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Mortality in people with Type 2 diabetes in the UK

H. E. Mulnier*, H. E. Seaman*, V. S. Raleigh*†, S. S. Soedamah-Muthu‡, H. M. Colhoun‡ and R. A. Lawrenson*

*Postgraduate Medical School, University of Surrey, Guildford, †Healthcare Commission, London and ‡Department of Epidemiology and Public Health, Royal Free and University College London Medical School, London, UK

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Abstract

Aims Under-reporting of diabetes on death certificates contributes to the unreliable estimates of mortality as a result of diabetes. The influence of obesity on mortality in Type 2 diabetes is not well documented. We aimed to study mortality from diabetes and the influence of obesity on mortality in Type 2 diabetes in a large cohort selected from the General Practice Research Database (GPRD).

Methods A cohort of 44 230 patients aged 35–89 years in 1992 with Type 2 diabetes was identified. A comparison group matched by year of birth and sex with no record of diabetes at any time was identified (219 797). Hazards ratios (HRs) for all-cause mortality during the period January 1992 to October 1999 were calculated using the Cox Proportional Hazards Model. The effects of body mass index (BMI), smoking and duration of diabetes on all-cause mortality amongst people with diabetes was assessed (n = 28 725).

Results The HR for all-cause mortality in Type 2 diabetes compared with no diabetes was 1.93 (95% CI 1.89–1.97), in men 1.77 (1.72–1.83) and in women 2.13 (2.06–2.20). The HR decreased with increasing age. In the multivariate analysis in diabetes only, the HR for all-cause mortality amongst smokers was 1.50 (1.41–1.61). Using BMI 20–24 kg/m^2 as the reference range, for those with a BMI 35–54 kg/m^2 the HR was 1.43 (1.28–1.59) and for those with a BMI 15–19 kg/m^2 the HR was 1.38 (1.18–1.61).

Conclusions Patients with Type 2 diabetes have almost double the mortality rate compared with those without. The relative risk decreases with age. In people with Type 2 diabetes, obesity and smoking both contribute to the risk of all-cause mortality, supporting doctrines to stop smoking and lose weight.

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Keywords General Practice Research Database, mortality, primary care, Type 2 diabetes

Abbreviations BMI, body mass index; CI, confidence interval; GPRD, General Practice Research Database; HR, hazard ratio; MSGP4, Fourth National Study of Morbidity Statistics from General Practice; OHA, oral hypoglycaemic agent; OXMIS, Oxford Medical Information System

Introduction

Type 2 diabetes mellitus is a common, chronic disease associated with reduced life expectancy [1–4]. Studies of mortality in Type 2 diabetes in the UK have commonly used local registers [1,5]. Such registers have relatively small sample sizes and potentially insufficient outcome data to provide accurate estimates of risk. Studies using national mortality statistics suffer because diabetes as a contributory cause is under-reported on death certificates [4]. A prospective study using a national general practice database with good prescribing and associated morbidity and mortality data may provide more reliable

Correspondence to: Henrietta Mulnier, Postgraduate Medical School, University of Surrey, Daphne Jackson Road, Manor Park, Surrey GU2 7WG, UK. E-mail: h.mulnier@surrey.ac.uk

estimates of relative and absolute risk of the mortality associated with diabetes.

Evidence of the influence of obesity on mortality is conflicting. Studies of obesity in the general population have demonstrated varying associations with all-cause mortality. Shaper *et al*. showed a U-shaped association, whilst Calle *et al*. described a J-shaped curve [6,7]. In people with diabetes, Hodge *et al*. described an inverse relationship between mortality and BMI, Walters *et al*. showed no association between obesity and mortality in insulin-treated or non-insulin-treated diabetes, whilst Rogers *et al*. showed a marked increased risk in mortality with increasing body mass index (BMI) in diabetes [8–10]. This study aimed to estimate the relative risk of mortality in Type 2 diabetes by age and sex, and the influence of BMI, smoking and duration of diabetes on mortality in a large cohort of patients with diabetes drawn from the UK general population.

