

# Diabetes Duration and Cause-Specific Mortality in the Verona Diabetes Study

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**OBJECTIVE** — To examine the 10-year mortality and effect of diabetes duration on overall and cause-specific mortality in diabetic subjects in the Verona Diabetes Study (VDS).

**RESEARCH DESIGN AND METHODS** — Records from diabetes clinics, family physicians, and a drug consumption database were used to identify 5,818 subjects  $\geq 45$  years of age with type 2 diabetes who were alive and residing in Verona, Italy, on 31 December 1986. Vital status of each subject was ascertained on 31 December 1996. Underlying causes of death were determined from death certificates. Death rates and death rate ratios (DRRs) were computed and standardized to the population of Verona in 1991.

**RESULTS** — During the study, 2,328 subjects died; 974 deaths were attributable to cardiovascular disease, 517 to neoplasms, 324 to diabetes-related diseases, 134 to digestive diseases, 250 to other natural causes, and 48 to external causes. There were 81 subjects who died of unknown causes. Death rates from natural causes were higher in men than in women (DRR 1.4, 95% CI 1.2–1.5) and rose in both sexes with increasing duration of diabetes ( $P = 0.001$ ). Among the natural causes of death, those for diabetes-related diseases were strongly related to diabetes duration ( $P = 0.001$ ); a modest relationship with duration was also found for ischemic heart disease in men ( $P = 0.07$ ).

**CONCLUSIONS** — Cardiovascular disease was the principal cause of death among people with type 2 diabetes in the VDS. Rates for natural causes of death rose with increasing duration of diabetes. Deaths from diabetes-related diseases in both sexes and from ischemic heart disease in men were largely responsible for this increase.

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Death rates are up to 3 times as high in people with type 2 diabetes as in those without (1–3), but the causes of these excess deaths may vary widely by population. In the U.S., cardiovascular disease is the principal cause of death in whites with type 2 diabetes (4), but renal disease is the major cause in Native Americans (5). One factor that plays an important role in determining the cause of death

in people with diabetes is the duration of diabetes.

The life-threatening complications of diabetes generally require many years to develop, but even deaths attributed to diseases other than diabetes, such as ischemic heart disease, may occur more frequently in people with diabetes of longer duration.

In this article, we focus on the effect of diabetes duration on overall and cause-spe-

cific mortality in subjects with type 2 diabetes from the Verona Diabetes Study (VDS). We also examine the 10-year cause-specific mortality, extending the 5-year follow-up study reported in a previous article (6).

## RESEARCH DESIGN AND

**METHODS** — The design of the VDS was described previously (7,8). Briefly, records from diabetes clinics, family physicians, and a drug consumption database were used to identify 7,148 type 2 diabetic patients who were alive and residing in Verona on 31 December 1986. This cohort represented 76% of the known type 2 diabetic population of Verona (9). The 5,818 subjects who were  $\geq 45$  years of age at baseline were included in this report, and the vital status of each of these subjects was ascertained on 31 December 1996. Underlying causes of death were determined from death certificates using the mortality records of the Verona Social Health Unit, coded in accordance with the guidelines of the *International Classification of Diseases, Ninth Revision* (ICD-9) (10). Deaths were considered “natural” if they were caused by disease (ICD-9 codes 001–799) and considered “external” if they were caused by injury or poisoning (ICD-9 codes 800–999).

## Statistical analysis

Death rates were calculated as the number of subjects who died, divided by the person-years of follow-up, and expressed per 1,000/year. The period of risk extended from 31 December 1986 to death or 31 December 1996. Person-time was accumulated in age- and sex-specific strata and, for some analyses, in diabetes duration-specific or diabetes treatment-specific strata. When subjects changed from one age or diabetes duration stratum to another, their person-time accumulated in the corresponding stratum.

Age and age-sex adjusted death rates were standardized to the population of Verona in 1991.

Death rate ratios (DRRs) were calculated from the standardized rates to evaluate sex differences in mortality. CIs were derived from the logarithms of the rate ratios (11). Standardized rate ratios (SRRs) were used to

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**Abbreviations:** DRR, death rate ratio; ICD-9, *International Classification of Diseases, Ninth Revision*; OHD, oral hypoglycemic drugs; SRR, standardized rate ratio; VDS, Verona Diabetes Study.

