plotted versus log(time), thus verifying that the assumption was justified. This was true for the main models in the primary cohort and in the sensitivity cohort that included only specific MI events.

When the Cox model was fitted to the primary outcome, a significant interaction between T2DM and sex ($P = 0.007$) was identified in the primary cohort. Thereafter, the models were stratified by sex (Table 3). Among women with a previous MI, patients with T2DM had a 41% higher risk of developing subsequent MI compared with non-T2DM subjects after controlling for covariates. Among men with a previous MI, patients with T2DM had a 23% higher risk of developing subsequent MI relative to non-T2DM patients. T2DM women with a previous MI also had a 50% higher risk for all-cause death than their non-T2DM counterparts; the risk of all-cause death was 40% higher among T2DM men. For the composite end point of all-cause death or subsequent MI, all covariates except obesity and family history of MI were retained in the Cox model. T2DM women had a 42% higher risk compared with non-T2DM subjects after controlling for confounders; the risk was 33% higher among T2DM men.

The HRs obtained from the sensitivity cohort, identified based on specific MI codes, were nearly identical compared with those from the primary cohort, indicating the stability of the results (Table 3).

When modeling patients with a baseline measurement of BMI, sample size was reduced to 39% for both the primary and sensitivity cohorts. The adjusted HRs were higher among men and women with wider CIs for all outcomes.

Table 2—Crude recurrence rate and rate ratio of the primary outcome (subsequent MI) and secondary outcomes (all-cause death and a composite outcome of all-cause death or subsequent MI) in the primary and sensitivity cohorts of patients with and without T2DM (per 1,000 person-years)

	n	Events	Person-years	Recurrence rate (95% CI)	Rate ratio (95% CI)
Primary cohort*					
Subsequent MI†					
Both sexes					
T2DM	7,411	1,198	36,499	32.8 (31.0–34.7)	1.44 (1.35–1.53)
Non-T2DM	48,726	6,114	268,137	22.8 (22.2–23.4)	1.0 (ref.)
Men					
T2DM	4,695	735	24,189	30.4 (28.2–32.7)	1.36 (1.26–1.47)
Non-T2DM	31,825	4,038	180,719	22.3 (21.7–23.0)	1.0 (ref.)