Patients and methods

Study population and data source

A cohort study was carried out using data from the General Practice Research Database (GPRD) in patients with Type 2 diabetes and a comparison group without diabetes. The GPRD provides longitudinal anonymized patient data from general practices across the UK and includes data on demographics, medical diagnoses and symptoms, prescriptions and hospital admissions. Data on patients' lifestyles such as smoking habit are also available. The age and sex distribution of the population on the database at any point in time closely matches that estimated by the Office for National Statistics for England and Wales in 1998 [11]. Data have been shown previously to be of high quality and validity, and have been used extensively for cohort and case-control studies [12–17]. According to the Royal College of General Practitioners, 98% of people in the UK are registered with a general practitioner (www.rcgp.org.uk/information/publications/information/infosheettitles_index.asp 'General Practitioner Workload' April 2004. Data accessed August 2005). Therefore, using primary care data allows us to study a population-based sample of patients with diabetes compared with a comparison group of people without diabetes drawn from the same population, but who are otherwise unselected. The version of the GPRD used for this study includes data from practices contributing between 1987 and October 1999, representing a total of 8 066 630 patient records. Only practices that were supplying data to the GPRD on 1 January 1992 and for at least 6 months prior to 1992 were included in the study.

Ethical permission was given for this study by the GPRD Scientific and Ethical Advisory Group.

Medical diagnoses and symptoms are recorded on the database using OXMIS (Oxford Medical Information System) or Read codes (the coding system adopted by the Department of Health for use in General Practice). All subjects present on the database on 1 January 1992 with a code or treatment for diabetes prior to this date were identified. Patients with a first code or treatment for diabetes on or after this date were excluded from the patient and comparison group. To allow comparison of prevalence with other studies, persons with any diabetes type were identified initially. Patients with diabetes were those with a diagnostic code and supporting evidence of diabetes, or treatment for diabetes and other supporting evidence such as home glucose monitoring or glycated haemoglobin testing. Patients with Type 1 or Type 2 diabetes were then distinguished using algorithms based on age at diagnosis, type of treatment and age at treatment. Patients with Type 2 diabetes were those who had a diagnosis of diabetes and were treated with diet only or with an oral hypoglycaemic agent, or if treated with insulin were aged 35 years or older at diagnosis. Those treated with insulin only and aged less than 35 years at diagnosis were deemed to have Type 1 diabetes. Those not selected by the Type 1 or Type 2 algorithms were considered indeterminate. The final cohort for this study included patients with Type 2 diabetes aged 35–90 years on 1 January 1992. For comparison, five subjects per patient were selected randomly from the GPRD matched by year of birth and sex. Comparison subjects had no record of or treatment for diabetes at any time on the database.

Mortality and risk factor detection

Deaths after 1 January 1992 were identified from the medical records using appropriate codes and registration status. Patients who die whilst registered with a contributing practice are generally assigned the appropriate deregistration status. All those with such a registration status were selected as definite deaths. Where the record contained a code for death but the patient had not been deregistered, subjects were only included as deaths if their medical record ended on the same day as the death code record. Very occasionally there is a death code and no deregistration and the medical record continues. These patients were not classified as dead.

In the diabetes group, BMI was calculated where height and weight recordings were available. The readings closest to baseline were used. Where there was no recording of height or weight within 3 years of baseline, data were considered missing. Patients were grouped by BMI range 15–19, 20–24, 25–29, 30–34, and 35–54 kgm^2. In the analysis, the range 20–24 kg/m^2 was used as the reference group.

Subjects were categorized as non-smokers, current smokers, ex-smokers or unknown based on the records of smoking closest to 1 January 1992, with the exception of some who were classified as ex-smokers if the closest record to 1992 was for non-smoking, but they had a prior record of smoking.

Duration of diabetes at baseline was estimated either from the date of the first OXMIS/Read code for diabetes or the date of the first diabetes-related prescription, whichever was earlier. If a general practitioner (GP) is unsure of the date of diagnosis, however, then this may be recorded as a historical date that upon investigation proves improbable, if not impossible. These patients were categorized as unknown duration of diabetes.

