Mortality Trends in Subjects With and Without Diabetes During 33 Years of Follow-up

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OBJECTIVE — Mortality rates have declined substantially over the past decades in the general population, but the situation among diabetic subjects is less clear. The aim of this study was to analyze mortality trends in diabetic and nondiabetic subjects during 1972–2004.

RESEARCH DESIGN AND METHODS — Since 1972, all patients with diabetes are entered in a diabetes register at Laxå Primary Health Care Center; 776 incident cases were recorded up to 2001. The register has been supplemented with a nondiabetic population of 3,880 subjects and with data from the National Cause of Death Register during 1972 to 2004.

RESULTS — During the 33-year follow-up period, 233 (62.0%) diabetic women and 240 (60.0%) diabetic men and 995 (52.9%) nondiabetic women and 1,082 (54.1%) nondiabetic men died. The age-adjusted hazard ratio (HR) for all-cause mortality among diabetic and nondiabetic subjects was 1.17 (P < 0.0021) for all, 1.22 (P < 0.007) for women, and 1.13 (P = 0.095) for men. The corresponding cardiovascular disease (CVD) mortality HRs were 1.33 (P < 0.0001), 1.41 (P < 0.0003), and 1.27 (P < 0.0093), respectively. The CVD mortality reduction across time was significant in nondiabetic subjects (P < 0.0001) and in men with diabetes (P = 0.014) but not in diabetic women (P = 0.69). The results regarding coronary heart disease (CHD) were similar (P < 0.0001, P < 0.006, and P = 0.17, respectively). The CVD and CHD mortality rate change across time was fairly linear in all groups.

CONCLUSIONS — Diabetic subjects had less mortality rate reduction during follow-up than nondiabetic subjects. However, the excess mortality risk for diabetic subjects was smaller than that found in other studies.

The excess mortality, mostly owing to cardiovascular disease (CVD), in diabetic subjects compared with nondiabetic subjects, is well documented (1–4) and has been shown to decline with increasing age at diagnosis (1,3,5). However, studies of the influence of sex on mortality risk for those with and without diabetes show conflicting results (1,6,7).

CVD incidence and mortality rates have declined in most developed countries, including Sweden, over the past decades (8–10). Because CVD is the major cause of death among diabetic and nondiabetic subjects, it would be expected that the general decline in mortality would be reflected in both groups. Data from Framingham reported parallel declines in CVD outcomes for diabetic and nondiabetic women and men between 1950 and 1995 (11). Another U.S. study (12) confirmed a mortality decline during 1971 to 2000 for diabetic men but not women, whereas a Canadian study (13) showed reduced mortality rates for both sexes during 1995 to 2005. A Danish study (14) reported a faster reduction in mortality in diabetic subjects than in a nondiabetic population between 1995 and 2006, and a Norwegian study (15) showed a substantial decrease in mortality from coronary heart disease (CHD) for both diabetic and nondiabetic subjects and for both sexes from the mid-1980s to the mid-1990s. A Swedish study (16) covering the period 1980–2004 showed improved survival rates in diabetic subjects, more so in diabetic women than in men, thereby narrowing the gap to nondiabetic women.

The aim of this study was to analyze mortality trends among diabetic and nondiabetic subjects over the time period 1972–2004 in a defined geographical area in Sweden and to test the hypothesis that changes in all-cause, CVD, and CHD mortality have been parallel among the two cohorts.

RESEARCH DESIGN AND METHODS

Diabetic subjects
The study was undertaken in Laxå, Örebro County, Sweden. From 1 January 1972 and onward all new cases of diabetes were entered into a diabetes register at Laxå Primary Health Care Center (PHCC). Patient record files at the local PHCC, at nearby PHCCs, at private practitioners’ offices, and at adjacent hospitals and prescription registers at the local pharmacies were scrutinized to find possible missing cases, as described in detail previously (17). During 1972 to 2001, altogether 776 new cases of diabetes were found, 36 type 1 and 740 type 2 diabetes.

