All-Cause and Cardiovascular Mortality in Middle-Aged People With Type 2 Diabetes Compared With People Without Diabetes in a Large U.K. Primary Care Database

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OBJECTIVE—Middle-aged people with diabetes have been reported to have significantly higher risks of cardiovascular events than people without diabetes. However, recent falls in cardiovascular disease rates and more active management of risk factors may have abolished the increased risk. We aimed to provide an up-to-date assessment of the relative risks associated with type 2 diabetes of all-cause and cardiovascular mortality in middle-aged people in the U.K.

RESEARCH DESIGN AND METHODS—Using data from the General Practice Research Database, from 2004 to 2010, we conducted a cohort study of 87,098 people, 40–65 years of age at baseline, comparing 21,798 with type 2 diabetes and 65,300 without diabetes, matched on age, sex, and general practice. We produced hazard ratios (HRs) for mortality and compared rates of blood pressure testing, cholesterol monitoring, and use of aspirin, statins, and antihypertensive drugs.

RESULTS—People with type 2 diabetes, compared with people without diabetes, had a twofold increased risk of all-cause mortality (HR 2.07 [95% CI 1.95–2.20], adjusted for smoking) and a threefold increased risk of cardiovascular mortality (3.25 [2.87–3.68], adjusted for smoking). Women had a higher relative risk than men, and people <55 years of age had a higher relative risk than those >55 years of age. Monitoring and medication rates were higher in those with diabetes (all $P < 0.001$).

CONCLUSIONS—Despite efforts to manage risk factors, administer effective treatments, and develop new therapies, middle-aged people with type 2 diabetes remain at significantly increased risk of death.

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In the U.K., cardiovascular disease (CVD) mortality rates in adults have fallen dramatically in recent years (1), by >40% in those 35–69 years of age during 2000–2010 alone (2). The fall in the rates of CVD in the general adult U.K. population may be attributed in part to using aspirin, hydroxymethylglutaryl-CoA reductase inhibitors (statins), and antihypertensive drugs and successfully incorporating lifestyle interventions, in particular reducing smoking (3). In people with type 2 diabetes, who are at increased risk of death from CVD, evidence has shown that statins, antihypertensive drugs (4), and smoking cessation (3,5) reduce the incidence of CVD (6,7). Consequently, these interventions, in addition to weight management strategies to target obesity, a known risk factor for CVD events (3), have been incorporated into the various clinical guidelines, national standards, and incentives relating to managing diabetes (8–10) and implemented by general practitioners with the aim of reducing the risk of complications.

The magnitude of the increase in risk of CVD and all-cause mortality in middle-aged people with diabetes, compared with those without diabetes, has been reported at two to four times higher, but these estimates are largely based on data from the 1990s or earlier (11–16). Given that the rates of CVD mortality in the general population have rapidly fallen in recent years (2), and since 2004, the remuneration for general practice actively rewards intensive management for cardiovascular risk factors in people with diabetes (10), the differences may have narrowed even in the past 8 years. Most studies with post-2000 data on relative risk have not distinguished type 1 from type 2 diabetes (17–20), or have been restricted to newly diagnosed type 2 diabetes (21,22). One exception, reporting relative risks for prevalent type 2 diabetes, was the National Diabetes Audit in England (23). Using follow-up data from 2008 to 2009, they presented standardized mortality ratios in the absence of a nondiabetic comparator group; the report's authors proposed that their results need replicating using survival analysis methods. Using data from the General Practice Research Database (GPRD), we aimed to provide a more up-to-date assessment of the risk of mortality in middle-aged people with prevalent type 2 diabetes in England, overcoming the acknowledged limitation of the National Diabetes Audit study and additionally considering mortality from CVD.

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RESEARCH DESIGN AND METHODS

Data sources and aims

We carried out a matched cohort study using data from the GPRD. The GPRD provided a reliable source of longitudinal, anonymous medical data from general practices across the U.K., with links to other healthcare databases with their database of 5 million patients representing ~8.5% of the population. Our study cohort was drawn from practices linked by the Office of National Statistics to the GPRD, all located in England. We obtained data on people with diabetes 40–65 years of age on 1 January 2004 (baseline date), diagnosed after 40 years of age. For each patient with diabetes, we matched up to three people without diabetes for age (within 1 year), sex, and general practice. We analyzed data over 7 years, from 1 January 2004 to 31 December 2010.