Statistical analysis

A Cox Proportional Hazards Model was used, adjusted for current age by setting date of birth as the origin and baseline 1 January 1992 as the cohort start date. Hazard ratios (HRs) were calculated for all-cause mortality in diabetes compared with no diabetes, and then in diabetes only adjusted for BMI, smoking and duration of diabetes (patients with missing data

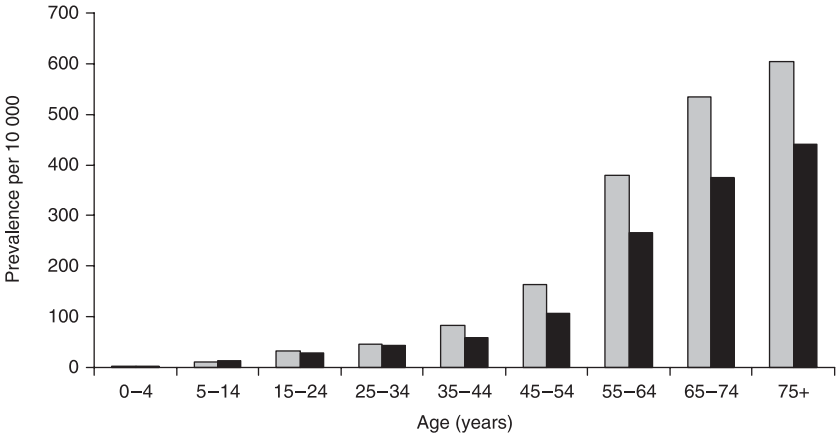

Figure 1 Age- and sex-stratified prevalence of all diabetes from the GPRD on 1 January 1992; (□) male and (■) female.

Table 1 Hazard ratios for all-cause mortality in people with Type 2 diabetes compared with people without diabetes by age and sex

Age (years)	Men hazard ratio (CI_{95})	Men (*n*) with diabetes/ without diabetes	Women hazard ratio (CI_{95})	Women (*n*) with diabetes/ without diabetes
35–54	3.35 (2.86,3.93)	4042/20 200	3.07 (2.37,3.97)	2523/12 606
55–64	2.21 (2.04,2.39)	6320/31 528	3.28 (2.94,3.65)	4530/22 626
65–74	1.84 (1.75,1.93)	7600/37 774	2.44 (2.30,2.60)	6392/31 840
75–84	1.58 (1.51,1.66)	4853/23 892	1.97 (1.88,2.07)	5824/28 830
85–89	1.44 (1.30,1.60)	732/3553	1.65 (1.52,1.78)	1414/6948
All	1.77 (1.72,1.83)	23 547/11 6947	2.13 (2.06,2.20)	20 683/102 850

were excluded from this analysis). The analysis was performed using STATA version 8 (STATA Corp., College Station, TX, USA).

Results

The GPRD population included 3 616 048 patients on 1 January 1992. We identified 61 097 patients who had codes and/or prescriptions for the treatment or management of diabetes. From this cohort we identified 54 703 with a diagnostic code and supporting evidence of diabetes, or treatment for diabetes and other supporting evidence such as home glucose monitoring or glycated haemoglobin testing. The prevalence of all diabetes on the database in 1992 was 1.5%. The age- and sex-specific prevalence rates for all diabetes are shown in Fig. 1.

We then categorized 7727 patients with Type 1 diabetes, and 44 887 with Type 2 diabetes. Those not selected by either algorithm (8483) as a result of uncertainty of age at diagnosis or age at first treatment with insulin, or not having a diabetes code and treatment or evidence of monitoring/follow-up for diabetes, were deemed indeterminate. Of the 44 887 patients with Type 2 diabetes, 290 (0.6%) were aged less than 35 years or ≥ 90 years at baseline and thus excluded from study. In a small proportion of cases (0.8%), death was found to have occurred late in 1991, but deregistration did not occur until early 1992. These were considered deaths prior to baseline and excluded from the cohort. The study is based on 44 230 patients alive with Type 2 diabetes and aged 35–89 years at baseline and 219 797 patients without diabetes for the comparison group. The average age of the study population was 67 years and 53.2% were male.

There were 11 165 (25.2%) definite deaths in the group with Type 2 diabetes and 31 742 (14.4%) in the comparison group. The mortality rate was 60.3 per 1000 person years (95% CI 59.19–61.42) in the cohort with diabetes and 32.7 (32.34–33.06), in the comparison group. The HR for death in patients with Type 2 diabetes was 1.93 (1.89–1.97) compared with people without diabetes. The HR for men [1.77 (1.72–1.83)] was significantly lower than for women [2.13 (2.06–2.20)], although men with diabetes were at greater risk than women with diabetes [HR 1.5 (1.48–1.53)]. The HR was greatest amongst men and women aged 35–54 years and decreased with increasing age (Table 1).

