Cause-Specific Mortality in a Population With Diabetes

South Tees Diabetes Mortality Study

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OBJECTIVE — To describe the mortality of a population with diabetes compared with the local nondiabetic population, using age-, sex-, and cause-specific death rates and relative and absolute differences in death rates.

RESEARCH DESIGN AND METHODS — A population-based cohort of 4,842 people with diabetes living within South Tees, U.K., was identified and followed from 1 January 1994 to 31 December 1999. Causes of death were obtained from death certificates, and mortality rates were compared with the nondiabetic population of the same area for the same time period.

RESULTS — There were 1,205 deaths (24.9%) in the study population during the 6 years of study. For type 2 diabetes, mortality from cardiovascular causes was significantly increased in both sexes and at all ages. Relative death rates for the age band 40–59 years were 5.47 (95% CI 4.18–7.15) for men and 5.60 (3.44–9.14) for women. The relative death rates declined with age for both sexes, but absolute excess mortality increased with age. There were no consistent differences in noncardiovascular death rates, other than for renal disease. Similar outcomes were found for type 1 diabetes, although these results were limited by a much smaller population size. People with diabetes and renal impairment had significantly higher mortality than people with diabetes alone, with a rate ratio of 7.27 for people with type 2 diabetes aged 40–59 years.

CONCLUSIONS — In an area of the U.K. with high cardiovascular death rates, people with diabetes had significantly higher cardiovascular death rates than people without diabetes. Interventions targeted at cardiovascular risk factors should be used to try and reduce this excess premature mortality, which is especially high in those with renal impairment.

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People with diabetes have higher all-cause mortality rates than similar people without diabetes (1–3), mainly attributable to cardiovascular causes (4–8). However, there is variability in the extent of this increase in mortality between countries (9). There are also variations in the effects of diabetes on other causes of death, with increased, unchanged, or reduced mortality for cancer and respiratory disease reported (5, 7,8,10–14). This variation in noncardiovascular mortality may be a reflection of different study methods, but it may also reflect genuine variation between different populations. The disparity in ischemic heart disease mortality between people with and without diabetes in the U.S. is increasing rather than declining (15), but it is not known whether this is the case in other countries. It is important, therefore, to have data from a variety of countries to determine which causes of death are increased in people with diabetes and to note any differences in the pattern of mortality. Ideally, data should come from unselected populations to avoid selection bias. Most previous U.K. studies have been limited by being confined to a particular setting, either community (12) or hospital (10,11), or have concentrated on groups selected by treatment type, usually insulin-treated people (6,10). These groups may be more easily identified but are not necessarily representative of all people with diabetes. The only U.K. mortality study of an unselected population of which we are aware did not differentiate between type 1 and type 2 diabetes, and it did not report age, sex, and cause-specific mortality rates, limiting the ability to compare results with other studies (14).

In this context we decided to study the causes of death in the diabetic population of our area, South Tees, in northeast England. This area comprises two local government districts, Middlesbrough and Redcar & Cleveland, and in 1994, they had a total population of 290,000. Mortality is above the national average; calculated standardized mortality ratios for South Tees, compared with England and Wales, during the period of study were 113 for both all-cause and cardiovascular mortality (16,17). Migration rates in the area are low. During the study <3% of the cohort registered with a health authority other than Tees, giving a stable population to study.

We present data on the extent to which diabetes increases cardiovascular mortality, in both relative and absolute terms, in an area with high background all-cause and cardiovascular mortality. We also present data on mortality from noncardiovascular causes. Age, sex, and cause-specific death rates are used to allow comparisons with other populations. All-cause death rates for the population with diabetes divided by baseline renal function are used to highlight the associ-

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A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

ation between renal impairment, diabetes, and premature death.

RESEARCH DESIGN AND METHODS

— The cohort comprised all people on the South Tees district diabetes register with an address within the local government districts of Middlesbrough and Redcar & Cleveland and who were known to be alive on 1 January 1994. The diabetes register contains demographic and clinical data on all people with known diabetes within the above area. Data are prospectively collected from the adult and pediatric secondary care diabetes services, all primary care centers within the area, and the diabetes eye service. Because of the methods originally used to identify subjects, estimation of ascertainment with capture-recapture methods was not possible. However, our population had age and ethnic distributions similar to the diabetic population of Tayside, Scotland (18), in a study in which ascertainment was calculated as 96%. Prevalences were 0.26% for type 1 diabetes and 1.41% for type 2 diabetes in our population, compared with 0.22% for type 1 diabetes and 1.49% for type 2 diabetes in Tayside in 1993 (19). Therefore, we feel confident that the ascertainment of diabetes in our population was high and reliable. The South Tees Ethical Committee granted approval for the study.