The GPRD provided data in accordance with our data specification document, which defined people with diabetes as those with a diagnostic code and/or a treatment code for diabetes, and excluded patients with secondary diabetes, e.g., gestational or corticosteroid-induced diabetes. From the dataset received from the GPRD, we excluded those who died before 1 January 2004, <40 years of age at baseline, with sex unrecorded, with diabetes but not matched to people without diabetes, with diabetes but not identified as having type 2 diabetes, and without diabetes matched to people with diabetes who had been excluded from the cohort. We identified people with type 2 diabetes using an algorithm, slightly modified from that published by the Royal College of General Practitioners and National Health Service (NHS) Diabetes (24), and based on the date of diagnosis and the diagnostic and treatment codes for diabetes (Fig. 1).

We aimed to compare the populations with and without diabetes in terms of the following: *1*) baseline characteristics, including smoking, BMI, systolic and diastolic blood pressures, plasma total cholesterol, LDL, HDL, and triglyceride concentrations, and use, by proportions, of aspirin, statins, and antihypertensive drugs; *2*) rates of all-cause mortality and cardiovascular mortality; and *3*) average annual rates of blood pressure readings, cholesterol monitoring, and prescriptions for aspirin, statins, and antihypertensive drugs. We also reported the average annual rates of prescriptions for glucose-lowering treatments in the people with diabetes.

Statistical analysis

All statistical analyses were carried out using STATA v.12 (StataCorp, College Station, TX). We defined the percentage of people on medication at baseline as having had a prescription issued within the 3 months before the baseline date. Baseline values of all other variables were means in the 2 years before the baseline date, except BMI and smoking status, which we based on the most recent reading in the 5 years before the baseline date. We used BMI if given or we calculated it from the closest value of weight and height. For some patients, we calculated total cholesterol using the Friedewald equation (25). We carried out tests of baseline differences using conditional logistic regression. We tested only variables for which at least 80% of patients had (nonmissing) data, as we could not rule out the possibility that the absence of data correlated with the variable would bias the results.

We measured the frequencies of blood pressure readings and cholesterol monitoring as the average number of tests per person per year, and the average annual prescription rates for aspirin, statins, antihypertensive drugs, and glucose-lowering treatments were measured by the average number of months with prescriptions for these drugs per person per year. We used conditional logistic regression to test for differences between those with and without diabetes.

Cox proportional hazards models were constructed to estimate hazard ratios (HRs) with 95% CIs of all-cause mortality and CVD mortality in those with diabetes compared with those without diabetes. Given the extent of missing data, in the analysis of all patients, we were able to adjust only for baseline smoking status, having previously matched for age, sex, and general practice. Analyzing the subcohort of patients with complete data for the most recent values of BMI, blood pressure, and cholesterol, we also adjusted for the baseline values of these factors. In patients with type 2 diabetes, we analyzed the relationship between the duration of diabetes and mortality.

We stratified the analyses by sex and age-group (<55 and >55 years of age) and calculated *P* values by the log-rank test. We plotted log cumulative hazard against time to test the proportional hazards assumption of the Cox models (26).

For all Cox regression models, all covariates were specified as categorical variables. We categorized smoking status as current smokers, nonsmokers (not

