Cause-Specific Mortality in a Population-Based Study of Diabetes

ABSTRACT

Background. Mortality from vascular diseases has been reported to be high in diabetic persons.

Methods. To evaluate mortality from these and other specific causes, we examined cause-specific age-sex standardized mortality ratios in a geographically defined population of younger onset (diagnosed before age 30 and taking insulin, n = 1200) and older onset (diagnosed after age 30, n = 1772) diabetic persons followed for 8.5 years. Cause of death was determined from death certificates.

Results. In younger onset persons, age-sex standardized mortality ratios were significantly high ($P < .05$) for all causes of death (7.5) as well as for diabetes (191), all heart disease (9.1), ischemic heart disease (10.1), other heart disease (6.3), nephritis and nephrosis (41.2), accidents (2.9), and all other causes (3.2). In older onset persons, age-sex standardized mortality ratios were significantly high for all causes of death (2.0) as well as for diabetes (16.8), all heart disease (2.3), ischemic heart disease (2.3), other heart disease (2.1), stroke (2.0), and pneumonia and influenza (1.7).

Conclusions. Diabetic persons experience very high mortality, especially from vascular diseases, compared to the general population. (*Am J Public Health.* 1991;81:1158–1162)

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Introduction

Diabetic persons have been shown to be at greater risk of mortality from cardiovascular disease,[1–18] stroke,[1,2,5,9,11] and renal disease[14,19] compared to nondiabetic persons. Risk estimates for cancer have been variable.[1,3,11,14,15,20] Many of these earlier results are based on clinic populations, include only people with type I or type II diabetes, include males only, or are based on small numbers of cases. Thus, the results of many of these studies may not be applicable to a wider diabetic population.

In the current investigation we examine data from a population-based study, the Wisconsin Epidemiologic Study of Diabetic Retinopathy. Cause-specific mortality from this sample of diabetic persons is compared to the general population.

Methods

The study population has been described in detail in previous reports.[21–23] The study area is composed of 11 counties in southern Wisconsin (1980 population of 839 324). Diabetic persons were identified by a review of the records of 452 of the 457 physicians providing primary care to diabetic persons in the year beginning July 1, 1979. Chart reviews were done on 9841 patients. Of these, 558 were excluded because they were confined to nursing homes, had died prior to July 1, 1979, had incorrect diagnostic codes, had moved, or had gestational diabetes.

A two-part sample of 2990 of the remaining 9283 patients was selected on July 1, 1980, for examination. The first part consisted of all persons diagnosed before age 30 and taking insulin, referred to as younger onset (n = 1210). The second part consisted of a probability sample of persons diagnosed as having diabetes after age 30 confirmed by a random or postprandial serum glucose of at least 11.1 mmol/L or a fasting serum glucose of at least 7.8 mmol/L on at least two occasions, referred to as older onset (n = 1780). The specifics of the sampling strategy and exact proportions appear in an earlier publication, but approximate proportions were 25% for eligible persons with 0 to 4 or 5 to 14 years duration and 100% for persons with 15 or more years of diabetes.[23] Of the older onset group, 824 were taking insulin and 956 were not. Because it was not possible to examine the entire population, these sample sizes were chosen to ensure that an adequate number of cases of diabetic retinopathy would be found to evaluate risk factors for this complication.

Of the original sample, 18 (10 younger onset and 8 older onset) had died or were lost prior to July 1, 1980. These persons were excluded from further analysis. The remaining persons were contacted annually by telephone to determine vital status. In addition, relatives, designated contact persons, and physicians were contacted, and newspaper obituaries were reviewed daily. An annual request was made to the Wisconsin Center for Health Statistics, Section of Vital Statistics, for death certificate information. Wisconsin death rec-

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ords through 1988 have been searched. Finally, information on persons who moved out of Wisconsin and were suspected of being deceased and persons lost to follow-up was submitted to the National Death Index at the National Center for Health Statistics for matching against national death data through 1987.