In people with diabetes, BMI data were available for 30 839 (70%), whilst smoking data were available for 36 637 (83%). The duration of diabetes could be ascertained for 42 847 (97%). Of the diabetes cohort, 65% (28 725) had BMI, smoking and diabetes duration data (Table 2). The average age was 66 years and 55% of the group was male. For those not included in the multivariate analysis, the average age in 1992 was 69.4 years, and 50% were male and the risk estimates for all-cause mortality was higher than the risk estimate in those with complete data, HR 2.61 (2.53–2.69) compared with 1.56 (1.51–1.60). The results of the multivariate analysis of mortality in people with Type 2 diabetes adjusted for age, sex, duration of diabetes, smoking and BMI are presented in Table 3. The adjusted mortality risk was significantly greater in men than in women,

Table 2 Characteristics of patients with Type 2 diabetes where body mass index (BMI), smoking and duration of diabetes are known (n = 28 725)

BMI group (kg/m^2)	Number of patients (%)	Percentage male	Mean age	Number of current smokers (%)	Number prescribed insulin (%)
15–19	557 (1.9)	35.6	71	136 (24.4)	124 (22.2)
20–24	6922 (24.1)	58.0	68	1447 (20.9)	1228 (17.7)
25–29	12 489 (43.5)	62.2	66	2422 (19.4)	1548 (12.4)
30–34	5992 (20.9)	50.5	63	1119 (18.7)	667 (11.1)
35+	2765 (9.6)	32.2	60	519 (18.8)	285 (10.3)

Table 3 Multivariate analysis of mortality in people with Type 2 diabetes adjusted for age, sex, body mass index (BMI), smoking, and duration of diabetes (n = 28 725)

Variable	Hazard ratio	95% CI
Male sex	1.33	1.27–1.41
Diabetes duration < 5 years	Reference	
Diabetes duration 5–9 years	1.14	1.06–1.21
Diabetes duration 10–14 years	1.27	1.17–1.37
Diabetes duration ≥ 15 years	1.38	1.27–1.50
Current smoker	1.50	1.41–1.61
Ex-smoker	1.25	1.15–1.36
Non-smoker	Reference	
BMI 15–19 kg/m^2	1.38	1.18–1.61
BMI 20–24 kg/m^2	Reference	
BMI 25–29 kg/m^2	0.97	0.91–1.03
BMI 30–34 kg/m^2	1.13	1.04–1.22
BMI 35–54 kg/m^2	1.43	1.28–1.59

increased with increasing duration of diabetes, and was 50% greater in smokers and 25% greater in ex-smokers compared with non-smokers. The mortality risk by BMI has produced a U-shaped curve. This curve was found in all ages and in both sexes, although was less pronounced in the older age groups. Compared with a BMI 20–25 kg/m^2, those with a BMI 15–19 or ≥ 30 kg/m^2 had a statistically increased risk of mortality. The hazard ratio for BMI 35–54 kg/m^2 was significantly greater than that for BMI 30–34 kg/m^2. The exclusion of patients from the multivariate analysis who had a code for cancer in their record (n = 1503) made no difference to the risk estimates for BMI group, the effect of duration of diabetes and of smoking.

Discussion

Patients with Type 2 diabetes are at almost twice the risk of dying from any cause than their peers without diabetes after adjusting for age. These results are comparable with previous studies of all-cause mortality in Type 2 diabetes [1,5,18–20]. We did not find the very high relative risks in younger patients with Type 2 diabetes found in some older studies, which quote rates of more than five times the mortality of comparison populations [21,22]. We have produced data from 5585 patients over the age of 75 years who would often be excluded from a prospective study or whose number would be few in a small cohort study. These data suggest that, although their relative risk of death compared with those with no diabetes is less than that found in younger patients, they still have a significant excess mortality and preventive care in these patients is well worthwhile. Although it should be noted that the absolute burden of diabetes mortality is greater in men, women with diabetes are at a greater proportional risk than women without diabetes (Table 1). Our prevalence estimate of all diabetes is consistent with the prevalence reported by other UK studies conducted between 1992 and 1998 [1,23].