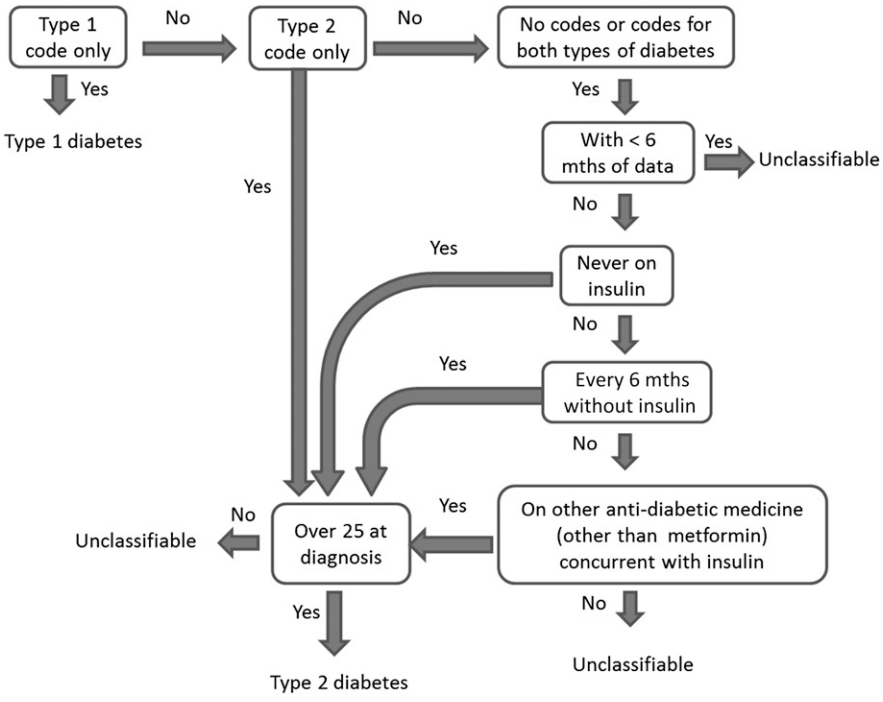

Figure 1—*Algorithm used to identify people with type 2 diabetes.*

having smoked in the previous 5 years), ex-smokers, and unknown. We considered smokers as those with a consultation and/or diagnostic code for smoking. BMI, measured as a continuous variable in kg/m^2, was divided into categories 9–18.5, 18.5–25, 25–30, 30–35, 35–40, 40–50, 50–70, >70, and unknown, incorporating categorization from the World Health Organization (27). We considered that a value for BMI on a threshold between categories would fall into the lower category, and values <9 kg/m^2 were implausible (and therefore categorized them as unknown). We defined systolic blood pressure categories as low (<120 mmHg), high (>120 mmHg), and unknown. We defined diastolic blood pressure categories as low (<80 mmHg), high (>80 mmHg), and unknown (28) and total cholesterol categories as low (up to 5 mmol/L), high (>5 mmol/L), and unknown (29). The duration of diabetes was categorized into <5, 5–10, and >10 years. We excluded values related to plasma LDL, HDL, and triglycerides in the Cox models, given the extent of missing data (70% or over).

We defined CVD mortality within the ICD-10 codes listed as the primary cause of death, I20–I25 (ischemic heart disease), I26–I28 (pulmonary heart disease and diseases of pulmonary circulation), and I60–I69 (cerebrovascular diseases).

For analysis of the risks of all-cause mortality, all survivors at 31 December 2010 were censored at that date. For analysis of the risks of CVD deaths, we censored survivors at 31 December 2010 and people died of causes other than CVD deaths at the date of death, reflecting our assumption that deaths from non-CVD causes were independent of the risk of CVD death.

We conducted three sensitivity analyses on all patients to test the robustness of the estimated HRs. In the first analysis, we classified smoking status into three categories, by grouping nonsmokers and those with unknown smoking status. In the second analysis, we censored all patients who left the practice or died before 31 December 2010 at the date they were recorded as having left the practice or the date of death, or the earlier of the two dates if both events occurred. In the third analysis, we censored controls who developed diabetes before 31 December 2010 at the date 5 years before diabetes was diagnosed. We chose 5 years as an estimate of the time lag that occurs between the onset of diabetes and diagnosis.

For comparability with the results of the National Diabetes Audit in England (24), we calculated standardized mortality ratios for the same follow-up period (1 November 2008 to 31 October 2009).

As our study compared a clinically defined exposure (diabetes) against a hard outcome measure (mortality), we did not need to consult patient or user groups.

RESULTS—The GPRD provided data on 99,151 people. After excluding 12,053 for the reasons given above, we analyzed data on 87,098, including 21,798 with type 2 diabetes and 65,300 matched people without diabetes. The baseline characteristics are shown in Table 1. The average duration of diabetes in the diabetes group was a median 3.9 years, with an interquartile range 1.8–8.0 years. The high levels of missing data for LDL, HDL, and triglycerides are apparent in Table 1. The percentage of people taking medications was significantly greater in those with diabetes for all drugs ($P < 0.001$). Of the patients with diabetes, 0.3% used short-acting insulin, 15.1% used long-acting insulin, and 68.6% used only noninsulin diabetes drugs.

In the 7 years after baseline, among the 21,789 people with diabetes, there were 2,146 deaths from all causes (9.8%) and 658 CVD deaths (3.0%). In the 65,300 without diabetes, there were 2,969 deaths from all causes (4.6%) and 574 CVD deaths (0.9%). Figure 2 shows cumulative hazard functions, split by sex and group. Log cumulative hazard plots are shown in Supplementary Fig. 1.

