

# Cause-specific mortality in a cohort of patients with diabetes mellitus: A population-based study in Sweden

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## Abstract

A cohort of patients with diabetes mellitus hospitalised in Sweden from 1965 to 1983 was followed up until 1989, by linkages of population-based registers. Standardised mortality ratios (SMR), adjusted for confounding variables, and 95% confidence intervals (CIs) were calculated. After exclusion of the first year of follow-up (to reduce the effect of selection bias), the cohort consisted of 144,427 patients, of whom 92,248 patients died during follow-up. The SMR for all causes of death combined was 2.62 (95% CI 2.58–2.67) among men and 3.23 (95% CI 3.18–3.28) among women. The excess mortality was still evident 20 years after first hospitalisation, but became less marked with longer follow-up time. Patients with presumably insulin-dependent diabetes mellitus (IDDM) had the highest SMRs (10.2; CI 9.5–11.0); however, there was a significant (34%) improvement over time in their mortality risk. We conclude that excess mortality persisted throughout all calendar periods and at all ages, indicating the need for health care prevention measures. © 2001 Elsevier Science Inc. All rights reserved.

**Keywords:** Diabetes mellitus; Standardised mortality ratio; Cohort study; Sweden; Epidemiology; Cause-specific mortality

## 1. Introduction

Diabetes mellitus is known to be underreported on death certificates as an underlying or contributing cause of death [1,2]. Therefore, cohort studies are the only satisfactory way to assess mortality risk among diabetes mellitus patients. As recently reviewed [3], relatively few large population-based studies, with long-term follow-up of patients with diabetes mellitus have been reported to date [4,5], and more of such studies are needed for a precise estimation of the mortality risks. It is unclear if development in diabetes during the last decades is reflected or not in lower mortality rates among diabetes mellitus patients [6,7].

We performed a large population-based cohort study in Sweden to assess the mortality in various subgroups of diabetes mellitus patients who were hospitalised at least once. In particular, we examined the effect of calendar year at enrolment in the cohort to explore whether development in diabetes care was reflected in discernible improvements in

mortality among diabetes mellitus patients during the 25 years of observation.

## 2. Patients and methods

### 2.1. The cohort

Since there is almost no private in-patient treatment in Sweden, hospital-provided medical services are, in effect, population based and referable to the county in which the patient lives. Beginning in 1964/1965, the National Board of Health and Welfare started collecting data on individual hospital discharges in the In-Patient Register. Each record included, among other things, the national registration number (a unique personal identifier assigned to all Swedish residents); dates of admission and discharge; data on hospital department; and up to eight discharge diagnoses, coded according to the seventh revision of the International Classification of Diseases (ICD-7) through 1968 and according to the eighth revision through 1986 (ICD-8).

The areas covered by the register expanded as the study progressed. In 1969 the register covered 60% of the Swedish population, in 1978 this percentage was 75%, and by the end

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of 1983 it was 85%. A more detailed description of this register has been reported previously [8]. We selected all patients in the In-patient Register with a discharge diagnosis of diabetes (ICD-7 code 260, ICD-8 code 250) and identified 216,827 unique national registration numbers with at least one such record between 1965 and 1983. Record linkage to the nationwide registers of the Total Population, Causes of Death, and Population Migration Registries identified 25,547 hospital records with incomplete or incorrect national registration numbers, not corresponding to any living, deceased or emigrated person. The latter records were removed since the erroneous national registration numbers would otherwise contribute person-years at no risk of death. We further excluded 6905 national registration numbers due to date discrepancies revealed during the record linkages, and 39,948 subjects who emigrated or died during the first year of follow-up. These deaths were excluded to reduce selection bias [9], since the outcome (death) affects the likelihood of being hospitalised. Therefore, the target population of this study is composed of patients who survived at least 1 year after the index hospitalisation (initial hospitalisation registered at the In-patient Registry with a discharge diagnosis of diabetes mellitus).

## 2.2. Analysis

As the cohort moved through time, the observed gender-specific person-years at risk were allocated to 5-year age groups and calendar-years. Person-years of observation were counted from 1 year after the index hospitalisation until emigration, death, or the end of the observation period (December 31, 1989), whichever occurred first.

Data were stratified by sex, age at first hospitalisation, birth cohort, comorbidity status and recorded hospitalisations for diabetes mellitus complications (as defined below), and duration of follow-up.

The ICD codes do not distinguish insulin-dependent (IDDM) from non-insulin-dependent diabetes mellitus (NIDDM). We made the following attempts to separate these diseases. First we stratified the cohort by age at index hospitalisation (< 40 vs.  $\geq$  40 years), since IDDM predominates in the younger group. Secondly, we stratified the cohort by birth cohort (born before 1900 vs. born during or after 1900), assuming the IDDM is rare among persons born before 1900 and surviving until 1965.

We also classified patients as having diabetes mellitus as their only hospital discharge diagnosis at index hospitalisation ('without comorbidity') as opposed to those to which diabetes mellitus was recorded as one among other diagnoses—related or not with the diabetes mellitus—on the index discharge summary record ('with comorbidity').