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

**Table 1—Deaths and death rates (per 1,000/year) by age and sex**

Age (years)	Men			Women		
	Deaths (n)	Person-years	Death rate	Deaths (n)	Person-years	Death rate
45–54	22	1,841.8	11.9	8	1,062.1	7.5
55–64	164	6,431.6	25.5	51	4,574.1	11.2
65–74	383	8,115.5	47.2	279	8,736.9	31.9
≥75	493	5,135.3	96.0	928	10,555.9	87.9
Total	1,062	21,524.2	49.3	1,266	24,929.0	50.8

compare the mortality in the VDS population with that in the population of Verona.

The *P* values for trend were determined by the Mantel extension test (12).

**RESULTS** — Of the 5,818 diabetic subjects (2,700 men, 3,118 women) ≥45 years of age, 2,328 (1,062 men, 1,266 women) died during the follow-up. The median age at baseline was 67 years (45–96), and the median duration of diabetes was 9.5 years (0.5–71). Death rates were higher in men than in women and rose with increasing age (Table 1).

Diabetes was treated with diet in 772 subjects (432 men, 340 women), with oral hypoglycemic drugs (OHD) in 4,630 subjects (2,140 men, 2,490 women), and with insulin alone or in combination with OHD in 386 subjects (149 men, 237 women). The age-sex-adjusted death rate was highest in subjects treated with insulin and lowest in those treated with diet.

Of the 2,328 deaths, 974 were attributable to cardiovascular disease, 517 to neoplasms, 324 to diabetes-related dis-

eases, 134 to digestive diseases, 250 to other natural causes, and 48 to external causes; 81 subjects died of unknown causes (Table 2).

Of the 974 deaths attributed to cardiovascular disease, 343 (35%) were attributable to ischemic heart disease and 235 (24%) to stroke. There were 396 (41%) deaths attributed to other causes: 136 to ill-defined complications of heart disease, 80 to hypertensive cardiovascular disease, 53 to atherosclerosis, 36 to dysrhythmias, 36 to heart failure, and 55 to other cardiovascular diseases.

Of the 517 deaths attributed to neoplasms, 202 (39%) were attributable to neoplasms of the digestive organs and peritoneum; 104 (20%) of the respiratory and intrathoracic organs; 84 (16%) of the genitourinary organs; 46 (9%) of the breast (all in women); 11 (2%) of the lip, oral cavity, and pharynx; and 70 (14%) of other or unspecified sites.

Of the 134 deaths attributed to digestive diseases, 90 (67%) were attributable to chronic liver disease and cirrhosis, 11

(8%) to hemorrhage, and 33 (25%) to other diseases.

Of the 250 deaths attributed to other natural causes, 142 (57%) were attributable to respiratory diseases, 35 (14%) to ill-defined conditions, 27 (11%) to genitourinary diseases, 24 (10%) to diseases of the nervous system and sense organs, 6 (2%) to diseases of blood and blood-forming organs, 6 (2%) to organic psychotic conditions, 5 (2%) to endocrine diseases or other metabolic and immunity disorders other than diabetes, 4 (2%) to infectious and parasitic diseases, and 1 (0.4%) to osteoarthritis.

The leading cause of death in both sexes was cardiovascular disease. Ischemic heart disease was the most common cause of cardiovascular deaths in men, and non-ischemic, principally hypertensive, atherosclerotic, or ill-defined cardiovascular diseases were the most common in women.