HRs for the analysis of all patients are shown in Table 2. The HR for all-cause mortality for people with diabetes compared with people without diabetes, adjusted for smoking status (model II) was 2.12 (95% CI 2.00–2.25) for all patients. People with diabetes were at a significantly higher risk of mortality than people without diabetes across all the subgroups. The adjusted relative risk of mortality was higher in women than in men (men, 1.93 [1.79–2.07]; women, 2.47 [2.23–2.72]) and higher in the <55 than in the >55 years of age-group (<55 years of age, 2.72 [2.42–3.06]; >55 years of age, 2.03 [1.89–2.17]).

The HR for CVD mortality for people with diabetes compared with people without diabetes, adjusted for smoking status (model II), was 3.28 (95% CI 2.91–3.70) for all patients. People with diabetes were consistently at a higher risk of CVD mortality than people without diabetes across all subgroups.

Sensitivity analyses showed that HRs were not changed measurably by classifying smoking into three categories, nor by censoring all patients who left the practice (16,047 additional patients were censored before 31 December 2010 and 588 who died were censored before their death), nor by also censoring the people without diabetes at baseline

Table 1—*Baseline characteristics*

	With diabetes n = 21,798		Without diabetes n = 65,300	
Sex, male	59.8%	21,798	59.8%	65,300
Age (years)	55.1 (6.6)	21,798	55.1 (6.6)	65,300
BMI (kg/m^2)	31.4 (6.3)	19,995	27.1 (4.9)	30,644
Smoker, current or ex-smoker	34.0%	19,494	31.5%	38,036
Duration of diabetes (years)	3.9 (1.8,8.0)	21,798	—	—
Systolic BP (mmHg)	140.8 (15.0)	20,811	137.1 (16.7)	37,424
Diastolic BP (mmHg)	82.8 (8.1)	20,811	82.4 (9.1)	37,424
LDL (mmol/L)	2.9 (0.9)	11,030	3.5 (1.0)	8,792
HDL (mmol/L)	1.2 (0.4)	15,087	1.4 (0.4)	11,967
Triglycerides (mmol/L)	2.2 (1.3)	16,006	1.7 (1.0)	12,191
Creatinine (μmol/L)	88.7 (33.7)	18,993	90.0 (26.4)	18,739
HbA_{1c} (%)	7.8 (1.6)	19,262	5.6 (0.8)	425
Cholesterol (mmol/L)	5.1 (1.0)	19,462	5.6 (1.0)	16,241
Medications				
Aspirin	35.0%	21,798	5.4%	65,300
Statins	47.6%	21,798	6.5%	65,300
Antihypertensive drugs	58.9%	21,798	17.1%	65,300

Data are median (interquartile range) for duration of diabetes, mean (SD), or n unless otherwise indicated.

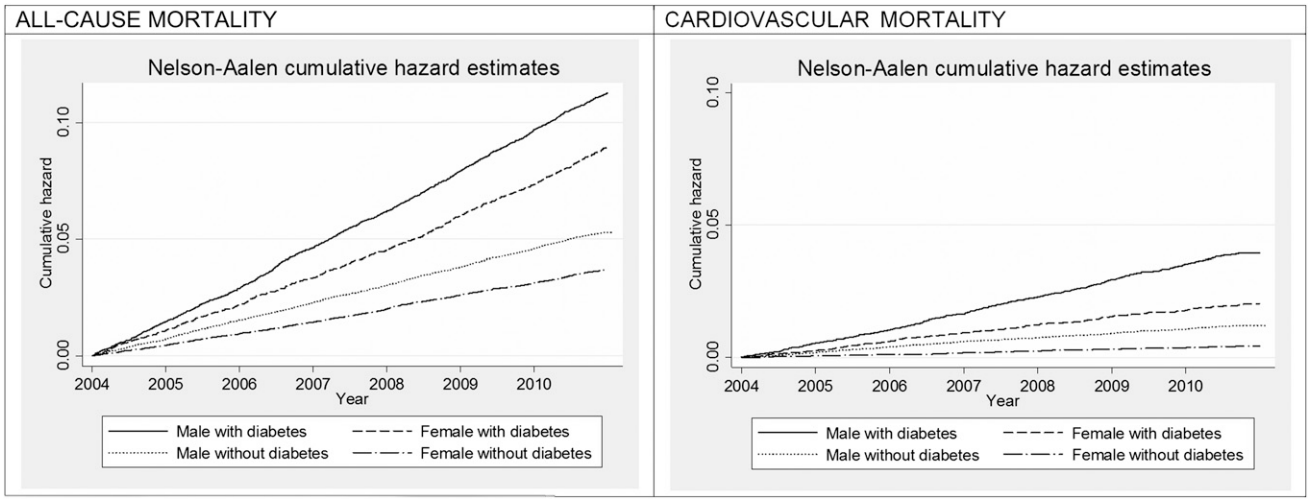

Figure 2—*Cumulative hazard functions.*

who developed diabetes before 31 December 2010 (involving 59 patients, of whom 5 died). The HRs for these analyses are shown in Supplementary Fig. 2.