Patients were classified as 'ever' or 'never' having been hospitalised for 'diabetes mellitus complications' [i.e., recorded hospitalisations at least once for one or more of the following discharge diagnoses: diabetic neuropathy (ICD-8 260.49), nephropathy (ICD-8 260.30) or retinopathy (ICD-8 260.21)]. If a patient was hospitalised for complications after

the index hospitalisation for noncomplicated diabetes mellitus, person-years before the discharge for complication were attributed to the noncomplication stratum. Therefore, subjects with complications may have contributed person-years to both strata, although mortality was attributed only to the complication stratum.

We further classified patients as being the underlying cause of death or being mentioned as a contributing cause of death (among patients that had a noncancer/nondiabetes as underlying cause of death).

The effects of explanatory variables—sex, age, calendar year at index hospitalisation, comorbidity, duration of follow-up, and birth cohort—were distinguished through Poisson multiple regression analysis. The analysis used as a baseline the number of deaths expected in the entire Swedish population, calculated by multiplying the observed person-years in strata by the corresponding age-, sex- and calendar-year-specific mortality rates for the Swedish population. The Poisson mean of an observed count was assumed multiplicative in the corresponding baseline count and in the effects of each variable. The effects were constrained (see below) such that their maximum likelihood estimates (MLEs) are like SMRs comparing cohort rates to Swedish population rates. We call the MLEs of effects of a variable adjusted SMRs because unlike ordinary SMRs, they adjust for the confounding effects of the other variables in the model. The excess mortality observed in this cohort of diabetic patients was more dependent on age at first hospitalization than we have observed in mortality analyses of other hospitalized cohorts, except perhaps splenectomy. In our study of patients hospitalized for splenectomy [15], which included many patients being treated for lymphoma, the (ordinary, unadjusted) SMRs decreased from 5.6 for index age less than 40, down to 0.9 for index age 80 or more. In our study of patients hospitalized for silicosis [16], however, the (ordinary) SMRs decreased from 2.4 for index age less than 40, down to 1.4 for index age 80 or more. Similarly, in unpublished mortality analyses, for patients hospitalized for rheumatoid arthritis, the (ordinary) SMRs decreased from 2.4 for index age less than 40, down to 1.6 for index age 80 or more. For patients hospitalized for obesity, the (ordinary) SMRs decreased from 3.4 for index age less than 40, down to 1.5 for index age 80 or more. . . . The excess mortality was much higher among our surrogate group for IDDM subjects (hospitalized at age 40 or less) compared to our surrogate group for NIDDM subjects (those born before 1900). While this difference may be confounded by age and birth cohort effects and enlarged by an adjustment to the SMR, after comparison to patients with splenectomy, silicosis, rheumatoid arthritis and obesity, it seems likely that the striking age effect in mortality that we observed for diabetic patients was due at least partially to different mortality patterns for patients with IDDM versus NIDDM.

The 95% confidence interval (CI), about an adjusted SMR was calculated, and a *P*-value (two-sided)  $\leq$  0.05 was considered statistically significant. A score test was used to test for linear trends [10].

Constraints were used to obtain unique MLEs of effects because the model was overparameterized. A similar non-uniqueness problem has also been solved with constraints [11]. We obtained unique MLEs for a variable by constraining the logs of the effects of each other variable to have a weighted mean of zero, where the weights were inversely proportional to the corresponding observed counts. These constraints imply that the mean effect for each other variable is approximately 1, which makes the effects of the variable under consideration interpretable as ratios of true cohort rates to corresponding Swedish population rates in the sense that they fully reflect discrepancies between the observed and expected counts. The MLEs of the effects under these constraints are then interpretable as adjusted SMRs. The MLEs of ratios of effects of a variable, which indicate trends in the variable, do not depend on our constraints because they are unique. The estimates are ratios of adjusted SMRs.

We corrected for overdispersion in the adjusted analysis by including a scaling factor when the standard errors were computed. The scaling factor was computed as the square root of the ratio of the Pearson chi-square statistic to the degrees of freedom for the model [12].

We also expanded the Poisson model to analyse for two-way interactions. We used the 'complete' two-way interaction model, except for the period\*(year of follow-up) and age\*(year of follow-up) interactions, for which there were few or no observations in certain combinations.

### 3. Results

After exclusion of the first year of follow-up, a total of 144,427 patients remained in the cohort. They were followed up for a total of 966,920 person-years, or on average 6.7 years per subject, with a range of 1–25 years. During the follow-up period, 92,248 deaths occurred. The mean age at start of follow-up was 61.3 years for men and 65.8 years for women, and the average calendar year at index hospitalization was 1977.