The study period was from July 1, 1980, through December 31, 1988. Only deaths that had been confirmed by a death certificate were included in the analysis. Persons who were thought to be deceased but for whom a death certificate could not be located were considered to be alive as of the last contact date they were known to be alive. An analysis was undertaken at this time because nearly half of the older onset group had died, affording adequate deaths to examine a number of underlying causes. While the number of deaths in the younger onset group is considerably smaller and should probably be regarded as preliminary, it is still large enough to investigate the major causes of death.

All medical conditions on the Wisconsin death certificate were coded by trained nosologists in the Wisconsin Division of Health using the International Classification of Diseases, Ninth Revision (ICD-9). The underlying cause of death was selected by the Automated Classification of Medical Entities computer program.[24,25] Out-of-state certificates were coded and processed in the same manner. The cause-specific mortality analysis of the present investigation was based on the underlying cause of death.

Standardized mortality ratios (SMR) were used to compare the mortality experience of the two diabetes groups with that of the general Wisconsin population.[26] The Wisconsin rather than the US population was used as the standard because it is closer in racial and ethnic composition to the diabetic population, which is predominately non-Hispanic White. Age-, sex-, and cause-specific deaths and age- and sex-specific population estimates for the standard population were obtained from published tables.[27,28]

Results

Males comprised 52.2% of the younger onset group and 45% of the older onset group. Mean age at diagnosis and standard deviation (SD) in the younger onset group was 14.6 ± 7.6 years. In the older onset group, mean age ± SD at diagnosis was 55.5 ± 12.6 years. Mean age ± SD at the start of the study was 28.4 ± 13.3 and 66.7 ± 11.5 years in the younger and older onset groups, respectively.

TABLE 1—Vital Status of Younger and Older Onset Diabetic Persons, Wisconsin Epidemiologic Study of Diabetic Retinopathy, 1980–1988

Status	Younger Onset		Older Onset	
	n	%	n	%
Confirmed dead	145	12.1	859	48.5
Suspected dead[a]	5	0.4	17	1.0
Alive at last contact	1039	86.6	883	49.8
Lost to follow-up[b]	11	0.9	13	0.7
Total	1200	100.0	1772	100.0

[a]Treated as alive as of last contact at which known to be living.
[b]No contact for more than 2 years.

The vital status of the younger and older onset groups is presented in Table 1. There have been 145 (12.1%) and 859 (48.5%) confirmed deaths in the younger and older onset groups, respectively. Only 5 (0.4%) younger onset and 17 (1%) older onset deaths have not been confirmed. In addition, only 11 (0.9%) younger onset and 13 (0.7%) older onset persons have been lost to follow-up.

Table 2 presents the distribution of underlying cause of death among diabetic persons for the 12 most common causes of death in Wisconsin. In the younger onset group, diabetes was the leading underlying cause of death, accounting for 44.1% of all deaths. This was followed by heart disease (30.3%) and accidents (6.2%). In the older onset group, heart disease (48.8%) was the leading underlying cause of death, followed by diabetes (15.3%), malignant neoplasms (9.9%), and cerebrovascular disease (9.5%).

Standardized mortality ratios (SMR) by cause of death in the younger onset group are shown in Table 3. Mortality from all causes was 7.5 times more than expected from the general Wisconsin population and was more in excess in females (8.9) than in males (6.8). Among specific underlying causes of death, mortality from diabetes was 191 times greater than that expected. The SMR for heart disease was 9.1, with the excess being greater in females (10.3) than in males (8.7). The difference was more pronounced for ischemic heart disease (SMR of 13.5 in females, 9.1 in males). However, excess mortality for other heart disease was greater in males (7.3) than in females (4.5). There was also a sex difference with respect to mortality from accidents. The SMR for females (5.9) was significantly different from unity while in males it was not (2.0). The only other statistically significant excess mortality was due to nephritis and nephrosis (41.2). There were too few deaths from this cause to separate the sexes. Other SMRs, while substantially greater than unity, were not statistically significant, possibly due to a lack of power because of the small numbers of observed and expected deaths (Table 3).