Women					
T2DM	2,716	463	12,310	37.6 (34.3–41.2)	1.58 (1.43–1.75)
Non-T2DM	16,901	2,076	87,418	23.7 (22.7–24.8)	1.0 (ref.)
All-cause death†					
Both sexes					
T2DM	7,411	3,412	40,781	83.7 (80.9–86.5)	1.61 (1.55–1.67)
Non-T2DM	48,726	15,400	295,465	52.1 (51.3–53.0)	1.0 (ref.)
Men					
T2DM	4,695	2,040	26,985	75.6 (72.4–79.0)	1.66 (1.58–1.74)
Non-T2DM	31,825	9,075	199,355	45.5 (44.6–46.5)	1.0 (ref.)
Women					
T2DM	2,716	1,372	13,796	99.5 (94.3–104.9)	1.51 (1.42–1.60)
Non-T2DM	16,901	6,325	96,110	65.8 (64.2–67.5)	1.0 (ref.)
All-cause death or subsequent MI†					
Both sexes					
T2DM	7,411	3,886	36,499	106.5 (103.1–109.9)	1.52 (1.47–1.58)
Non-T2DM	48,726	18,755	268,137	69.9 (68.9–71.0)	1.0 (ref.)
Men					
T2DM	4,695	2,344	24,189	96.9 (93.0–100.9)	1.53 (1.46–1.60)
Non-T2DM	31,825	11,434	180,719	63.3 (62.1–64.4)	1.0 (ref.)
Women					
T2DM	2,716	1,542	12,310	125.3 (119.1–131.7)	1.50 (1.42–1.58)
Non-T2DM	16,901	7,321	87,418	83.7 (81.8–85.7)	1.0 (ref.)
Sensitivity cohort*					
Subsequent MI†					
Both sexes					
T2DM	7,316	1,185	35,899	33.0 (31.2–34.9)	1.44 (1.36–1.54)
Non-T2DM	48,164	6,046	264,375	22.9 (22.3–23.5)	1.0 (ref.)
Men					
T2DM	4,624	725	23,770	30.5 (28.3–32.8)	1.36 (1.26–1.47)
Non-T2DM	31,401	3,983	177,882	22.4 (21.7–23.1)	1.0 (ref.)
Women					
T2DM	2,692	460	12,129	37.9 (34.5–41.6)	1.59 (1.43–1.76)
Non-T2DM	16,763	2,063	86,493	23.9 (22.8–24.9)	1.0 (ref.)
All-cause death†					
Both sexes					
T2DM	7,316	3,392	40,094	84.6 (81.8–87.5)	1.61 (1.55–1.67)
Non-T2DM	48,164	15,321	291,315	52.6 (51.8–53.4)	
Men					
T2DM	4,624	2,024	26,490	76.4 (73.1–79.8)	1.66 (1.58–1.74)
Non-T2DM	31,401	9,024	196,214	46.0 (45.0–46.9)	
Women					
T2DM	2,692	1,368	13,604	100.6 (95.3–106.0)	1.52 (1.43–1.61)
Non-T2DM	16,763	6,297	95,101	66.2 (64.6–67.9)	
All-cause death or subsequent MI†					
Both sexes					
T2DM	7,316	3,859	35,899	107.5 (104.1–110.9)	1.53 (1.47–1.58)
Non-T2DM	48,164	18,622	264,375	70.4 (69.4–71.5)	1.0 (ref.)
Men					
T2DM	4,624	2,323	23,770	97.7 (93.8–101.8)	1.53 (1.46–1.60)
Non-T2DM	31,401	11,340	177,882	63.8 (62.6–64.9)	1.0 (ref.)
Women					
T2DM	2,692	1,536	12,129	126.6 (120.4–133.1)	1.50 (1.42–1.59)
Non-T2DM	16,763	7,282	86,493	84.2 (82.3–86.1)	1.0 (ref.)