Adjusted SMRs indicated an excess mortality that remained significant throughout the study period (Table 1). The adjusted SMRs (deaths from any cause) by age at index hospitalisation decreased from 10.24 among 20,350 patients aged less than 40 years to 1.61 among 17,225 patients in the

Table 1  
Characteristics of the Swedish diabetes cohort, adjusted standardised mortality ratios (SMR) and 95% confidence intervals (CI) for all causes of death<sup>a</sup>

	Person-years	Observed No. deaths	SMR <sup>b</sup>	CI <sup>c</sup>
Duration of follow-up (years)				
1–4	468,168	48,993	3.30	3.24–3.35
5–9	328,399	30,928	2.76	2.70–2.81
10–14	123,262	9,586	2.23	2.15–2.31
15–19	35,183	2,380	1.88	1.75–2.03
20+	5,908	361	1.64	1.35–1.98
Age at index hospitalisation (in years)				
<40	230,220	2,382	10.24	9.51–11.03
40–49	89,082	3,116	7.12	6.67–7.59
50–59	163,098	10,017	5.00	4.83–5.19
60–69	226,757	24,972	3.65	3.56–3.73
70–79	194,073	35,767	2.42	2.37–2.47
80+	57,691	15,994	1.61	1.56–1.65
Birth cohort				
Born before 1900	111,994	27,183	2.62	2.56–2.68
Born during or after 1900	854,926	65,065	3.08	3.03–3.12
Year of index hospitalisation <sup>d</sup>				
1965–1974	113,006	9,493	3.06	2.95–3.18
1970–1974	272,005	24,872	3.04	2.97–3.11
1975–1979	330,018	32,729	2.90	2.84–2.96
1980–1983	245,891	25,154	2.82	2.76–2.89
Recorded comorbidity at index hospitalisation				
No	319,519	15,091	2.42	2.35–2.49
Yes	647,401	77,157	3.04	3.00–3.08
Sex				
Males	458,816	42,955	2.62	2.58–2.67
Females	508,104	49,293	3.23	3.18–3.28

<sup>a</sup>Excluding first year of follow-up.

<sup>b</sup>Maximum likelihood estimate (MLE), or adjusted SMR, based on a Poisson regression model with mean multiplicative in baseline, expected number of deaths calculated from Swedish nationwide, age-, sex-, and calendar-year-specific mortality rates, and in the effects of sex, year, index age, duration of follow-up, comorbidity, and birth cohort. MLEs of effects for a variable were computed under the constraints of means of zero for the logs of the effects for each other variable weighed inversely by corresponding observed counts. These constraints were chosen to produce unique MLEs of effects that are like SMRs comparing cohort rates to Swedish population rates while adjusting for the effects of the other variables in the model.

<sup>c</sup>Corrected for overdispersion, estimated as a scale factor by the Pearson chi-square divided by the degrees of freedom for the model.

<sup>d</sup>First recorded hospitalisation in the Swedish In-Patient Register with a discharge diagnosis of diabetes mellitus (ICD-7 code 260, ICD-8 code 250).

group aged 80 years or more. This inverse trend to age was significant ( $P$  for trend  $< .0001$ ).

The attempt to compare IDDM subjects (less than 40 years of age) to non-IDDM subjects (born before 1900) revealed a large difference between the groups. The adjusted SMR for subjects less than 40 years of age was 10.24 (95% CI 9.51–11.03), while the SMR for subjects born before 1900 was 2.62 (95% CI 2.56–2.68).

There was a significant decrease in risk with increasing duration of follow-up ( $P$ -value from score test for linear trend  $< .0001$ ): the adjusted SMR fell from 3.30 during follow-up years 1–4 to 1.64 during the follow-up period greater than 20 years.

The excess mortality among patients with their index hospitalisation in 1965–69 (adjusted SMR 3.06) was significantly larger than that observed among those first hospitalised in 1980–83 (2.82) ( $P$  for trend  $< .0001$ ). However, a significant interaction was observed between calendar time and index age. There was no significant decrease in overall mortality over time except for the youngest age group (index age  $< 40$ ), for which the decrease was 34%. The main underlying cause of death that decreased by calendar year for this group (aged  $< 40$  at entry into the cohort) was 'diabetes.' The number of deaths (for the group with index age  $< 40$ ) decreased for 787 in 1965–1974 (SMR 234.7, 95% CI 218.6–251.7) to 248 in 1975–1979 (SMR = 158.2, 95% CI

139.1–179.2) and to 78 in 1980–1983 (SMR = 107.8, 95% CI 85.2–134.6).

Patients with recorded comorbidity at index hospitalisation presented a higher excess mortality (SMR 3.04 95% CI 3.02–3.07) compared with patients having diabetes as their only hospital discharge diagnosis on their initial visit (SMR 2.42; 95% CI 2.35–2.49,  $P$ -value  $< .0001$ ).

The overall excess mortality risk in women (SMR 3.23) was significantly larger than that in men (SMR 2.62) ( $P$ -value  $< .0001$ ). However, due to a significant interaction between index age and gender, this difference was most pronounced at younger ages (threefold below age 50, twofold in the 50s, and less than twofold at ages 60–79), and almost disappeared at the oldest ages (10% at age 80 and above).