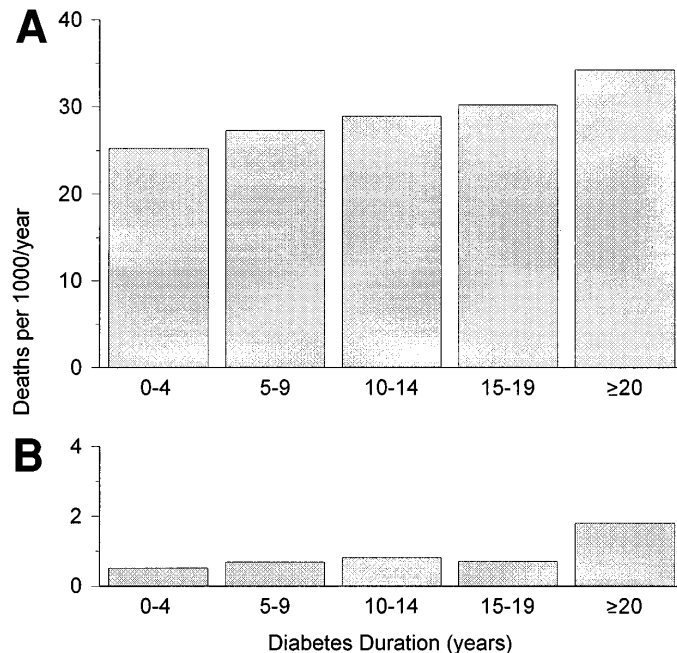
The overall death rate from natural causes was significantly higher in men than in women (DRR [men/women] 1.3; 95% CI 1.2–1.5). Higher death rates for malignant neoplasms (DRR 2.0; 1.6–2.6) and ischemic heart disease (1.8; 1.4–2.3) contributed to the excess mortality in men (Table 2). Men were also more likely to die from unknown causes (DRR 2.8; 1.6–4.7). Women had slightly higher death rates than men (DRR 0.9; 0.7–1.1) for only diabetes-related diseases.

Death rates rose with increasing duration of diabetes (Table 3). The death rate for natural causes was positively related to the duration of diabetes (*P* = 0.001) (Fig. 1A), but the death rate for external causes was unrelated to the duration (*P* = 0.95) (Fig.

**Table 2—Deaths, death rates (per 1,000/year), and DRRs for men and women for underlying causes of death**

Underlying cause of death	Men		Women		Both sexes		DRR (95% CI)
	Deaths (n)	Death rate	Deaths (n)	Death rate	Deaths (n)	Death rate	
Cardiovascular disease (390–459)	395	13.8	579	11.4	974	12.6	1.2 (1.1–1.4)
Ischemic heart disease (410–414)	168	6.3	175	3.6	343	4.7	1.8 (1.4–2.3)
Stroke (430–438)	83	2.7	153	2.8	235	2.8	1.0 (0.7–1.3)
Other cardiovascular diseases	116	4.9	279	5.0	396	5.0	1.0 (0.8–1.2)
Diabetes (250)	120	3.8	204	4.4	324	4.2	0.9 (0.7–1.1)
Digestive diseases (520–579)	74	3.0	60	2.2	134	2.5	1.4 (0.8–2.5)
Neoplasms (140–239)	299	10.5	218	5.1	517	7.3	2.0 (1.6–2.6)
Other natural causes	106	3.7	144	2.9	250	3.3	1.3 (0.9–1.8)
All natural causes	994	34.9	1,205	26.0	2,199	29.9	1.3 (1.2–1.5)
All external causes (800–999)	25	0.9	23	0.8	48	0.8	1.2 (0.5–3.1)
Unknown causes	43	2.0	38	0.7	81	1.3	2.8 (1.6–4.7)
All causes	1,062	37.8	1,266	27.5	2,328	32.0	1.4 (1.2–1.5)

Death rates are age-adjusted for each sex and age- and sex-adjusted for both sexes combined. The numbers in parentheses that follow the underlying causes of death are ICD-9 codes.



**Figure 1**—Age-sex-adjusted death rates (per 1,000/year) in the Verona diabetes cohort for natural ( $P = 0.001$ ) (A) and external ( $P = 0.95$ ) (B) causes in relation to duration of diabetes.

1B). Among the natural causes of death, those for diabetes-related diseases were strongly related to diabetes duration ( $P = 0.001$ ) (Fig. 2A); a modest relationship with duration was also found for deaths from ischemic heart disease in men ( $P = 0.07$ ) (Fig. 2B).

After exclusion of the group with  $\geq 20$  years' diabetes duration, the trend in diabetes duration was still significant for diabetes-related deaths in both men ( $P = 0.013$ ) and women ( $P = 0.014$ ).