*The primary cohort was identified with specific and nonspecific Read codes for MI, and the sensitivity cohort was identified with specific Read codes for MI. †The primary outcome was subsequent MI, and the secondary outcomes were all-cause death and a composite outcome of all-cause death or subsequent MI.

Table 3—Adjusted HRs stratified by sex for primary outcome (subsequent MI) and secondary outcomes (all-cause death and a composite outcome of all-cause death or subsequent MI) for T2DM versus non-T2DM patients in the primary cohort and sensitivity cohort

	Events	Adjusted HR (95% CI)*	Covariates adjustment (HR)†
Primary cohort (*n* = 56,137)‡			
Recurrent MI			
Men	4,773	1.23 (1.14–1.34)	Age (1.02), unstable angina (1.44), personal history of MI (1.46)
Women	2,539	1.41 (1.27–1.56)	Age (1.02), unstable angina (1.33), dyslipidemia (1.14), personal history of MI (1.27), statins (1.15)
All-cause death			
Men	11,115	1.40 (1.33–1.47)	Age (1.09), unstable angina (1.13), smoking (1.17), dyslipidemia (0.90), hypertension (1.23), personal history of MI (1.38), statins (1.07)
Women	7,697	1.50 (1.41–1.60)	Age (1.08), unstable angina (1.28), smoking (1.19), dyslipidemia (0.86), hypertension (1.18), obesity (0.92), personal history of MI (1.30), statins (1.11)
All-cause death or recurrent MI			
Men	13,778	1.33 (1.27–1.39)	Age (1.06), unstable angina (1.14), smoking (1.12), hypertension (1.06), personal history of MI (1.37)
Women	8,863	1.42 (1.34–1.50)	Age (1.06), unstable angina (1.28), smoking (1.16), dyslipidemia (0.92), personal history of MI (1.32), statins (1.10)
Sensitivity cohort (*n* = 55,480)			
Recurrent MI			
Men	4,708	1.24 (1.14–1.34)	Age (1.02), unstable angina (1.49), personal history of MI (1.45)
Women	2,523	1.41 (1.27–1.56)	Age (1.02), unstable angina (1.34), dyslipidemia (1.13), personal history of MI (1.26), statins (1.16)
All-cause death			
Men	11,048	1.40 (1.33–1.47)	Age (1.09), unstable angina (1.14), smoking (1.17), dyslipidemia (0.91), hypertension (1.24), personal history of MI (1.37), statins (1.08)
Women	7,665	1.50 (1.41–1.60)	Age (1.08), smoking (1.20), hypertension (1.19), unstable angina (1.29), obesity (0.92), dyslipidemia (0.85), personal history of MI (1.29), statins (1.12)
All-cause death or recurrent MI			
Men	13,663	1.33 (1.27–1.39)	Age (1.06), unstable angina (1.16), smoking (1.12), personal history of MI (1.37), hypertension (1.07)
Women	8,818	1.42 (1.34–1.50)	Age (1.06), unstable angina (1.29), smoking (1.16), dyslipidemia (0.91), personal history of MI (1.31), statins (1.11)
Primary cohort with BMI (*n* = 21,981)			
Recurrent MI			
Men	1,858	1.26 (1.15–1.40)	Age (1.02), unstable angina (1.46), personal history of MI (1.37), dyslipidemia (1.18)
Women	1,005	1.46 (1.28–1.67)	Age (1.02), unstable angina (1.32), personal history of MI (1.21), dyslipidemia (1.34)
All-cause death			
Men	4,390	1.47 (1.38–1.56)	Age (1.09), hypertension (1.38), smoking (1.26), personal history of MI (1.38), statins (1.12), underweight (BMI $<$18.5 kg/m^2, 3.11), overweight (BMI 25.0–29.9 kg/m^2, 0.80), class I obesity (BMI 30.0–34.9 kg/m^2, 0.89)
Women	2,755	1.60 (1.48–1.74)	Age (1.08), smoking (1.29), dyslipidemia (0.90), unstable angina (1.30), personal history of MI (1.35), statins (1.15), underweight (BMI $<$18.5 kg/m^2, 1.83), overweight (BMI 25.0–29.9 kg/m^2, 0.85), class I obesity (BMI 30.0–34.9 kg/m^2, 0.82)
All-cause death or recurrent MI			
Men	5,367	1.37 (1.30–1.45)	Age (1.06), smoking (1.20), hypertension (1.19), personal history of MI (1.34), statins (1.10), underweight (BMI $<$18.5, 2.56 kg/m^2), overweight (BMI 25.0–29.9 kg/m^2, 0.82), class I obesity (BMI 30.0–34.9 kg/m^2, 0.91)