In Table 2, we present adjusted SMRs for specific causes of death for males and females adjusted for the effects of age and comorbidity. The majority of the deaths (62%) was attributed to diseases of the circulatory system, followed by malignant neoplasms (10%), diseases of the respiratory system (6%), digestive system (3%), external causes (2%), and diseases of the genitourinary system (1.5%). The excesses were significant for all these causes. Diabetes mellitus was judged to be the underlying cause of 12% of the deaths, and was mentioned as a contributing cause of death in 43% of noncancer/nondiabetes deaths. For patients having cancer as the underlying cause of death, we did not have any informa-

Table 2  
Adjusted standardised mortality ratio (SMR) by gender: follow-up 1–26 years<sup>a</sup>

ICD-8	Cause of death	Males			Females		
		No.	SMR <sup>b</sup>	95% CI <sup>c</sup>	No.	SMR <sup>b</sup>	95% CI <sup>c</sup>
001–139	Infectious and parasitic	240	2.60	2.27–2.97	275	2.69	2.43–2.97
038	Septicaemia	104	3.87	3.26–4.60	124	3.92	3.35–4.58
140–208	Malignant neoplasms	4,919	1.51	1.46–1.55	4,742	1.54	1.49–1.58
309–459	Circulatory system	26,038	3.01	2.95–3.07	31,615	3.24	3.16–3.33
401–405	Hypertensive heart disease	213	3.90	3.44–4.42	375	3.77	2.99–4.76
410–414	Ischaemic heart	18,384	3.19	3.12–3.27	19,368	3.70	3.60–3.82
420–429	Other non-pulmonary heart disease	1,636	2.58	2.46–2.71	2,323	2.53	2.39–2.69
430–438	Cerebro-vascular disease	4,266	3.00	2.90–3.10	6,989	2.98	2.90–3.07
440–448	Arterial disease	1,029	1.83	1.73–1.95	1,656	1.99	1.89–2.09
451–453	Veins and thromboembolics	359	2.24	2.00–2.51	540	2.17	1.99–2.36
460–519	Respiratory diseases	2,598	2.26	2.17–2.36	2,716	2.23	2.14–2.33
480–486,507	Pneumonia	1,751	2.62	2.50–2.76	2,048	2.34	2.23–2.45
490–491	Bronchitis	288	1.58	1.42–1.77	157	1.75	1.52–2.02
492	Emphysema	139	1.48	1.22–1.79	70	1.72	1.40–2.12
493	Asthma	188	2.77	2.38–3.21	186	2.98	2.66–3.33
520–579	Digestive system	1,585	3.61	3.43–3.79	1,267	2.49	2.35–2.64
580–629	Genito-urinary system	715	2.67	2.50–2.86	680	3.02	2.79–3.26
580–599	Urinary diseases	622	2.93	2.73–3.14	671	3.02	2.79–3.26
580–583	Nephritis	90	3.45	2.87–4.15	74	3.34	2.58–4.33
600–629	Genital diseases	93	1.62	1.33–1.98	9	4.25	2.02–8.97
680–709	Skin and connective tissue	25	5.61	3.20–9.84	33	2.88	2.14–3.89
800–999	External causes	968	1.59	1.50–1.68	902	1.64	1.54–1.76

<sup>a</sup>Excluding the first year of follow-up.

<sup>b</sup>Maximum likelihood estimate (MLE), or adjusted SMR, based on a Poisson regression model with mean multiplicative in baseline, expected number of deaths calculated from Swedish nationwide age-, sex-, and calendar-year-specific mortality rates, and in the effects of index age and comorbidity. MLEs of effects for a variable were computed under the constraints of means of zero for the logs of the effects for each other variable weighted inversely by corresponding observed counts. These constraints were chosen to produce unique MLEs of effects that are like SMRs comparing cohort rates to Swedish populations rates while adjusting for the effects of the other variables in the model.

<sup>c</sup>Corrected for overdispersion.

Table 3  
Adjusted standardised mortality ratio (SMR) by age at index hospitalisation<sup>a</sup> and birth cohort

ICD-8	Cause of death	First hospitalisation <40 (probable IDDM)			Born before 1900 (probable NIDDM)		
		No.	SMR <sup>b</sup>	CI <sup>c</sup>	No.	SMR <sup>b</sup>	CI <sup>c</sup>
001–139	Infectious and parasitic	11	7.72	5.05–11.80	124	1.59	1.34–1.88
038	Septicaemia	5	8.29	3.98–17.27	41	2.04	1.52–2.73
140–208	Malignant neoplasms	111	1.73	1.45–2.05	2,653	1.46	1.40–1.52
309–459	Diseases circulatory system	560	11.29	10.26–12.42	17,462	2.06	1.98–2.14
401–405	Hypertensive heart disease	3	10.49	0.48–229.4	172	2.37	2.10–2.69
410–414	Ischaemic heart disease	410	16.77	14.47–19.45	10,886	2.23	2.14–2.32
420–429	Other non-pulmonary heart disease	45	5.86	3.98–8.63	1,285	1.70	1.58–1.83
430–438	Cerebro-vascular disease	82	7.62	6.42–9.04	3,689	2.07	1.97–2.17
440–448	Arterial disease	5	3.71	1.98–6.94	1,118	1.47	1.37–1.58
451–453	Veins and thromboembolics	10	9.96	5.17–19.19	263	1.47	1.31–1.65
460–519	Respiratory diseases	93	11.60	9.71–13.87	1,900	1.67	1.59–1.76
480–486,507	Pneumonia	63	15.75	12.77–19.42	1,482	1.77	1.67–1.87
490–491	Bronchitis	3	6.13	3.12–12.04	124	1.28	1.08–1.52
492	Emphysema	4	10.58	4.04–27.68	51	1.20	0.95–1.53
493	Asthma	6	5.40	2.98–9.80	59	1.91	1.53–2.39
520–579	Diseases digestive system	92	8.15	6.81–9.76	696	1.63	1.51–1.76
580–629	Diseases genito-urinary system	22	14.12	10.42–19.14	429	1.69	1.53–1.86
580–599	Urinary diseases	22	15.00	11.01–20.45	377	1.72	1.55–1.92
580–583	Nephritis	11	15.24	9.10–25.52	21	1.15	0.85–1.56
600–629	Genital diseases	0	—	—	52	1.51	1.19–1.91
680–709	Skin and connective tissue	4	58.77	30.79–112.2	13	1.55	0.86–2.80
800–999	External causes	228	2.12	1.88–2.39	487	1.21	1.10–1.33