The data on BMI show that amongst patients with diabetes those with a BMI of 35–54 kg/m^2 have a 43% greater risk of death than those with a 'normal' BMI (20–24 kg/m^2). The increased risk amongst those with a BMI 30–34 kg/m^2 is also significantly raised whilst those who are overweight but not obese have no increase in mortality. This would suggest that efforts to encourage weight loss should be aimed at the obese and at preventing those who are overweight from becoming obese. This study has demonstrated a U-shaped curve associated with BMI and mortality in diabetes, consistent with that found by Shaper *et al*. in the general population [6]. The high risk in those with a BMI < 20 kg/m^2 is based on mortality in only 2% of the patients with Type 2 diabetes. The risk in this group was almost as high as those with a BMI of 35–54 kg/m^2. A small number of patients with a BMI of < 20 kg/m^2 would be expected in a study of people with Type 2 diabetes. This group was older, more likely to smoke, to be female and to be treated with insulin (Table 2). The U-shaped curve remained even when all patients with a diagnostic code for cancer were excluded, suggesting that this finding was not due to cachexia. The increased mortality amongst patients with a low BMI may be associated with weight loss as a result of poorly controlled diabetes.

There are known limitations of the GPRD. It is not a 'fixed' population, i.e. patients may deregister from a contributing practice or a practice may cease to contribute to the database. Information on ethnicity is not recorded and there is a slight over-representation of large practices. It could be said that general practitioners contributing to the GPRD may have better management systems leading to better monitoring, recall and preventive medicine and lower risk estimates and rates. In fact, the mortality rate in our study is slightly higher than that found

by the Diabetes Audit and Research in Tayside Scotland study, which reported an annual rate of 50 per 1000 patients with Type 2 diabetes compared with 60 per 1000 patient years in our study [24]. Using a large general practice computerized database has the advantage that a comparison group can be selected from the same population base as the patients of interest. We chose a comparison group taken from the GPRD who were selected on the same criteria as the patients with diabetes, except that they had no record of diabetes anywhere in their record. We randomly selected the comparison group from all those available on the database but matched by age and sex so that the age structure of the patients and comparison group were the same. We did not match by practice because previous unpublished work by our group has shown practice matching of large cohort studies does not alter the hazard ratios. Matching by practice reduces the number of available patients in the older age groups and is in itself a potential source of bias.

A further strength of the study is the opportunity to examine in people with diabetes the risk estimates associated with BMI, smoking and duration of diabetes. We were able to ascertain duration of diabetes, smoking and BMI data in a very large cohort of 28 725 people with diabetes. Although the hazard ratio was higher in the patients not included in the multivariate than for those who had complete data, we believe the findings from such a large cohort of patients with Type 2 diabetes being managed in primary care are of value. It is likely that the individuals who have complete data attend more regularly and thus benefit from treatment to reduce the risk of complications.

When assessing the risk in the comparison group it is important to highlight that those with diabetes diagnosed after January 1992 were excluded from the potential comparison group prior to selection. According to Harris *et al*., the average time from onset to diagnosis of Type 2 diabetes is 4–7 years [25]. Therefore, as our follow-up period was of this length, most of those with undiagnosed diabetes will have been excluded from the comparison group. However, the comparison group will still contain a small number of patients with undiagnosed diabetes. It is likely that these patients may have made a small contribution to the risk estimates of the comparison group, which would marginally reduce the risk estimates reported here. However, the absence of known diabetes in the comparison group makes the risk estimates in our study a robust representation of the true risk.

The study has shown that patients with Type 2 diabetes have almost double the mortality rate compared with those without diabetes, that younger patients with Type 2 diabetes have three times the mortality rate of their peers without diabetes and that the relative risk reduces with age. Our analysis on the effects of BMI and smoking on the mortality of people with diabetes provides strong evidence to advise patients with Type 2 diabetes of the benefits of smoking cessation and weight loss. We believe these risk estimates will be of use in clinical decision making, in particular when treating younger patients with Type 2 diabetes, or when considering risk factor management in the very elderly.

Competing interests

HMC has received speaker fees and consulting fees from Pfizer Ltd and has had research funded by Pfizer Ltd.

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