Continued on p. 1335

Table 3—Continued

	Events	Adjusted HR (95% CI)*	Covariates adjustment (HR)†
Women	3,229	1.53 (1.42–1.65)	Age (1.06), unstable angina (1.25), smoking (1.25), personal history of MI (1.33), statins (1.10), underweight (BMI $<$18.5 kg/m^2, 1.55), overweight (BMI 25.0–29.9 kg/m^2, 0.86), class I obesity (BMI 30.0–34.9 kg/m^2, 0.84)
Sensitivity cohort with BMI (*n* = 21,677)			
Recurrent MI			
Men	1,828	1.26 (1.15–1.40)	Age (1.02), unstable angina (1.46), personal history of MI (1.37), dyslipidemia (1.18)
Women	1,001	1.46 (1.28–1.67)	Age (1.02), unstable angina (1.32), personal history of MI (1.21), dyslipidemia (1.34)
All-cause death			
Men	4,366	1.46 (1.37–1.56)	Age (1.09), smoking (1.26), hypertension (1.39), personal history of MI (1.37), statins (1.14), underweight (BMI $<$18.5 kg/m^2, 3.08), overweight (BMI 25.0–29.9 kg/m^2, 0.81), class I obesity (BMI 30.0–34.9 kg/m^2, 0.90)
Women	2,747	1.61 (1.48–1.74)	Age (1.08), smoking (1.30), dyslipidemia (0.89), unstable angina (1.31), personal history of MI (1.33), statins (1.16), underweight (BMI $<$18.5 kg/m^2, 1.82), overweight (BMI 25.0–29.9 kg/m^2, 0.85), class I obesity (BMI 30.0–34.9 kg/m^2, 0.81)
All-cause death or recurrent MI			
Men	5,323	1.37 (1.30–1.46)	Age (1.06), unstable angina (1.14), smoking (1.21), hypertension (1.18), personal history of MI (1.32), statins (1.11), underweight (BMI $<$18.5 kg/m^2, 2.53), overweight (BMI 25.0–29.9 kg/m^2, 0.83), class I obesity (BMI 30.0–34.9 kg/m^2, 0.91)
Women	3,219	1.53 (1.42–1.65)	Age (1.06), unstable angina (1.26), smoking (1.26), personal history of MI (1.32), statins (1.11), underweight (BMI $<$18.5 kg/m^2, 1.55), overweight (BMI 25.0–29.9 kg/m^2, 0.86), class I obesity (BMI 30.0–34.9, kg/m^2, 0.84)

*All *P* values for these adjusted HRs were $<$0.0001. †Covariates (binary variables unless specified) used to fit the stepwise proportional hazards models consisted of age (continuous), unstable angina, dyslipidemia, hypertension, smoking, personal history of MI, family history of MI, and obesity. For cohorts with BMI, the covariate obesity was replaced with four dummy variables (underweight [BMI $<$18.5 kg/m^2], overweight [BMI 25.0–29.9 kg/m^2], class I obesity [BMI 30.0–34.9 kg/m^2], and class II and up obesity [BMI $\geq$35 kg/m^2]) in the model, leaving normal weight (BMI 18.5–24.9 kg/m^2) as the reference group. ‡Primary cohort was identified with specific and nonspecific Read codes for MI. Sensitivity cohort was identified with specific Read codes for MI.

For patients who were eligible to be linked to the ONS mortality data (56% of the primary cohort), T2DM was associated with higher risk of cardiovascular mortality (HR 1.49 [95% CI 1.36–1.64] in men; 1.46 [1.30–1.65] in women) and noncardiovascular mortality (1.44 [1.30–1.59 in men]; HR 1.38 [1.22 – 1.57] in women) (Supplementary Table 2).

In the fourth sensitivity analysis, which required at least 28 days instead of 90 days of registration with a general practice, the sample size for our primary cohort increased by 2,145, as expected; events of subsequent MI, all-cause death, and the composite end point all increased owing to redefining the minimum time to outcomes to 28 days. The adjusted HR decreased slightly for subsequent MI (1.25 [95% CI 1.14–1.37]) in women vs. 1.15 [1.07–1.23] in men), all-cause death (1.46 [1.38–1.55] in women vs. 1.38 [1.32–1.45] in men), and the composite end point (1.35 [1.28–1.43] in women vs. 1.27 [1.21–1.32] in men) (Supplementary Table 3).

CONCLUSIONS

To the best of our knowledge, this was the first study to describe the association between T2DM and risk of subsequent MI in a nationally representative sample with current data. We observed that the subsequent MI risk was ~41% higher among T2DM women and 23% higher among T2DM men compared with non-T2DM subjects. These findings are consistent with findings from previous studies, which had adjusted HRs ranging from 1.14 to 1.68 (4,5). Haffner et al. (6) first reported the incidence of fatal or nonfatal MI in those with T2DM (45.0 per 100 person-years, *n* = 169) and non-T2DM (18.8 per 100 person-years, *n* = 69) among subjects with a history of MI, with a derived crude risk ratio of 2.39 and no adjusted HR reported. Several factors could contribute to a higher risk ratio in their study. Their baseline data were collected from 1982 to 1984 in Finland. Considering the first statin was approved in late 1980s, the standard of care of MI was very different in their study, with far fewer statin users. Their sample size was small, and patients were much younger. Bui et al. (4) reported an increased risk associated with diabetes mellitus for recurrent MI (adjusted odds ratio 1.14 [95% CI 1.05–1.24]) and for in-hospital mortality (1.18 [1.13–1.23]) among 232,927 patients from the Canadian National Registry (2002–2006) of MI. However, detailed patient characteristics and analysis methods were unavailable. Using data from an international clinical trial (37