<sup>a</sup>First recorded hospitalisation with a discharge diagnosis of diabetes mellitus (ICD-7 code 260, ICD-8 code 250). Excluding the first year of follow-up.

<sup>b</sup>Maximum likelihood estimate (MLE), or adjusted SMR, based on a Poisson regression model with mean multiplicative in baseline, expected number of deaths calculated from Swedish nationwide age-, sex-, and calendar-year-specific mortality rates, and in the effects of index age and comorbidity. MLEs of effects for a variable were computed under the constraints of means of zero for the logs of the effects for each other variable weighted inversely by corresponding observed counts. These constraints were chosen to produce unique MLEs of effects that are like SMRs comparing cohort rates to Swedish populations while adjusting for the effects of the other variables in the model.

<sup>c</sup>Corrected for overdispersion.

tion on contributing causes. The SMR for ischaemic heart disease was significantly higher for women than for men ( $P < .0001$ ), and the large difference for this common cause of death led to the higher overall SMR for women than for men described above. The SMRs for diseases of the digestive system ( $P = .017$ ) and pneumonias ( $P = .063$ ) were higher among men than among women, but not statistically significant.

Table 3 gives adjusted SMRs for specific causes of death for patients aged less than 40 years at index hospitalisation (probably IDDM) and patients born before 1900 and surviving until 1 year after the index hospitalisation (probably NIDDM). The SMRs are adjusted for sex and comorbidity. For every cause of death, probable IDDM patients had markedly higher SMRs than probable NIDDM patients, except for malignant neoplasms, where no significant difference was observed ( $P = .08$ ).

Age- and sex-adjusted SMRs for specific causes of death among patients initially hospitalised with comorbidity (Table 4) were particularly high for hypertensive heart diseases, asthma, and disease of the digestive system. However, initial comorbidity clearly did not explain most of the increased mortality risk for this cohort.

Compared with patients with no recorded hospitalisation for diabetes mellitus complications, patients with such hos-

pitalisations had higher SMRs for all causes of death, with the exception of malignant diseases, skin and connective tissue diseases (data not shown).

#### 4. Discussion

Our results show an almost tripled mortality risk for all causes of death among diabetes mellitus patients, compared with the general Swedish population. The excess mortality decreased with calendar time, but only for the youngest diabetics (hospitalised at age under 40).

The decrease in excess mortality with calendar year when the index hospitalisation occurred suggests that there have been improvements in the health management of diabetes mellitus patients, but perhaps only for IDDM patients. Since an increasing proportion of all diabetes patients are now being managed as outpatients in Sweden (Dr Martin Engqvist, Epidemiologic Centre, Stockholm, personal communication), this probably leaves an increasing proportion of 'serious cases' in the cohort that may have partly cancelled the improvement in survival. However, the initial management of a newly developed case of IDDM includes almost always (97% of the cases) an in-hospital assessment [13]. Therefore, the selection of 'serious cases'—with higher excess in mortality—should be more marked among patients with

Table 4  
Adjusted standardised mortality ratio (SMR) by comorbidity: follow-up 1–26 years<sup>a</sup>

ICD-8	Cause of death	Co-morbidity					
		No			Yes		
		Observed number	SMR <sup>b</sup>	CI <sup>c</sup>	Observed number	SMR <sup>b</sup>	CI <sup>c</sup>
001–139	Infectious and parasitic	43	2.27	1.88–2.74	472	2.77	2.53–3.02
038	Septicaemia	21	3.82	3.01–4.84	207	3.95	3.47–4.49
140–208	Malignant neoplasms	661	1.21	1.15–1.27	9,000	1.59	1.54–1.63
309–459	Circulatory system	5,465	2.76	2.68–2.84	52,188	3.20	3.12–3.27
401–405	Hypertensive heart disease	85	2.42	1.91–3.06	503	4.03	3.40–4.77
410–414	Ischaemic heart disease	3,702	3.11	2.98–3.24	34,050	3.49	3.40–3.58
420–429	Other non-pulmonary heart disease	376	2.15	1.93–2.40	3,583	2.63	2.53–2.74
430–438	Cerebro-vascular disease	1,014	2.57	2.45–2.70	10,241	3.07	2.98–3.15
440–448	Arterial disease	224	1.58	1.43–1.75	2,461	1.99	1.90–2.07
451–453	Veins and thromboembolics	72	1.92	1.64–2.26	827	2.25	2.07–2.44
460–519	Respiratory diseases	526	2.06	1.93–2.20	4,788	2.28	2.21–2.36
480–486,507	Pneumonia	405	2.51	2.33–2.70	3,394	2.46	2.37–2.56
490–491	Bronchitis	33	1.09	0.85–1.39	412	1.73	1.58–1.90
492	Emphysema	15	1.13	0.78–1.63	194	1.65	1.41–1.93
493	Asthma	30	1.51	1.15–1.98	344	3.07	2.71–3.48
520–579	Digestive system	232	1.91	1.73–2.11	466	3.27	3.14–3.41
580–629	Genito-urinary system	137	2.33	2.00–2.71	1,258	2.93	2.77–3.10
580–599	Urinary diseases	126	2.40	2.05–2.82	1,167	3.08	2.91–3.27
580–583	Nephritis	22	3.19	2.07–4.92	142	3.44	2.94–4.03
600–629	Genital diseases	11	2.18	1.35–3.51	91	1.70	1.39–2.09
680–709	Skin and connective tissue	1	4.85	2.94–8.02	57	3.67	2.75–4.90
800–999	External causes	207	1.48	1.35–1.62	1,663	1.66	1.58–1.74