Nondiabetic subjects

For each new diabetic subject, five (maximum number available) nondiabetic subjects were sampled in 2007 from the Laxå general population register, matched to the diabetic subjects by sex and age, sampled from the population register version of the diagnosis year, and required to not have a diabetes diagnosis at any time from baseline to end of follow-up. Several diabetes screening rounds during the study period were used to eliminate misclassification. No clinical
Mortality trends with and without diabetes

Table 1—Baseline characteristics among diabetic women and men

|                  | Women |          |          | Men |          |          |
|------------------|-------|----------|----------|-----|----------|----------|
|                  | Decade 1: 1972–1981 | Decade 2: 1982–1991 | Decade 3: 1992–2001 | Decade 1: 1972–1981 | Decade 2: 1982–1991 | Decade 3: 1992–2001 |
| n                | 131   | 140      | 105      | 133 | 154      | 113      |
| Age at diagnosis (years) | 65.0 ± 15.3 | 66.1 ± 13.4 | 62.1 ± 15.1 | 62.6 ± 14.1 | 61.2 ± 17.1 | 58.4 ± 14.6 |
| FBG (mmol/l)     | 9.6 ± 2.8 | 8.3 ± 2.3 | 7.4 ± 2.2* | 9.1 ± 2.6 | 9.1 ± 12.4 | 8.6 ± 3.6 |
| BMI (kg/m²)      | 30.2 ± 6.1 | 29.7 ± 6.0 | 31.2 ± 5.6 | 28.8 ± 3.4 | 28.0 ± 4.5 | 30.6 ± 4.8* |
| Smokers (%)      | 3.8    | 7.9      | 14.3†     | 12.0  | 15.6     | 18.6     |
| Ex-smokers (%)   | 3.1    | 5.0      | 7.6       | 8.3   | 20.1     | 31.0*    |
| AHD (%)          | 51.9   | 63.6     | 53.3‡     | 51.9  | 50.0     | 38.0     |
| Diabetes treatment during the first year |  |  |  |  |  |  |
| Diet only (%)    | 67.9   | 77.9     | 76.2†     | 63.2  | 71.4     | 82.3*    |
| OHA (%)          | 29.8   | 16.4     | 15.2†     | 32.3  | 20.1     | 8.8*     |
| OHA and insulin (%) | 2.3   | 0.0      | 0.0       | 3.0   | 0.6      | 3.5      |
| Insulin (%)      | 0.0    | 5.7      | 8.6       | 1.5   | 7.8      | 5.3      |

Data are means ± SD or %. *P < 0.001; †P < 0.01; ‡P < 0.05. AHD, antihypertensive drug; FBG, fasting blood glucose; OHA, oral hypoglycemic agent.

Statistical considerations

The data were analyzed using SAS (release 9.1, SAS Institute, Cary, NC). Simple differences between groups were tested with Student’s t test, variance analysis, or the X² test.

Survival analyses were performed with Cox’s proportional hazards regression, modeled with the outcome and time as the dependent variables and age, diabetes status, and year of diagnosis and inclusion to the study as independent variables and stratified for sex. In addition, two interaction terms, diabetes status-year of diagnosis and diabetes status-year of diagnosis-sex, were tested. The former was significant for some outcomes, which was used for further modeling.

For illustration purposes some of the results are shown for the three periods 1972–1981, 1982–1991, and 1992–2001, all based on the time of diabetes diagnosis. The follow-up time was right-truncated at 26, 20, and 10 years for the three partial study periods owing to small numbers.