The trend is not significant for ischemic heart deaths in men ( $P = 0.29$ ) and women ( $P = 0.50$ ), as already observed when the group with  $\geq 20$  years' diabetes duration was included. We also tested whether the relationship between duration and mortality is different in men and women (Cox model). The association was not significant for either diabetes ( $P = 0.49$ ) or ischemic heart diseases ( $P = 0.41$ ). In testing for an association between age and diabetes duration, we found a significant interaction only for diabetes in both men ( $P = 0.01$ ) and women ( $P < 0.01$ ).

**CONCLUSIONS** — In Verona, cardiovascular disease is the leading cause of death in individuals with type 2 diabetes, accounting for 44% of the deaths from natural causes. Ischemic heart disease was the single largest cause of cardiovascular

deaths in men, and the death rate rose with increasing duration of diabetes. By contrast, deaths from ischemic heart disease did not rise substantially with increasing duration in women, and the majority of cardiovascular deaths in women were attributed to causes other than ischemia. Whether these differences were attributable to sex differences in the certification or coding of causes of death (13) or to real differences in the causes of cardiovascular death cannot be determined from this study. A previous study in this population (6) found that although the death rate from cardiovascular disease in the diabetic patients was higher than in the general population, the impact of diabetes on cardiovascular deaths was not nearly as great as that in the U.S.

The relationship between diabetes duration and deaths from ischemic heart disease is controversial (14–16). In most studies, however, the duration of diabetes cannot be estimated precisely, and the misclassification of duration may obscure an important relationship. In Pima Indians, periodic glucose tolerance testing permits more precise estimates of the onset and duration of diabetes, and in this population, ischemic heart disease is strongly related to the duration of diabetes (15). Some investigators have suggested, however, that the increased cardiovascular disease mortality in people with type 2 diabetes is attributable to greater exposure to cardiovascular risk factors that precede the onset of diabetes and that the relationship with diabetes duration simply reflects increasing age and exposure to these factors (17).

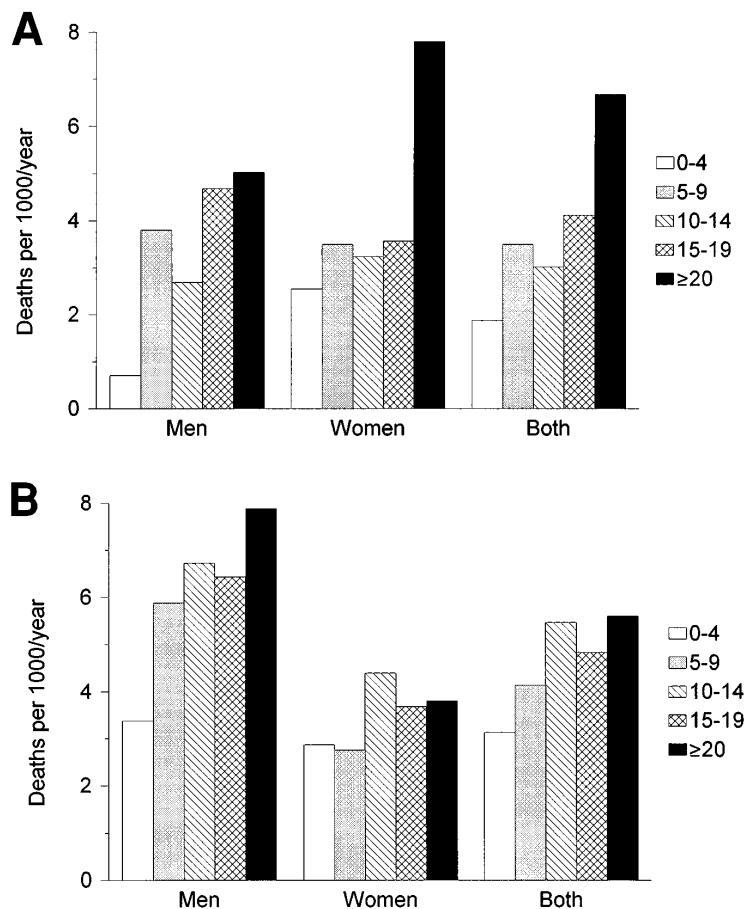
Malignant neoplasms accounted for 24% of the deaths from natural causes and were the second leading cause of death. Men were twice as likely to die from malignant neoplasms than women, undoubtedly as a consequence of a higher frequency of heavy smoking, since men had far more smoking-related neoplasms than women. All 11 neoplasms of the lip, oral cavity, and pharynx and 82 of 104 (79%) neoplasms of the larynx, trachea, bronchus, lung, and pleura occurred in men.