When analyzing the relationship between mortality and duration of diabetes (Supplementary Table 1) and comparing these with people diagnosed with diabetes 5–10 years before baseline, we observed a significantly reduced risk of all-cause mortality in those diagnosed <5 years before baseline (HR 0.77 [95% CI 0.70–0.86]) and a significantly increased risk in those diagnosed >10 years before baseline (1.69 [1.51–1.90]). The risk of CVD mortality also increased with duration of diabetes (<5 years, 0.75 [0.62–0.91]; >10 years, 2.21 [1.80–2.72]). Increases in relative risk were observed in all subgroups and reached statistical significance in men, women, and the under 55 years of age-group considering all-cause mortality but only in women for CVD mortality.

To estimate how much adjusting for major CVD risk factors would attenuate the HRs, we conducted a secondary analysis restricted to 29,361 people with complete data for BMI, blood pressure, and total cholesterol (18,591 people with type 2 diabetes and 10,146 without diabetes). In this subgroup, adjusting for smoking only did not alter the HR for all-cause mortality, which was 1.63 (95% CI 1.49–1.79) with or without adjusting for smoking, but adjusting for smoking, BMI, blood pressure, and cholesterol reduced the HR to 1.51 (1.37–1.67). The corresponding HRs for CVD mortality were 2.28 (1.90–2.75) unadjusted, 2.26 (1.88–2.73) with adjustment for smoking, and 2.03 (1.66–2.47) with adjustment for smoking, BMI, blood pressure, and total cholesterol.

The frequencies of blood pressure testing and cholesterol monitoring were significantly higher in those with diabetes than those without (all $P < 0.001$) (Table 3), as was the average annual use of aspirin, statins, and antihypertensive drugs (all $P < 0.001$) (Table 3).

Standardized mortality ratios for the same 1-year follow-up period as for the National Diabetes Audit were 2.91 (95% CI 2.54–3.14) in men and 3.75 (3.11–4.35) in women 40–65 years of age. Standardized mortality ratios reported by the National Diabetes Audit were 2.55 in men and 3.38 in women 35–64 years of age.

Table 2—*HRs of all-cause mortality and cardiovascular mortality*

	With diabetes (deaths/total)	Without diabetes (deaths/total)	Model I	Model II
All-cause mortality				
All patients	2,146/21,798	2,969/65,300	2.22 (2.10–2.35)	2.12 (2.00–2.25)
Men	1,391/13,035	2,012/39,031	2.13 (1.99–2.28)	1.93 (1.79–2.07)
Women	755/8,763	957/26,269	2.42 (2.20–2.67)	2.47 (2.23–2.72)
<55 years of age	596/10,057	688/30,125	2.64 (2.37–2.95)	2.72 (2.42–3.06)
>55 years of age	1,550/11,741	2,281/35,175	2.11 (1.97–2.25)	2.03 (1.89–2.17)
Cardiovascular mortality				
All patients	658/21,798	574/65,300	3.52 (3.15–3.94)	3.28 (2.91–3.70)
Men	487/13,035	463/39,031	3.23 (2.85–3.67)	2.85 (2.49–3.78)
Women	171/8,763	111/26,269	4.72 (3.72–6.00)	4.80 (3.73–6.17)
<55 years of age	155/10,057	124/30,125	3.81 (3.01–4.82)	3.91 (3.02–5.04)
>55 years of age	503/11,741	450/35,175	3.46 (3.05–3.93)	3.24 (2.83–3.71)

Data are HRs (95% CI) for people with type 2 diabetes compared with people without diabetes matched on age, sex, and general practice and unadjusted (model I) or adjusted for smoking with four categories for smoking status (current smoker, nonsmoker, ex-smoker, and unknown) (model II).