Finally, to allow equal exposure times when mortality rate per year of diagnosis was analyzed, 3-year follow

Table 2—Mortality during follow-up 1972–2004 among diabetic and nondiabetic subjects

|                  | Women |          |          | Men |          |          |
|------------------|-------|----------|----------|-----|----------|----------|
|                  | Diabetes | No diabetes |          | Ratio diabetic and nondiabetic |          | Ratio diabetic and nondiabetic |
|                  | Women | Men | Women | Men | HR (95% CI) | P | HR (95% CI) | P |
| CVD              | 141 (37.6) | 147 (36.7) | 523 (27.8) | 587 (29.3) | 1.41 (1.17–1.70) | 0.0003 | 1.27 (1.06–1.52) | 0.0093 |
| CHD              | 80 (21.3) | 103 (25.8) | 274 (14.6) | 385 (19.3) | 1.50 (1.17–1.92) | 0.0015 | 1.35 (1.08–1.68) | 0.0072 |
| Cerebrovascular disease | 33 (8.8) | 28 (7.0) | 130 (6.9) | 97 (4.8) | 1.39 (0.94–2.04) | NS | 1.49 (0.98–2.27) | NS |
| Other CVD        | 28 (7.5) | 16 (4.0) | 119 (6.3) | 105 (5.2) | 1.22 (0.81–1.84) | NS | 0.78 (0.46–1.33) | NS |
| Malignant neoplasms | 32 (8.5) | 41 (10.2) | 211 (11.2) | 241 (12.0) | 0.76 (0.53–1.11) | NS | 0.87 (0.63–1.22) | NS |
| Respiratory disease | 14 (3.7) | 11 (2.8) | 62 (3.3) | 65 (3.2) | 1.21 (0.68–2.16) | NS | 0.85 (0.45–1.61) | NS |
| Endocrine disease | 14 (3.7) | 12 (3.0) | 13 (0.7) | 11 (0.5) | 5.53 (2.59–11.81) | <0.0001 | 5.89 (2.59–13.40) | <0.0001 |
| Digestive disease | 11 (2.9) | 9 (2.2) | 42 (2.2) | 40 (2.0) | 1.37 (0.70–2.67) | NS | 1.14 (0.55–2.34) | NS |
| Injury           | 6 (1.6) | 5 (1.2) | 33 (1.7) | 53 (2.7) | 0.91 (0.38–2.18) | NS | 0.46 (0.19–1.16) | NS |
| MB disorder      | 5 (1.3) | 0 | 23 (1.2) | 13 (0.7) | 1.46 (0.55–3.91) | NS | — | — |
| Infectious disease | 3 (0.8) | 3 (0.8) | 13 (0.7) | 14 (0.7) | 1.24 (0.35–4.36) | NS | 1.05 (0.30–3.64) | NS |
| GU disease       | 3 (0.8) | 7 (1.8) | 18 (1.0) | 23 (1.2) | 0.90 (0.26–3.06) | NS | 1.62 (0.69–3.79) | NS |
| Nervous disease  | 1 (0.3) | 1 (0.3) | 20 (1.1) | 13 (0.7) | 0.26 (0.03–1.90) | NS | 0.38 (0.05–2.94) | NS |
| All other diseases | 3 (0.8) | 4 (1.0) | 37 (2.0) | 22 (1.1) | 0.44 (0.13–1.41) | NS | 0.93 (0.32–2.70) | NS |
| All causes       | 233 (62.0) | 240 (60.0) | 995 (52.9) | 1,082 (54.1) | 1.12 (1.06–1.40) | 0.0071 | 1.13 (0.98–1.30) | NS |

Data are n (%) or HR (95% CI). Ratios between diabetic and nondiabetic subjects were adjusted for the influence of age, sex, and calendar year. GU, genitourinary disease; MB, mental and behavioral disorder.
up was used, because those entering the study in 2001 only had 3 years of follow-up. \( P < 5\% \) was regarded as statistically significant.

**RESULTS**

**Characteristics of the study population**

Mean ± SD age at diagnosis for diabetic subjects and fasting blood glucose decreased over the three decades, whereas BMI and the proportion of smokers and former smokers increased, as did the proportion of subjects using diet only as diabetes treatment (Table 1).

**Trends in all-cause mortality**

During the 33-year follow-up period, 233 (62.0%) diabetic women and 240 (60.0%) diabetic men and 995 (52.9%) nondiabetic women and 1,082 (54.1%) nondiabetic men died (Table 2). Age- and sex-adjusted hazard ratios (HRs) for all-cause mortality during 1972 to 2004 in diabetic and nondiabetic subjects were \( 1.17 (P = 0.0021) \) for the total sample (data not shown), \( 1.22 (P < 0.007) \) for women, and \( 1.13 (P = 0.095) \) for men.