Table 4 displays SMRs by cause of death in the older onset group. Mortality from all causes was twice the expected, and the excess was slightly greater in females (2.2) than males (1.9). As in the younger onset group, the greatest excess was due to diabetes (16.8). Mortality from heart disease was 2.3 times the expected and affected the sexes equally. Excess mortality due to ischemic heart disease was slightly higher in males while that due to other heart disease was higher in females. Cerebrovascular disease mortality was twice the expected. The only other statistically significant excess mortality was due to pneumonia and influenza (1.7).

Discussion

Many of the studies of cause-specific mortality among diabetic persons compared to nondiabetic persons are of clinic populations,[2,5,14,20] industrial or worker groups,[1,4,9,10,17] or other groups that are not population-based.[11] Clinic populations of diabetic persons may be biased in that they may be more likely to be suffering from complications of diabetes and have a poorer survival experience. Indeed, we have shown that in terms of all-cause mortality, diabetic persons with ocular diseases are at a disadvantage compared to those without.[29] On the other hand, studies based on worker groups may experience bias due to the "healthy worker" effect. Thus, population-based studies or studies based on a representative sample of a population offer the best opportunities for assessing the effect of diabetes on mor-

TABLE 2—Distribution of Cause of Death in Younger and Older Onset Diabetic Persons, Wisconsin Epidemiologic Study of Diabetic Retinopathy, 1980–1988

Cause of death	ICD-9 Codes	Younger Onset		Older Onset	
		n	Cause of Death (%)	n	Cause of Death (%)
Malignant neoplasms	140–208	4	2.8	85	9.9
Diabetes mellitus	250	64	44.1	131	15.3
Heart disease	391–398,402,404–429	44	30.3	419	48.8
Ischemic heart disease	410–414	36	24.8	326	38.0
Other heart disease	391–398,402,404,415–429	8	5.5	93	10.8
Cerebrovascular disease	430–438	3	2.1	82	9.5
Atherosclerosis	440	0	0	10	1.2
Other arterial disease	441–448	0	0	6	0.7
Pneumonia and influenza	480–487	2	1.4	27	3.1
Chronic obstructive pulmonary disease	490–496	1	0.7	12	1.4
Chronic liver disease and cirrhosis	571	2	1.4	7	0.8
Nephritis and nephrosis	580–589	4	2.8	8	0.9
Accidents	800–949	9	6.2	12	1.4
Suicides	950–959	4	2.8	1	0.1
All other causes	—	8	5.5	59	6.9
Total	—	145	100.0	859	100.0

TABLE 3—Observed (O) and Expected (E) Deaths, Age- and Sex-standardized Mortality Ratios (SMR), and 95% Confidence Intervals (CI) by Cause of Death and Sex in Younger Onset Diabetic Persons, Wisconsin Epidemiologic Study of Diabetic Retinopathy, 1980–1988