countries), Deedwania et al. (5) reported that diabetes mellitus was significantly associated with recurrent nonfatal MI (HR 1.68 [95% CI 1.23–2.31]) but not significantly with fatal acute MI (1.42 [0.88–2.28]).

Differences between our study findings and those by Deedwania et al. (5) could be due to the following factors: *1*) Study populations were different. Deedwania et al. used clinical trial data and included only 52% of diabetic patients who were successfully matched to nondiabetic control subjects. This study included all eligible patients, with a much larger sample size (7 times). And *2*) the exposure definition differed. Deedwania et al. assessed diabetes mellitus including type 1 as the exposure. Despite these differences, our results show a similar pattern with much narrower CI and that women have a higher risk than men, which adds new knowledge to the limited body of related literature.

Patients with T2DM have been found to have increased incidence of coronary atherosclerosis compared with nondiabetic subjects (13), with proposed pathophysiologic mechanisms including endothelial dysfunction, diabetic dyslipidemia, hypercoagulability, impaired fibrinolysis, and platelet hyperaggregability. Women with T2DM, compared with age-matched nondiabetic women, exhibit fivefold to eightfold higher rates of death related to coronary artery disease (14). The risk of subsequent MI in this study, which could be the second or the third MI for some patients (unknown based on data alone), was reduced to 1.41 in women and 1.23 in men among T2DM patients who already had an MI event. The reduction of HR could probably reflect that the occurrence of previous MI contributed to maximizing the risk of subsequent MI between patients with T2DM and those without. At the same time, having previous MI did not remove all the differences between them. T2DM itself still contributes to an average of 30% increase in risk for subsequent MI from this analysis. The higher relative risk for MI in women than in men was consistent with the findings from the Stockholm Heart Epidemiology Program study in which the relative risk for MI among patients with diabetes mellitus was 4.4 among women and 2.5 among men compared with nondiabetic subjects (15). The findings of a higher risk of subsequent MI among diabetic patients highlight the importance of managing T2DM among MI patients and the need for future research to prevent both incident MI and T2DM.

Our finding that patients with T2DM had a higher risk of all-cause death (50% higher risk among women and 40% higher risk among men) is also consistent with previous studies. In 1997, Behar et al. (16) reported that the relative risk for 10-year mortality was 1.32 (95% CI 1.10–1.58) for men with non–insulin-treated diabetes mellitus, 1.75 (1.26–2.45) for men treated with insulin, 1.41 (1.10–1.82) for women treated with oral hypoglycemic drugs, and 2.59 (1.89–3.56) for diabetic women treated with insulin. The analysis was based on data from 5,839 consecutive patients hospitalized for MI in 1981–1983 in 13 coronary care units throughout Israel, and among them, 2,149 patients were included in a secondary prevention trial using nifedipine 7 –21 days after hospitalization. In 1998, Miettinen et al. (17) reported that, after the first MI, the adjusted HR for 1-year mortality was 1.38 (95% CI 1.18–1.61) in diabetic men and 1.86 (1.40–2.46) in diabetic women in Finland compared with their nondiabetic counterpart. In 2002, Kaplan et al. (18) reported that treated diabetes mellitus was associated with an adjusted HR of 1.63 (1.30–2.03) for death among insured patients (n = 2,677, aged 30–79 years) who survived a first hospitalized MI during 1986–1996 in the U.S. (mean follow-up of 3.4 years). In 2012, Nauta et al. (19) reported that diabetes mellitus was associated with 1.5-fold increased risk of mortality at the 20-year follow-up.