Cumulative mortality rates during the whole follow-up period in the three decades are shown in Fig. 1A–F. Mortality decreased in nondiabetic subjects of both sexes \( (P < 0.0001) \). For diabetic men there was a similar tendency \( (P = 0.045) \), whereas no such development could be seen for diabetic women \( (P = 0.72) \). The mortality trends during the follow-up period in relation to age and year of diagnosis for diabetic and nondiabetic subjects are shown in Table 3. For both cohorts and for both sexes the all-cause mortality risk (HR) increased by age \( (P < 0.0001) \).

The nondiabetic subjects had a decreased mortality rate over time by almost 30% per 10 years. Diabetic subjects had no significant change over time, although there was a tendency toward a decrease among men with diabetes. No significant interactions between time period and diabetes status for all-cause mortality were found.

Figure 1—Cumulative mortality among diabetic and nondiabetic women and men during three time periods. A: Exposed diabetic \( (n = 131) \) and nondiabetic women \( (n = 655) \) 1972–1981. B: Exposed diabetic \( (n = 140) \) and nondiabetic women \( (n = 700) \) 1982–1991. C: Exposed diabetic \( (n = 105) \) and nondiabetic women \( (n = 525) \) 1992–2001. D: Exposed diabetic \( (n = 133) \) and nondiabetic men \( (n = 665) \) 1972–1981. E: Exposed diabetic \( (n = 154) \) and nondiabetic men \( (n = 770) \) 1982–1991. F: Exposed diabetic \( (n = 113) \) and nondiabetic men \( (n = 565) \) 1992–2001.
**Mortality trends with and without diabetes**

Table 3—Associations between age and diagnosis year on mortality from all causes, CVDs, and malignant diseases among diabetic and nondiabetic subjects

|                      | Women |          | Men |          | Women |          | Men |          |
|----------------------|-------|----------|-----|----------|-------|----------|-----|----------|
|                      | Diabetes | X² | 95% CI | CHD | X² | 95% CI | 95% CI | CHD | X² | 95% CI | 95% CI |
| Mortality, all causes|         |       |       |       |         |       |       |       |       |       |       |
| Age, 10-year groups | 2.42  (2.07–2.82) | 125.3 | 2.20 (1.93–2.51) | 137.1 | 2.47 (2.31–2.66) | 629.6 | 2.31 (2.18–2.46) | 705.7 |
| Diagnosis year, by 10 years | 1.02 (0.84–1.24) | 0.04 | 0.83 (0.68–1.01) | 3.5 | 0.71 (0.65–0.78) | 48.5 | 0.72 (0.66–0.79) | 51.5 |
| CVD mortality | 2.45 (2.00–2.99) | 76.8 | 2.22 (1.87–2.63) | 84.9 | 3.08 (2.78–3.41) | 455.0 | 2.61 (2.39–2.84) | 463.9 |
| Diagnosis year, by 10 years | 0.95 (0.74–1.22) | 0.2 | 0.73 (0.57–0.94) | 6.0 | 0.70 (0.62–0.80) | 26.9 | 0.69 (0.61–0.78) | 37.0 |
| CHD mortality | 2.09 (1.63–2.69) | 33.5 | 2.06 (1.69–2.52) | 51.3 | 2.97 (2.58–3.41) | 230.1 | 2.43 (2.19–2.70) | 273.7 |
| Diagnosis year, by 10 years | 0.79 (0.56–1.11) | 1.9 | 0.65 (0.48–0.88) | 7.6 | 0.59 (0.49–0.71) | 31.8 | 0.63 (0.54–0.73) | 38.0 |
| Cerebrovascular disease | | | | | | | | |
| Mortality | 3.44 (2.17–5.46) | 27.7 | 2.70 (1.81–4.10) | 23.3 | 3.23 (2.61–3.98) | 118.4 | 3.16 (2.52–3.97) | 99.0 |
| Diagnosis year, by 10 years | 1.24 (0.73–2.09) | 0.6 | 0.98 (0.53–1.78) | 0 | 0.77 (0.58–1.01) | 3.5 | 0.76 (0.56–1.03) | 3.0 |
| Malignant neoplasm mortality | | | | | | | | |
| Age, 10-year groups | 1.43 (1.04–1.97) | 4.8 | 1.93 (1.43–2.60) | 18.5 | 1.61 (1.42–1.83) | 52.2 | 1.85 (1.64–2.10) | 99.3 |
| Diagnosis year, by 10 years | 1.37 (0.83–2.24) | 1.5 | 1.27 (0.80–2.03) | 1.0 | 0.68 (0.56–0.83) | 14.6 | 0.72 (0.59–0.88) | 10.8 |
| Mortality from all other causes | | | | | | | | |
| Age, 10-year groups | 3.59 (2.52–5.11) | 49.9 | 2.39 (1.78–3.19) | 34.3 | 2.47 (2.15–2.84) | 164.7 | 2.22 (1.96–2.52) | 154.8 |
| Diagnosis year, by 10 years | 1.01 (0.67–1.53) | 0.002 | 0.84 (0.54–1.30) | 0.6 | 0.77 (0.63–0.93) | 7.5 | 0.81 (0.67–0.97) | 5.3 |