<sup>a</sup>Excluding the first year of follow-up.

<sup>b</sup>Maximum likelihood estimate (MLE), or adjusted SMR, based on a Poisson regression model with mean multiplicative in baseline, expected number of deaths calculated from Swedish nationwide age-, sex-, and calendar-year-specific mortality rates, and in the effects of index age and comorbidity. MLEs of effects for a variable were computed under the constraints of means of zero for the logs of the effects for each other variable weighted inversely by corresponding observed counts. These constraints were chosen to produce unique MLEs of effects that are like SMRs comparing cohort rates to Swedish populations while adjusting for the effects of the other variables in the model.

<sup>c</sup>Corrected for overdispersion.

NIDDM. Another potential source of bias may be underrecording of the diagnosis of diabetes in the In-Patient Registry, used to identify the cohort. In the UK, Williams et al. [14] found that the diagnosis of NIDDM on the admission register was omitted in 10% of admissions in which diabetes or its complications was known to be the cause of the admission. Similar data are unfortunately not available from the Swedish In-Patient registry. However, if an underregistration of the NIDDM diagnosis is present in the Swedish In-Patient Registry, our results could only be underestimated.

Although the ICD codes do not distinguish between the two major types of diabetes mellitus, our attempts to separate NIDDM from IDDM patients according to birth cohort and age at enrolment into the cohort revealed a clear pattern of more increased mortality among probable IDDM patients, compared with probable NIDDM patients. However, by definition the difference is confounded by age and birth cohort effects.

The excess mortality observed in this cohort of diabetic patients was more dependent on age at first hospitalisation than we have observed in mortality analyses of other hospitalised cohorts, except perhaps splenectomy. In our study of patients hospitalised for splenectomy [15], which included many patients being treated for lymphoma, the (univariate)

SMRs decreased from 5.6, for index age less than 40, down to 0.9, for index age 80 or more. In our study of patients hospitalised for silicosis [16], however, the (univariate) SMRs decreased from 2.4, for index age less than 40, down to 1.4, for index age 80 or more. Similarly, in unpublished mortality analyses, for patients hospitalised for rheumatoid arthritis, the (univariate) SMRs decreased from 2.4, for index age less than 40, down to 1.6, for index age 80 or more. For patients hospitalised for obesity, the (univariate) SMRs decreased from 3.4, for index age less than 40, down to 1.5, for index age 80 or more. The excess mortality was much higher among our surrogate group for IDDM subjects (hospitalised at age 40 or less) compared with our surrogate group for NIDDM subjects (those born before 1900). While this difference may be confounded by age and birth cohort effects and enlarged by a multivariate adjustment to the SMR, after comparison to patients with splenectomy, silicosis, rheumatoid arthritis and obesity, it seems likely that the striking age effect in mortality that we observed for diabetic patients was due at least partially to different mortality patterns for patients with IDDM versus NIDDM.

An important point to recognise is that the observed decreasing mortality risk with increasing age, and the decreasing effects of sex and calendar time with increasing age, are

influenced by heterogeneity among individuals in their susceptibility to dying, otherwise known as *frailty*. Frailty has been discussed primarily in the context of survival analysis [17]. In our analysis, individuals reaching later age groups may not be representative of individual mortality risk because they may be less frail, having survived until that age group, or more frail, because their diabetes was diagnosed late. The selection of these individuals biases estimation of effects. The decreasing mortality risk with increasing age suggests that, on average, individuals in later age groups are less frail than those in earlier age groups. Consequently, it is not surprising that sex and calendar-year have smaller effects on later age groups (the less frail) than on earlier age groups (the more frail). Some of the individual variation in frailty was removed by our truncating the cohort to individuals who lived past 1 year after initial hospitalisation to reduce Berkson bias [9].

Another point to remember is that age, calendar period, and birth cohort effects confound one another in that any two determine the other. We were able to include all three of these variables in our model because birth cohort was divided into fewer categories (just two) than age and calendar period and therefore none of the variables was determined by the other two.