CONCLUSIONS—In this cohort, people with type 2 diabetes had twice the risk of dying from any cause and three times the risk of CVD death compared with people without diabetes. Men were at a greater absolute risk of mortality than women, but the relative risk associated with diabetes in men was lower than in women. Younger middle-aged people with type 2 diabetes (<55 years of age) were at a greater relative risk than older middle-aged people without diabetes (>55 years of age). The association between diabetes and the risk of death was largely independent of smoking

Table 3—*Average annual monitoring and medication per person*

	With diabetes n = 21,798	Without diabetes n = 65,300
Monitoring		
Blood pressure	2.3 (1.3–3.3)	0.6 (0.1–1.6)*
Cholesterol	1.1 (0.7–1.6)	0.1 (0–0.6)*
Medications		
Aspirin	1.1 (0–5.0)	0 (0–0)*
Statins	3.1 (0–6.6)	0 (0–0)*
Antihypertensive drugs	5.6 (0.7–8.6)	0 (0–2.1)*

Data are medians (interquartile ranges) of average numbers of tests per person per year (monitoring) and of average numbers of months with prescriptions per person per year (medications). *$P < 0.001$.

status. A secondary analysis, in a subcohort for which the relevant data were nonmissing, suggested that the relative risk was also largely independent of BMI, blood pressure, and cholesterol. Among people with diabetes, the risk appeared to increase with the duration of diabetes.

The strengths of our study included the data sources, with high-quality data on a large representative sample of the English population, complete and accurate data on date of death, and access to longitudinal data on the monitoring and treating of cardiovascular risk factors (30,31). However, our study was limited by the extent of missing data for some covariates of interest. In our view, the assumptions necessary for multiple imputation (32) would not be justified. Hence, we explored how far adjusting for BMI, blood pressure, and cholesterol might modify the results in a subcohort who had complete data for these variables. To identify patients with type 2 diabetes, it was necessary to modify the algorithm published by the Royal College of General Practitioners and NHS Diabetes (24), as the date of diagnosis of diabetes may be unreliable in people whose diagnosis predated entry to the GPRD. A recent study showed that data on the duration of diabetes is ~90% accurate for a duration <5 years, but only 67% accurate for a duration >15 years (33). Our modified algorithm was intended to produce a cohort that was representative of type 2 diabetes as far as possible. As we could not adjust for factors such as renal function, or ethnicity, some residual confounding may exist.

Our findings are consistent with those of both older and more recent studies of middle-aged people with type 2 diabetes, in providing evidence of risk of mortality lower than before, although elevated with respect to the nondiabetic population, with a greater relative risk in women than men (11–13,15–18,21,23,34), and with a lower relative risk at older ages (11,16,20,23,34). Our study is directly comparable with one of these studies, which also used GPRD data to examine the risk of mortality associated with type 2 diabetes (13). We produced HRs that were lower than the standardized mortality ratios reported by the National Diabetes Audit (23). When we calculated standardized mortality ratios for the same 1-year period and compared with National Diabetes Audit results for a similar age-group, we obtained consistent results, but our standardized mortality ratios were higher than our HRs. This suggests that the differences between our HRs and the National Diabetes Audit results are attributable to methodological differences (weakness of one-sample design and standardized mortality ratios) rather than underlying differences in the mortality rates between these two large samples from the English population.

Although there is some evidence suggesting falling rates of mortality in people with incident (35,36) and prevalent type 2 diabetes (37), our study shows that middle-aged patients with type 2 diabetes remain at a significantly increased risk of mortality, compared with people without diabetes, despite more active management of cardiovascular risk factors. Therefore, mortality rates do not appear to have fallen more quickly in people with type 2 diabetes than in the general population.

Our study highlights the important need to continue efforts to improve life expectancy in people with type 2 diabetes. This appears to be particularly important for women and for younger middle-aged people.

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No potential conflicts of interest relevant to this article were reported.

This study is based in part on data from the Full Feature GPRD obtained under license from the MHRA. However, the interpretation and conclusions contained in this study are those of the authors alone.

K.S.T. conducted the statistical analysis, interpreted the results, and led the writing of the manuscript. C.J.H. and A.J.F. wrote the study protocol, interpreted the results, and contributed to writing the manuscript. A.M.F. prepared and interpreted the data and contributed to writing the manuscript. A.I.A. and J.K.A. interpreted the results and contributed to writing the manuscript. R.J.S. wrote the study protocol, advised on statistical analysis, interpreted the results, and contributed to writing the manuscript. R.J.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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