Cause of Death (ICD-9 Code)	Male			Female			Total		
	O/E	SMR	95% CI	O/E	SMR	95% CI	O/E	SMR	95% CI
Malignant neoplasms (140–208)	—	—	—	—	—	—	4/5.1	0.8	0.2–2.0
Diabetes mellitus (250)	37/0.19	199.6	140.5–275.1	27/0.15	180.3	118.8–262.3	64/0.34	190.9	147.0–243.8
Heart disease (391–398, 402, 404–429)	31/3.6	8.7	5.9–12.3	13/1.3	10.3	5.5–17.7	44/4.8	9.1	6.6–12.2
Ischemic heart disease (410–414)	25/2.8	9.1	5.9–13.4	11/0.81	13.5	6.7–24.2	36/3.6	10.1	7.1–13.9
Other heart disease (391–398, 402, 404, 415–429)	6/0.82	7.3	2.7–15.9	2/0.44	4.5	0.5–16.3	8/1.3	6.3	2.7–12.5
Cerebrovascular disease (430–438)	—	—	—	—	—	—	3/0.74	4.1	0.8–11.8
Atherosclerosis (440)	—	—	—	—	—	—	0/0.05	0	—
Other arterial disease (441–448)	—	—	—	—	—	—	0/0.16	0	—
Pneumonia and influenza (480–487)	—	—	—	—	—	—	2/0.26	7.6	0.9–27.4
Chronic obstructive pulmonary disease (490–496)	—	—	—	—	—	—	1/0.40	2.5	0–13.9
Chronic liver disease and cirrhosis (571)	—	—	—	—	—	—	2/0.42	4.8	0.5–17.2
Nephritis and nephrosis (580–589)	—	—	—	—	—	—	4/0.10	41.2	11.1–105.5
Accidents (800–949)	5/2.4	2.0	0.7–4.8	4/0.68	5.9	1.6–15.2	9/3.1	2.9	1.3–5.5
Suicides (950–959)	—	—	—	—	—	—	4/1.4	2.8	0.8–7.3
All other causes	5/1.6	3.2	1.0–7.4	3/0.91	3.3	0.7–9.6	8/2.5	3.2	1.4–6.4
Total	89/13.1	6.8	5.5–8.4	56/6.3	8.9	6.7–11.5	145/19.4	7.5	6.3–8.8

Note. Sex-specific SMRs are not given where there are fewer than five total deaths.

tality. The present population-based study is notable for its substantial population of both younger and older onset diabetic persons of both sexes.

The population-based studies carried out in the United States have all found an excess mortality from cardiovascular disease.[3,6,7,12,16,18] These studies found SMR and relative risks (RR) in the range of 1.7 to 4.9. Although SMR and RR are not strictly comparable, they may give similar results in practice. The studies cited include both insulin- and noninsulin-dependent diabetic persons and thus are probably most comparable with our older onset group. In our older onset group we found an SMR of 2.3 for cardiovascular disease. This agrees remarkably well with the other population-based studies.[3,6,7,12,16,18] In addition, several of these studies note a differential effect of sex on cardiovascular disease

TABLE 4—Observed (O) and Expected (E) Deaths, Age- and Sex-standardized Mortality Ratios (SMR), and 95% Confidence Intervals (CI) by Cause of Death and Sex in Older Onset Diabetic Persons, Wisconsin Epidemiologic Study of Diabetic Retinopathy, 1980–1988

	Male			Female			Total		
Cause of Death (ICD-9 Code)	O/E	SMR	95% CI	O/E	SMR	95% CI	O/E	SMR	95% CI
Malignant neoplasms (140–208)	38/49.0	0.8	0.5–1.1	47/41.1	1.1	0.8–1.5	85/90.2	0.9	0.8–1.2
Diabetes mellitus (250)	49/3.2	15.4	11.4–20.4	82/4.6	17.6	14.0–21.9	131/7.8	16.8	14.0–19.9
Heart disease (391–398, 402, 404–429)	216/94.9	2.3	2.0–2.6	203/89.4	2.3	2.0/2.6	419/184.3	2.3	2.1–2.5
Ischemic heart disease (410–414)	179/73.2	2.4	2.1–2.8	147/65.8	2.2	1.9–2.6	326/139.0	2.3	2.1–2.6
Other heart disease (391–398, 402, 404, 415–429)	37/21.7	1.7	1.2–2.3	56/23.6	2.4	1.8–3.1	93/45.3	2.1	1.7–2.5
Cerebrovascular disease (430–438)	30/17.1	1.8	1.2–2.5	52/23.4	2.2	1.7–2.9	82/40.6	2.0	1.6–2.5
Atherosclerosis (440)	6/3.3	1.8	0.7–4.0	4/4.3	0.9	0.3–2.4	10/7.6	1.3	0.6–2.4
Other arterial disease (441–448)	3/3.6	0.8	0.2–2.5	3/2.2	1.4	0.3–4.0	6/5.8	1.0	0.4–2.3
Pneumonia and influenza (480–487)	14/8.7	1.6	0.9–2.7	13/7.6	1.7	0.9–2.9	27/16.3	1.7	1.1–2.4
Chronic obstructive pulmonary disease (490–496)	10/9.9	1.0	0.5–1.9	2/4.5	0.4	0–1.6	12/14.4	0.8	0.4–1.5
Chronic liver disease and cirrhosis (571)	5/1.9	2.6	0.8–6.2	2/1.2	1.7	0.2–6.2	7/3.1	2.3	0.9–4.7
Nephritis and nephrosis (580–589)	3/2.3	1.3	0.3–3.9	5/1.9	2.6	0.8–6.1	8/4.2	1.9	0.8–3.8
Accidents (800–949)	3/4.0	0.7	0.2–2.2	9/2.9	3.1	1.4–5.9	12/6.9	1.7	0.9–3.0
Suicides (950–959)	—	—	—	—	—	—	1/2.0	0.5	0–2.8
All other causes	31/21.6	1.4	1.0–2.0	28/24.4	1.1	0.8–1.7	59/46.0	1.3	1.0–1.7
Total	409/221.1	1.9	1.7–2.0	450/208.0	2.2	2.0–2.4	859/429.1	2.0	1.9–2.1