The mortality patterns did not differ significantly between sexes in the SMR analysis, except for a significant increase of ischaemic heart disease in women compared with men. This finding is in accordance with many previous studies of mortality from ischaemic heart diseases among women [18–22], except for some studies [23,24]. The increase caused a higher overall mortality risk among women, in accordance with many previous studies [3,17–20,24,25], except for one study [24].

The overall excess mortality in this cohort, and particularly the pattern of mortality for cardiovascular diseases, confirms previous reports [3,18,19,23,26]. The small proportion of deaths for diseases of the genitourinary system (1.5%) contrasts with studies on IDDM patients in other populations [27–29], where this group of diseases represented about one third or more of the overall mortality. In the group aged less than 40 years at the index hospitalisation, the proportion of deaths due to diseases of the genitourinary system was also small, compared to previous studies.

The results of previous studies (most of them not population based) may, perhaps, reflect more cases with renal complications. Another possible explanation for our results may be that deaths from renal diseases in subjects with diabetes mellitus might have been categorised to diabetes mellitus as the main cause of death.

Diabetes mellitus was the underlying cause of 12% of the deaths, and was mentioned as a contributing cause of death in 43% of noncancer/nondiabetes deaths. This reflects an underreporting of the disease in the death certificates, at least as a contributing cause of death.

The increased mortality for diseases of the digestive system, mainly cirrhosis in subjects of both sexes, is also in accordance with previous studies [23,25,30], but it contrasts

with a recent British study [3]. This association could be due to alcoholism leading to diabetes mellitus. However, in our cohort a clear excess was also observed in the group of patients first hospitalised before the age of 40 (probably IDDM), where diabetes mellitus secondary to alcoholism is likely to be rare. A recent report on cancer incidence in the Swedish diabetes mellitus cohorts shows a significant increase in risk of primary liver cancer [31].

Given the characteristics of the public health system in the country, and the availability of nationwide registers, this study may be considered truly population based, with a follow-up of virtually 100%. It also represents a country with a high standard of health care, and therefore the latest advances in management of diabetes mellitus patients should have optimal chances of making an impact on disease outcome statistics. Moreover, the availability of computerised mortality statistics (death certificates) for the general population enabled us to assess the impact on different disease outcomes in the cohort. The availability of death certificates ensures that the cohort mortality is comparable with the mortality in the general population.

However, the findings of our study need to be interpreted somewhat cautiously before generalising their results. The cohort was restricted to patients who received in-hospital care for their diabetes mellitus. The need for hospitalisation may have been determined either by a more severe diabetes mellitus or by coexistence of other medical conditions, or both. We do not believe, however, that the Berkson fallacy explains more than a fraction of the excess mortality observed. First, to reduce this possibility somewhat, we excluded the first year of follow-up from all analyses. Moreover, stratification by comorbidity at the index hospitalisation revealed a significantly increased mortality risk also for those having no other initial disease diagnoses recorded besides diabetes mellitus. Further, the excess mortality persisted after 20 years of follow-up. Multiple comparisons (at alpha level 5%) should lead to significant results of 5% of the time, by chance. The consistency of our findings, however, with significant excesses and similar trends in most of the analyses, cannot be explained by chance alone.

In summary, our data show evidence of a 34% decrease in the overall risk of death among diabetes mellitus patients hospitalised under age 40 in Sweden during the period 1965–1983. However, there was still substantial excess mortality at all ages. We believe that our data can be extrapolated to other societies where similar patterns of health care are widely available. Because of the high prevalence of diabetes particularly in Western countries, the excess mortality certainly has an important public health impact in terms of years-of-life-lost, and as a heavy burden on the health care economy. Public health measures to diminish or delay the onset of NIDDM and to avoid the complications of both NIDDM and IDDM are the challenge to health care systems in the forthcoming years. Both primary and secondary prevention measures are needed in order to diminish the impact of diabetes mellitus on overall mortality.