Death registration

The Office for National Statistics registered all subjects, and the date of death, causes of death, and underlying cause of death were obtained from death certificates. Inconsistent inclusion of diabetes on death certificates creates problems when comparing the underlying causes of death between diabetic and nondiabetic populations. For example, death from myocardial infarction in a diabetic person could be coded with either myocardial infarction or diabetes as the underlying cause, dependent entirely on whether, or in which section of the certificate, the certifying physician included diabetes. Moreover, it is well recognized that the inclusion of diabetes on death certificates is low (6,8,20,21); in our study, diabetes was mentioned on the death certificates of only 45.4% of men and 50.6% of women. To correct for this, we allocated a new underlying cause of death code whenever the original underlying cause of death was diabetes (ICD-9 code 250). This was done by removing diabetes from the original causes of death and recoding the underlying cause of death using ICD-9 rules. Diabetes remained the underlying cause of death if it was the only listed cause or if the immediate cause of death was a short-term metabolic complication, i.e., hyperosmolar coma or ketoacidosis.

As the death certification of diabetes demonstrates, chronic diseases are underreported. Therefore, because of the possible underreporting of renal disease, we went on to analyze the all-cause death rates of the cohort divided according to baseline renal function, defined as the higher of the mean creatinine for 1993 and the mean creatinine for 1994, comparing those with a creatinine of either above or below 150 μmol/l.

Comparison population

The local population without diabetes was used as the comparison population. This population was derived by subtracting the study population (who were sex- and 5-year age band–matched and adjusted for the decline in cohort numbers each year) from the local population data for each year, obtained from the Tees Health Authority. Mortality data were calculated by subtracting deaths in the study population from local mortality data (16), matched by year of death, sex, 5-year age band, and the underlying cause of death, and adjusted for the decline in cohort numbers each year.

Analysis

The study population was divided into those with type 1 or type 2 diabetes, using similar criteria to previous studies (1,19), i.e., for type 1 diabetes: people aged ≤35 years at diagnosis and on insulin treatment at the start of the study; for type 2: people aged >35 years at diagnosis or not on insulin.

Crude death rates were calculated using person-years of follow-up in that age band as denominator, 95% CIs were estimated using the Chiang method (22,23). Relative death rates were also calculated using a person-years method (22,24), and the associated CIs were estimated using Miettinen's significance test–based limits (22,25).

RESULTS

— The cohort comprised 4,842 people followed from 1 January 1994 to 31 December 1999 or death, total follow-up was 25,610 person-years, and only 22 subjects (0.45%) could not be traced. Overall, 1,205 subjects died (24.9%), 659 men (24.6%) and 546 women (25.2%). Tables 1 and 2 show the age-and cause-specific death rates for people with type 2 and type 1 diabetes, respectively.

Type 2 diabetes

Death rates in people with type 2 diabetes rose with age and were higher in men than women for all causes, with the exception of cerebrovascular disease. The relative death rates revealed consistent excess in deaths from cardiovascular causes in subjects with diabetes compared with those without diabetes, including both ischemic heart disease and cerebrovascular disease, although the smaller number of events in the cerebrovascular disease category means that some of the CIs include unity. The relative excess declined with age as background population death rates rose; however, the absolute excess mortality, that is, the study death rate minus the reference death rate (Fig. 1), increased with age for cardiovascular causes and ischemic heart disease. There were no consistent increases in deaths from neoplasia, respiratory disease, or accidents and poisoning compared with the local population without diabetes. Three deaths were certified as caused by acute metabolic complications of diabetes.

There was a large excess of deaths from renal failure in the 60- to 79-year-old age band for both men and women: relative rates, compared with the local population without diabetes, were 10.75 (95% CI 5.67–20.37) and 7.21 (2.79–18.61), respectively. The death rates comparing people with baseline creatinine above or below 150 μmol/l are shown in Table 3 and demonstrate significantly higher rates in those with renal impairment compared with those with normal, or relatively normal, renal function (maximum rate ratio 7.27 [4.11–12.86]).