Note: Sex-specific SMRs are not given where there are fewer than five total deaths.

mortality in diabetic persons wherein females are at greater risk relative to nondiabetic persons than males.[6,7,12] However, this finding is not universal.[16,18] We also find no sex differential for either all heart disease or ischemic heart disease in the older onset group, but we do find one in the younger onset group, especially with respect to ischemic heart disease. However, in the Framingham study a trend is noted where the sex differential in cardiovascular disease incidence diminishes with advancing age.[6] If this effect carried over to mortality, it could explain our result.

Several studies have also investigated cerebrovascular disease mortality among diabetic persons.[1,2,5,9,11] Although none of these studies are population based, most of them found varying degrees of excess cerebrovascular disease mortality among diabetic persons. We found a significant twofold excess mortality from cerebrovascular disease in our older onset group. In the younger onset group there is a fourfold excess cerebrovascular disease mortality, but it does not reach statistical significance. However, the SMR is based on only three deaths.

Cancer was investigated in several studies with varying results.[1,3,11,14,15,20] In some studies cancer mortality did not differ from expected,[1,3,11,14] in one it was higher than expected,[15] and in one it was lower than expected in males only.[20] In two of these the results are based on small numbers of deaths,[1,14] and only two are population based.[3,15] We did not find that cancer mortality differed from the expected in either the younger or older onset groups.

Renal disease mortality has been found to be high in younger diabetic persons,[14] but the effect decreases sharply with age.[19] We also found excess mortality due to renal disease in the younger onset group. Mortality due to renal disease in the older onset group, while nearly double that expected, was not statistically significant. However, the real impact of renal disease on mortality in our population may be underestimated because some cases may also be included under diabetes as ICD-9 code 250.4, Diabetes with renal manifestations. If we add these to the other cases of renal disease, then the SMR for nephritis and nephrosis in the younger onset group is 72.1 (95% CI = 28.9–148.5), and in the older onset group it is 2.6 (95% CI = 1.3–4.7).

Two studies reporting on mortality from accidents and suicides combined, showed lower than expected mortality in males and higher than expected mortality in females.[2,14] In the younger onset group, we found higher than expected mortality from accidents in both males and females. In the older onset group, males had lower than expected and females had higher than expected mortality from accidents. In both groups only the result for females was statistically significant. Also, we found higher than expected suicide mortality in the younger onset group and lower than expected in the older onset group, but neither is statistically significant.

The only other significant result is higher than expected mortality due to pneumonia and influenza in the older onset group. We have not found this specific cause of death reported elsewhere. However, because we have a large number of deaths, especially in the older onset group, we are able to examine more specific causes of death than other population-based studies with smaller samples of diabetic persons. □

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