Data are HRs (95% CI) or X² estimate.

However, when sex-specific analyses were performed, a statistically significant interaction was found for diabetic women (P < 0.004) but not for diabetic men (P = 0.15).

**Trends in CVD and CHD mortality**

The age- and sex-adjusted CVD and CHD mortality rates were significantly higher for diabetic than for nondiabetic subjects: CVD mortality HR 1.33 (P < 0.0001) and CHD mortality HR 1.41 (P < 0.0001) (data not shown). Both diabetic women and men had significantly higher risk than nondiabetic subjects of dying from CVD and within this group of disease from CHD but not from other cardiovascular causes (Table 2). The associations between age and CVD mortality trends were similar to the associations between age and all-cause mortality (Table 3). Diabetic and nondiabetic men had a similar average decrease over calendar time, whereas diabetic women had no such change (nondiabetic subjects P < 0.0001, diabetic men P = 0.014, and diabetic women P = 0.69). For CHD mortality, the associations were similar for both age and diagnosis year to those for CVD mortality (nondiabetic subjects P < 0.0001, diabetic men P < 0.006), and diabetic women P = 0.17). No significant interactions between time period and diabetes status for CVD and CHD mortality were found (P > 0.10).

**Trends in non-CVD mortality**

As expected, the mortality risk was significantly increased for endocrine disease among diabetic subjects. For all other causes, there were no significant differences (Table 2). A pronounced increase in mortality risk by age was seen for diabetic and nondiabetic subjects for cerebrovascular disease. No significant associations of diagnosis year, either among diabetic subjects or among nondiabetic subjects, were detected. There was a significantly increased HR for malignant neoplasm mortality and mortality from all other causes by age for diabetic and nondiabetic subjects of both sexes, but only nondiabetic subjects had a significant decrease in HR with calendar time (Table 3). There was a significant interaction between time period and diabetes status for malignant neoplasm mortality (P = 0.02) but not for mortality from all other causes (P > 0.10).

**Trends across time**

A more detailed analysis of the time sequence in the course of events was made on the basis of year of inclusion of diabetic and nondiabetic subjects and with 3 years of follow-up. The course of events regarding CVD and CHD mortality is shown in Fig. 2A–D. Generally, the mortality rates fell gradually by year of inclusion, but faster among nondiabetic than diabetic subjects.