Type 1 diabetes

Interpretation of the data for people with type 1 diabetes was limited by fewer deaths in this younger and smaller group. However, patterns of mortality similar to the type 2 diabetic population were seen, with a consistent excess mortality from cardiovascular and ischemic heart disease. Both the relative and absolute excesses in mortality from cardiovascular causes and ischemic heart disease tended

Table 1—*Mortality of the population with type 2 diabetes compared with the population of Teesside without diabetes, 1994–1999*

Cause (ICD-9 codes)	Age (years)	Baseline no. of subjects	Person-years of follow-up	Deaths (*n*)	Death rate per 1,000 person-years (95% CI)	Nondiabetic death rate	Relative rate* (95% CI)
All causes							
Male subjects							
	40–59	749	3,297	73	22.14 (18.09–26.20)	5.27	2.56 (1.73–3.80)
	60–79	1,297	7,196	411	57.12 (54.23–60.00)	39.27	1.96 (1.74–2.21)
	80+	131	919	143	155.56 (143.67–167.45)	148.17	1.25 (1.09–1.43)
Female subjects							
	40–59	464	2,163	24	11.09 (7.12–15.06)	3.30	3.15 (2.51–3.95)
	60–79	1,037	5,401	279	51.66 (48.23–55.08)	24.50	1.41 (1.28–1.56)
	80+	250	1,620	218	134.55 (127.70–141.41)	111.20	1.09 (0.92–1.29)
Cardiovascular causes (390–459)							
Male subjects							
	40–59	749	3,297	48	14.56 (11.00–18.12)	2.05	5.47 (4.18–7.15)
	60–79	1,297	7,196	248	34.46 (31.47–37.46)	17.01	1.96 (1.72–2.23)
	80+	131	919	74	80.50 (74.47–86.53)	60.17	1.39 (1.10–1.76)
Female subjects							
	40–59	464	2163	14	6.47 (3.29–9.65)	0.83	5.60 (3.44–9.14)
	60–79	1,037	5,401	185	34.25 (30.80–37.71)	9.71	3.24 (2.81–3.74)
	80+	250	1,620	118	72.83 (67.62–78.04)	51.06	1.47 (1.22–1.77)
Ischemic heart disease (410–414)							
Male subjects							
	40–59	749	3,297	38	11.53 (8.26–14.79)	1.59	5.50 (4.07–7.43)
	60–79	1,297	7,196	185	25.71 (22.86–28.56)	11.43	2.18 (1.88–2.53)
	80+	131	919	50	54.39 (46.20–62.59)	34.21	1.64 (1.23–2.19)
Female subjects							
	40–59	464	2,163	12	5.55 (2.58–8.52)	0.41	9.28 (5.60–15.38)
	60–79	1,037	5,401	123	22.77 (19.58–25.97)	5.79	3.62 (3.04–4.32)
	80+	250	1,620	65	40.12 (33.74–46.49)	24.84	1.65 (1.29–2.12)
Cerebrovascular disease (430–438)							
Male subjects							
	40–59	749	3,297	8	2.43 (0.79–4.07)	0.27	7.15 (3.74–13.69)
	60–79	1,297	7,196	45	6.25 (4.54–7.97)	3.05	1.98 (1.46–2.68)
	80+	131	919	14	15.23 (8.39–22.07)	15.15	1.05 (0.61–1.80)
Female subjects							
	40–59	464	2,163	0	0	0.26	—
	60–79	1,037	5,401	44	8.15 (5.93–10.36)	2.31	3.22 (2.39–4.33)
	80+	250	1,620	36	22.22 (16.43–28.01)	17.65	1.31 (0.93–1.83)

Relative death rates are shown only where ≥3 deaths occurred. *Local people with diabetes relative to the local nondiabetic population.

to be higher for people with type 1 diabetes than those with type 2 diabetes. Two deaths were certified as caused by acute metabolic complications of diabetes. The all-cause death rates of people with type 1 diabetes and renal impairment are shown in Table 3 (as well as the data on type 1 diabetes), and the data on type 2 diabetes show significantly higher death rates in people with renal impairment compared with those with normal, or relatively normal, renal function (maximum relative rate 4.98 [95% CI 2.35–10.57]).

CONCLUSIONS — These data demonstrate that there is significant excess mortality from cardiovascular causes in our population, in both sexes and for both type 1 and type 2 diabetes. There were no consistent increases in noncardiovascular death rates, except for renal disease.