Deaths from chronic liver disease and cirrhosis accounted for 67% of the deaths attributed to digestive diseases. In a previous study (6), the Verona diabetic cohort was reported to have more than twice the death rate from liver cirrhosis than the general population. This observation was attributed in part to the effect of alcohol consumption on glucose tolerance and to a high rate of hepatitis infections in diabetic patients (6). In the present study, deaths from malignant neoplasms of the liver and intrahepatic bile ducts were also common, accounting for 10% ( $n = 53$ ; 32 men, 21

**Table 3**—Deaths and death rates (per 1,000/year) by duration of diabetes

Diabetes duration (years)	Deaths (n)	Person-years	Death rate (95% CI)	SRR (95% CI)
0–4	144	4,322.2	27.1 (22.3–31.9)	1.23 (1.19–1.27)
5–9	418	10,176.4	29.6 (26.2–32.9)	1.34 (1.30–1.38)
10–14	533	11,528.5	31.7 (28.1–35.2)	1.44 (1.40–1.48)
15–19	538	10,121.6	31.8 (28.3–35.2)	1.44 (1.41–1.48)
$\geq 20$	695	10,304.5	36.7 (31.3–42.2)	1.66 (1.62–1.70)

The death rates have been standardized for sex and age to the Verona population of 1991. SRRs have been computed with respect to the Verona population of 1991.



**Figure 2**—Age-sex-adjusted death rates (per 1,000/year) in the Verona diabetes cohort in relation to duration of diabetes. For diabetes-related causes,  $P = 0.004$  in men,  $P = 0.001$  in women, and  $P = 0.001$  in both sexes combined (A); for ischemic heart diseases,  $P = 0.07$  in men,  $P = 0.53$  in women, and  $P = 0.09$  in both sexes combined (B).

women) of all cancer deaths, and the death rates from these malignancies were significantly higher than those in the general population (standardized mortality ratio 1.3; 95% CI 1.0–1.8;  $P = 0.03$ ). To what extent the increased deaths from liver and intrahepatic bile duct neoplasms are attributable to alcohol consumption and hepatitis infection is not known (18,19).

In the VDS (7) and in studies performed in other populations (1–4), diabetes had a relatively greater impact in women than in men, as shown by the partial loss of the female survival advantage in diabetic patients. However, when absolute rates were considered, diabetes-related deaths were the only causes of death that occurred more frequently in women (Table 2), although the difference was not significant. These deaths were strongly related to the duration of diabetes in both sexes. Indeed, the significant increase in death rates with increasing duration of diabetes for all nat-

ural causes was almost entirely attributable to the rise in diabetes-related deaths. The higher death rate in subjects treated with insulin than in those treated with either diet or OHD is consistent with a previous study in this population that demonstrated that poorer glycemic control was associated with higher mortality (8). The data are also in agreement with those of the National Health and Nutritional Examination Survey I, in which mortality rates among diabetic subjects were higher in men than in women and higher in subjects using insulin than in those treated with diet alone (20).

The present study, like all studies comparing mortality in diabetic patients and the general population (21,22), is subject to the limitation of diabetes underreporting as an underlying cause of death (23,24). It was also only considered the underlying cause of death and not the associated cause.

In conclusion, cardiovascular disease was the principal cause of death among

people with type 2 diabetes in the VDS. Ischemic heart disease was the most frequent cause of cardiovascular death in men, whereas nonischemic cardiovascular deaths were more common in women. Rates for natural causes of death rose with increasing duration of diabetes. Deaths from diabetes-related diseases in both sexes and from ischemic heart disease in men were largely responsible for this increase.

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