**CONCLUSIONS** — The excess mortality risk for diabetic than for nondiabetic subjects was low in our study and especially so for men. Nondiabetic but not diabetic subjects had significantly improved survival during the study period. However, diabetic men had substantially lower CVD mortality, particularly CHD mortality, during the third compared with the previous decades, whereas diabetic women had a slower rate of improvement. The improved survival for nondiabetic subjects was due to reduced mortality from CVD, malignant disease, and all other causes. Diabetic subjects showed no such improvement over the study period. Together with the unchanged CVD mortality, this constituted the basis of the lack of improvement of survival for the diabetic subjects. However, an interesting and promising finding was that diabetic men had as good an improvement in survival as nondiabetic men regarding CVD and CHD...
mortality. This was not true for diabetic women, although a positive tendency was seen (Table 3).

The reduced CVD and CHD mortality among men but not among women with diabetes, was similar to what others have found (12,18). On the other hand, other studies showed the opposite, a higher mortality rate among men (2,7), and still others found no sex differences (11,15).

The lack of improvement among women in our study may have several explanations ranging from sex differences in care provision and/or care adherence, to the diabetes disease itself, which has been claimed to have a greater adverse affect on CVD risk factors in women than in men (19).

Several factors may explain the decrease in mortality among nondiabetic subjects over the last decades. These include successful primary prevention of CVD risk factors such as smoking, improved lipid and blood pressure treatments, and accompanying lifestyle changes in addition to improvements in life-saving technologies for those developing acute CHD over the years.

All of these improvements in CVD mortality in the nondiabetic population may also be seen in the diabetic population, but they occur later and are not of the same order of magnitude and diabetic women lag behind diabetic men. Some possible explanations for this unfavorable development might be that diabetic subjects are smokers and overweight or obese to a larger extent than nondiabetic subjects and do not reach the treatment goals for blood pressure, lipids, and A1C according to the guidelines (20). A further negative circumstance for diabetic compared with nondiabetic subjects and especially so for diabetic women is their worse prognosis after an acute myocardial infarction (21).

Good scientific evidence about the effects of treatment of hyperglycemia, high blood pressure and dyslipidemia came fairly late in our study with the UK Prospective Diabetes Study (UKPDS) (22,23). The UKPDS was followed by several other reports: one meta-analysis showing the advantages of treating hypercholesterolemia (24) and another focusing on multifactorial intervention (25). It will take some time before these findings are implemented in clinical practice widely enough to have an impact on the health and survival of diabetic subjects.

When interpreting the improvements in CVD mortality among diabetic subjects, one should keep in mind the case-finding strategies started in 1983. A possible lead time bias introduced by these strategies might have affected the three diabetes cohorts differently. Subjects with diabetes diagnosed in the last compared with the first decade were younger and had lower fasting blood glucose, indicating a more favorable prognosis. However, taking the influence of these factors into account in the analyses did not affect the result.

The strengths of this study include the fact that all incident diabetic subjects in a defined geographical area were identified using uniform diagnostic criteria and followed over a long time period. All Swedish residents have a unique 12-digit personal identification number, which is an excellent and highly reliable tool for record linkage. Patient fees for hospital outpatient and general practice appoint-
Mortality trends with and without diabetes

ments are heavily subsidized by central and local governments, which means that private financial resources are seldom an obstacle to health care utilization. These factors, together with excellent continuity in the diabetes care given, may be one explanation for the low excess mortality risk seen in our study compared with what others have found (6,7,11,15).

Moreover, the absence of known diabetes in the reference group makes the risk estimates in our study a forceful representation of the true risk. Furthermore, in our study, as opposed to many other studies, all incident diabetic subjects regardless of age were included. The mortality data were based on the official Cause of Death Register and were 100% complete.

The limitations of the study include the fairly small study area with an ethnically homogeneous Caucasian population. As a result, generalizations to ethnically different populations should be made cautiously. Furthermore, nondiabetic subjects sampled for the period 1972–1982 who died before the opportunistic case finding procedures started in 1983 may have included some subjects with undiagnosed diabetes, causing a dilution of the mortality comparisons for this period.

In summary, the novel findings in this study were the low excess mortality risk for diabetic than for nondiabetic subjects. Nondiabetic but not diabetic subjects had a significant all-cause, CVD, and CHD mortality reduction during the 33-year follow-up whereas diabetic men but not women had a significant average reduction of CVD and especially CHD mortality rates.

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