Direct comparison of our results with other studies is difficult because most previous U.K. reports have used selected groups as the basis of their study and are thus open to selection bias (6,10–12). Also, the variety of studied age groups and methods hinders comparison. In particular, the often-quoted standardized mortality ratio is affected by the age structure of the population under study and may therefore vary considerably, even if age-specific mortality rates are constant. Populations with diabetes have very different age structures compared with general populations, having a much lower proportion of young people (who make up a large proportion of general populations but have few deaths) and a much higher proportion of older people (who make up

Table 2—*Mortality of the population with type 1 diabetes compared with the population of Teesside without diabetes, 1994–1999*

Cause (ICD-9 codes)	Age (years)	Baseline no. of subjects	Person-years of follow-up	Deaths (*n*)	Death rate per 1,000 person-years (95% CI)	Nondiabetic death rate	Relative rate* (95% CI)
All causes							
Male subjects							
	0–39	286	1,542	4	2.59 (0.18–5.01)	0.86	2.73 (1.06–7.05)
	40–59	117	775	16	20.65 (12.44–28.85)	5.27	4.21 (2.68–6.33)
	60–79	23	156	9	57.73 (38.20–77.25)	39.27	1.72 (0.90–3.29)
Female subjects							
	0–39	230	1,236	3	2.43 (0–5.04)	0.45	5.15 (1.85–14.34)
	40–59	96	602	11	18.27 (9.29–27.25)	3.30	6.20 (3.68–10.43)
	60–79	9	82	9	109.48 (94.26–124.70)	24.60	7.31 (4.18–12.77)
Cardiovascular causes (390–459)							
Male subjects							
	0–39	286	1,542	1	0.65 (0–1.90)	0.09	—
	40–59	117	775	9	11.62 (4.86–18.37)	2.05	6.13 (3.44–10.93)
	60–79	23	156	9	57.73 (38.20–77.25)	17.01	4.06 (2.22–7.42)
Female subjects							
	0–39	230	1,236	0	0	0.04	—
	40–59	96	602	5	8.30 (1.61–15.00)	0.83	11.51 (5.72–23.19)
	60–79	9	82	8	97.32 (89.45–105.18)	9.71	18.31 (11.09–30.25)
Ischemic heart disease (410–414)							
Male subjects							
	0–39	286	1,542	1	0.65 (0–1.91)	0.04	—
	40–59	117	775	7	9.03 (2.92–15.15)	1.59	6.21 (3.23–11.94)
	60–79	23	156	9	57.73 (38.20–77.25)	11.43	5.96 (3.35–10.61)
Female subjects							
	0–39	230	1,236	0	0	0.01	—
	40–59	96	602	4	6.64 (0.55–12.74)	0.41	19.46 (9.57–39.55)
	60–79	9	82	5	60.82 (34.51–87.14)	5.79	19.24 (10.26–36.09)

Relative death rates are shown only where ≥3 deaths occurred. *Local people with diabetes relative to the local non diabetic population.

a smaller fraction of the general population but contribute the most deaths). The age structure of populations with diabetes varies internationally (26), reflecting variations in general populations, differences in the age of onset of diabetes between populations, and differences in the death rates of people with diabetes. It is therefore difficult to know how much of the variation in standardized mortality ratios between studies is caused by true differences in mortality and how much is caused by differences in the age structures of the standard populations used. Therefore, the best measures to use in such comparisons are age- and cause-specific death rates, which are rarely reported, perhaps because of sample size limitations.

We could find only two reports from the last 10 years containing age- and cause-specific death rates, and we have compared our results with data from these reports. In the 1980s, the ischemic heart disease death rates of U.S. people with diabetes were 19.5 deaths per 1,000 person years for men and 7.2 for women aged 55–64 years, and those rates were 37.7 for men and 23.3 for women aged 65–74 years (15). These data for men are comparable to our study results (Table 1), although we did not find significantly lower death rates in women. However, it should be noted that the same study (15) demonstrated that ischemic heart disease death rates for diabetic women in the U.S. had risen since a previous survey, whereas the rates for diabetic men had been static or had declined. The lower death rates of diabetic U.S. women in comparison to our study may therefore be a consequence of the different time period of study, or they may reflect a genuine difference in mortality between the U.S. and South Tees. We have derived cardiovascular death rates of 10.44 deaths per 1,000 person-years for men and 6.35 for women aged 40–59 years from a recently published U.K. study of patients with young-onset diabetes (27). These data are similar to those for people of the same age with type 1 diabetes in our study (11.62 and 8.30, respectively).