Several factors may contribute to the increased risk of all-cause death associated with diabetes mellitus. In addition to the heightened risk of subsequent MI, patients with T2DM double their risk to develop congestive heart failure (20) and stroke (21) and are more likely to develop end-stage renal disease (22) and certain site-specific cancers, including cancers of the breast, colon-rectum, bladder, non-Hodgkins lymphoma, pancreas, liver, and endometrium (23). All these factors could have led to increased deaths among patients with diabetes mellitus, considering that among people ≥65 years old, heart disease, cancer, and stroke are the three leading causes of death in both men and women (24,25). As expected, patients with T2DM had a slightly higher risk of a composite end point of all-cause death or subsequent MI, compared with those without T2DM, with the risk in between that of subsequent MI and that of all-cause death.

In the GPRD, general practitioners could possibly code MI as "ischemic heart disease" because coronary heart disease, not MI, is one of the clinical indicators in the Quality and Outcomes Framework, the U.K. national primary care pay-for-performance scheme introduced in 2004, which rewards practices for quality of care through both fixed and performance-related funding streams (26). However, confirmatory laboratory values, such as elevated creatinine phosphokinase-MB isoenzyme or troponin, are not captured in the database. Therefore, we modified the international standardized diagnostic criteria for acute MI by requiring only specific criteria except laboratory creatinine phosphokinase-MB isoenzyme and troponin for patients with nonspecific Read codes for MI (27). Any potential misclassification in ascertaining subsequent MI would likely bias the results toward the null because we applied the same definition to both groups. A sensitivity analysis conducted to assess the impact with the inclusion of nonspecific Read codes confirmed that our result was very reliable.

This study has some limitations. Firstly, T2DM is a disease with gradual development. Patients could have developed T2DM without a physician diagnosis. Therefore, we classified patients who were newly diagnosed with T2DM within 28 days after the index date as having T2DM at baseline, assuming patients developed T2DM before the index date. Misclassification bias could occur during this reclassification and could bias the results toward the null. Secondly, any residual confounding due to measured confounders or confounding due to unmeasured confounders is likely to cause the bias of HRs toward either direction. Finally, the ethnicity data in the GPRD, after linkage with the HES data, are available for 26,574 (47.9% of 56,137) patients in the current study. Among them, 97.3% were white, 1.7% were Asian, and 1.0% were of other ethnicity. The predominantly white population in our study is consistent with that of the U.K. national data (28). Study findings from this study can be well generalizable to the U.K.

population but may not be generalizable to other countries in the world with a different ethnicity distribution or a different health care system.

In a nationally representative sample of the U.K. population, this study showed that among patients with a previous MI, those with T2DM, compared with those without T2DM, had an ~30% higher risk (41% in women vs. 23% in men) for subsequent MI and 40% higher risk for all-cause death (50% in women vs. 40% in men). These findings highlight the need for future research to prevent incident MI and T2DM, as well as to manage patients post–incident MI, especially those with T2DM.

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Author Contributions. H.L. contributed to study concept and design, application for protocol approval by the GPRD Independent Scientific Advisory Committee, data analysis, drafting of the manuscript, project coordination, data interpretation, critical revision for important intellectual content, and final approval of the manuscript. C.V. contributed to study design, data acquisition, data analysis, drafting of the manuscript, data interpretation, critical revision for important intellectual content, and final approval of the manuscript. G.J. contributed to study design, data interpretation, critical revision for important intellectual content, and final approval of the manuscript. S.M. contributed to data acquisition, data cleaning, data analysis, data interpretation, critical revision for important intellectual content, and final approval of the manuscript. A.P. served as a scientific advisor and contributed to study design, data interpretation, critical revision for important intellectual content, and final approval of the manuscript. S.Z. served as a scientific advisor and contributed to study design, data analysis, drafting of the manuscript, data interpretation, critical revision for important intellectual content, and final approval of the manuscript. H.L. and C.V. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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