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## References

- [1] Fuller JH, Elford J, Goldblatt P, Adelstein AM. Diabetes mortality: new light on an underestimated public health problem. *Int J Epidemiol* 2000;29(1):140–8.
- [2] Waugh MR, Dallas JH, Jung RT, Newton RW. Mortality in a cohort of diabetic patients. Causes and relative risks. *Diabetologia* 1983;24(5):336–41.
- [3] Swerdlow AJ, Jones ME. Mortality during 25 years of follow-up of a cohort with diabetes. *Diabetologia* 1989;32(2):103–4.
- [4] Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. The DECODE study group. European Diabetes Epidemiology Group. *Diabetes Epidemiology: Collaborative Analysis of Diagnostic criteria in Europe*: Lancet 1999;354(9179):617–21.
- [5] de Vegt F, Dekker JM, Ruhe HG, Stehouwer CD, Nijpels G, Bouter LM, Heine RJ. Hyperglycaemia is associated with all-cause and cardiovascular mortality in the Hoorn population: the Hoorn Study. *Diabetologia* 1999;42(8):926–31.
- [6] Gu K, Cowie CC, Harris MI. Diabetes and decline in heart disease mortality in US adults. *JAMA* 1999;281(14):1291–7.
- [7] Nusselder WJ, Mackenbach JP. Lack of improvement of life expectancy at advanced ages in The Netherlands. *JAMA* 1999;281(14):1291–7.
- [8] Naessén T, Parker R, Persson I, Zack M, Adami HO. Time trends in incidence rates of first hip fracture in the Uppsala Health Care Region, Sweden, 1965–1983. *Int J Epidemiol* 1996;25(6):1250–61.
- [9] Berkson J. Limitations of the application of four-fold table analysis to hospital data. *Biomet Bull* 1946;2:47–53.
- [10] Breslow NE, Day NE. Statistical methods in cancer research. Volume II—the design and analysis of cohort studies. *Am J Epidemiol* 1989;130(2):289–99.
- [11] Mantel N, Stark CR. Computation of indirect-adjusted rates in the presence of confounding. *Biometrics* 1968;24(4):997–1005.
- [12] Efron B. Poisson overdispersion estimates based on the method of asymmetric maximum likelihood. *J Am Stat Assoc* 1992;87:98–107.
- [13] Nationella riktlinjer för vård och behandling vid diabetes mellitus. Stockholm: Socialstyrelsen, 1999 [in Swedish].
- [14] Williams DR, Fuller JH, Stevens LK. Validity of routinely collected hospital admissions data on diabetes. *IARC Sci Publ No 82*, 1987:1–406.
- [15] Linet MS, Nyren O, Gridley G, Adami HO, Buckland JD, McLaughlin JK, Fraumeni JF. Causes of death among patients surviving at least one year following splenectomy. *Diabetes Med* 1989;6(4):320–4.
- [16] Brown LM, Gridley G, Olsen JH, Mellemejaer L, Linet MS, Fraumeni JF. Cancer risk and mortality patterns among silicotic men in Sweden and Denmark. *Am J Surg* 1996;172(4):320–3.
- [17] Aalen OO. Heterogeneity in survival analysis. *J Occup Environ Med* 1997;39(7):633–8.
- [18] Kessler, II. Mortality experience of diabetic patients. A twenty-six-year follow-up study. *Stat Med* 1988;7(11):1121–37.
- [19] Moss SE, Klein R, Klein BE. Cause-specific mortality in a population-based study of diabetes. *Am J Public Health* 1991;81(9):1158–62.
- [20] Reunanen A. Mortality in type 2 diabetes. *Ann Clin Res* 1983;15 (Suppl 37):26–8.
- [21] Kannel WB, McGee DL. Diabetes and glucose tolerance as risk factors for cardiovascular disease: the Framingham study. *Diabetes Care* 1979;2(2):120–6.
- [22] Pan WH, Cedres LB, Liu K, Dyer A, Schoenberger JA, Shekelle RB, Stamler R, Smith D, Collette P, Stamler J. Relationship of clinical diabetes and asymptomatic hyperglycemia to risk of coronary heart disease mortality in men and women. *Am J Epidemiol* 1986;123(3):504–16.
- [23] Sasaki A, Horiuchi N, Hasegawa K, Uehara M. Mortality and causes of death in type 2 diabetic patients. A long-term follow-up study in Osaka District, Japan. *Diabetes Res Clin Pract* 1989;7(1):33–40.
- [24] Kleinman JC, Donahue RP, Harris MI, Finucane FF, Madans JH, Brock DB. Mortality among diabetics in a national sample. *Am J Epidemiol* 1988;128(2):389–401.
- [25] Shenfield GM, Elton RA, Bhalla IP, Duncan LJ. Diabetic mortality in Edinburgh. *Diabetes Metab* 1979;5(2):149–58.
- [26] Krolewski AS, Czyzyk A, Janeczko D, Kopczynski J. Mortality from cardiovascular diseases among diabetics. *Diabetologia* 1977;13(4):345–50.
- [27] Dorman JS, Laporte RE, Kuller LH, Cruickshanks KJ, Orchard TJ, Wagener DK, Becker DJ, Cavender DE, Drash AL. The Pittsburgh insulin-dependent diabetes mellitus (IDDM) morbidity and mortality study. Mortality results. *Diabetes* 1984;33(3):271–6.
- [28] Borch-Johnsen K, Nissen H, Henriksen E, Kreiner S, Salling N, Deckert T, Nerup J. The natural history of insulin-dependent diabetes mellitus in Denmark: 1. Long-term survival with and without late diabetic complications. *Diabetes Med* 1987;4(3):201–10.
- [29] International evaluation of cause-specific mortality and IDDM. Diabetes Epidemiology Research International Mortality Study Group. *Diabetes Care* 1991;14(1):55–60.
- [30] Balkau B, Eschwege E, Ducimetiere P, Richard JL, Warnet JM. The high risk of death by alcohol related diseases in subjects diagnosed as diabetic and impaired glucose tolerant: the Paris Prospective Study after 15 years of follow-up. *J Clin Epidemiol* 1991;44(6):465–74.
- [31] Adami HO, Chow WH, Nyrén O, Berne C, Linet MS, Ekblom A, et al. Excess risk of primary liver cancer in patients with diabetes mellitus. *J Natl Cancer Inst* 1996;88(20):1472–7.