We have chosen to highlight both the relative and absolute increases in death rates because although relative differences are useful in highlighting the importance of particular risk factors in disease etiology, they may be less useful in guiding clinical interventions, when a person's absolute risk of an adverse event is of more interest. The relative excess of cardiovascular mortality is greater in women than in men, particularly for type 1 diabetes, suggesting that diabetes is a more important risk factor in women than

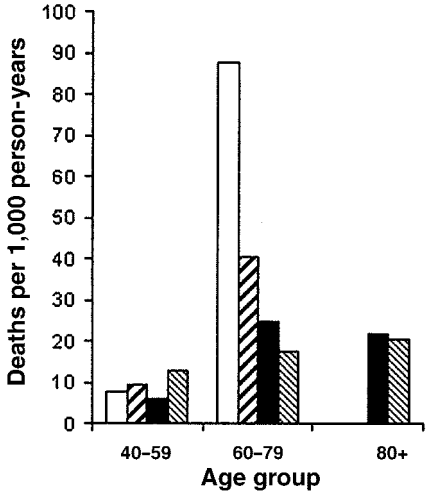

Figure 1—*Absolute excess cardiovascular mortality (i.e., age-, sex-, and cause-specific mortality) in the diabetic cohort minus mortality in the nondiabetic population. □, Female subjects with type 1 diabetes; ▨, male subjects with type 1 diabetes; ■, female subjects with type 2 diabetes; ▧, male subjects with type 2 diabetes.*

men, in accordance with previous studies (28,29). It can be seen from Fig. 1 that the absolute excess of cardiovascular deaths is also higher in women age >60 years, perhaps surprising when you consider that in the nondiabetic population aged 60–79 years, the cardiovascular death rate in women is approximately half that of men (9.71 vs. 17.01 deaths per 1,000 person-years). The high absolute excess mortality is of importance when considered from a public heath perspective because it suggests that diabetes will lead to more premature deaths in women than men, since the vast majority of cardiovascular deaths occur in the >60-year age group, where women have the highest absolute excess mortality. Because the majority of these excess deaths are as a result of ischemic heart disease, there is a potential for rigorous risk factor management and prevention.

The data on death rates in the subset of our cohort with renal impairment at baseline emphasize the dramatic relationship between renal dysfunction and the survival of people with diabetes. This increased mortality is not as apparent when relying only on a certified underlying cause of death of renal failure. It is now accepted that data relying on an underlying cause of death of diabetes markedly underestimated the impact of diabetes on mortality (30,31). The situation for renal disease is likely to be similar; for example, one study reported renal disease being certified as the underlying cause of death in only 40% of patients with end stage renal failure (32). The data for deaths certified as caused by renal failure will therefore substantially underestimate the contribution of renal failure to excess mortality in people with diabetes. From our data (Table 3), people with diabetes and renal impairment are clearly at extremely high risk of death and, because 75% of deaths in this group were from cardiovascular disease, they might also benefit from early identification and treatment of risk factors.

In conclusion, we have shown that diabetes confers an excess mortality from cardiovascular causes, even in a community with an increased death rate in the background population. This excess is present in both sexes and in absolute terms is highest in women aged >60 years and in those with renal impairment. These populations might benefit from very aggressive management of cardiovascular risk factors.

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Table 3—*All-cause death rates in the population with diabetes of Teesside, 1994–1999, by baseline renal function*

Baseline renal status	Age (years)	Baseline no. of subjects	Percentage who died during study	Person-years of follow-up	Death rate per 1000 person-years (95% CI)	Relative rate (95% CI)*
Type 1 diabetic subjects						
<150 μmol/l						
	0–39	510	1.8	2750	2.55 (0.75–4.34)	—
	40–59	204	12.7	1,330	17.29 (11.35–23.22)	—
	60–79	28	39.3	222	63.14 (47.42–78.86)	—
>150 μmol/l						
	0–39	6	0	28	0	N/A
	40–59	9	55.6	46	86.09 (63.03–109.16)	4.98 (2.35–10.57)
	60–79	4	75	16	244.11 (89.30–398.92)	3.87 (1.79–8.35)
Type 2 diabetic subjects						
<150 μmol/l						
	40–59	1,194	10.9	5,402	16.66 (13.75–19.57)	—
	60–79	2,250	31.3	12,307	51.60 (49.33–53.86)	—
	80+	351	61.5	2,409	135.73 (130.00–141.46)	—
>150 μmol/l						
	40–59	19	57.9	58	121.16 (93.40–148.92)	7.27 (4.11–12.86)
	60–79	84	69	290	189.67 (161.78–217.56)	3.68 (3.03–4.46)
	80+	30	90	130	260.90 (202.35–319.46)	1.92 (1.60–2.31)

*Death rates in those with creatinine >150 μmol/l compared with those with creatinine <150 μmol/l.

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