

# Long-term cardiovascular and non-cardiovascular mortality in women and men with type 1 and type 2 diabetes mellitus: A 30-year follow-up in Switzerland

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## Summary

**Background:** While studies from other countries have shown an excess mortality in diabetic individuals when compared with the general population, comparable long-term data is not available for Switzerland.

**Aims:** To assess gender-specific cardiovascular and non-cardiovascular mortality of patients with type 1 and type 2 diabetes compared with the general Swiss population between 1974 and 2005.

**Design:** 533 patients (225 type 1, 308 type 2 diabetes, 52.2% men) were followed for 30 years (10349 person-years).

**Results:** Diabetic patients had an increased all-cause mortality compared with the general population (SMR [95% CI] 3.8 [3.5–4.3]). Standardised mortality ratio (SMR) was higher for type 1 compared with type 2 diabetic patients (4.5 [3.8–5.3] vs 3.5 [3.1–4.0],  $p = 0.032$ ). For cardiovascular and non-cardiovascular deaths SMRs were 5.6

(95% CI 4.8–6.6) and 2.7 (2.3–3.1) and did not differ according to type of diabetes. SMRs for all-cause and cardiovascular mortality were significantly higher in women compared with men in type 1 ( $p < 0.05$  and  $p < 0.01$ ) and type 2 diabetes ( $p < 0.001$  and  $p < 0.01$ ). In both types of diabetes, SMRs significantly decreased during the last two decades ( $p$  for trend 0.004 and 0.002).

**Conclusions:** Patients with type 1 and type 2 diabetes had an increased long-term mortality compared with the general Swiss population. Excess mortality was higher in type 1 compared with type 2 diabetes and in women compared with men for both types of diabetes, but steadily decreased over the last two decades.

**Key words:** type 1 diabetes; type 2 diabetes; gender; mortality; epidemiology

## Introduction

A large number of studies from various countries corroborate an increased mortality in diabetic patients when compared with the general population which is mainly attributable to cardiovascular disease [1–3]. However, estimates for the excess mortality due to cardiovascular causes in diabetic patients have been shown to vary widely across European countries: While studies from the United Kingdom report mortality rates which are two to 17 fold higher than in the general population [4, 5], a recent study from Italy revealed a considerably lower excess mortality around 50% [6]. Moreover, few studies directly compare type 1 and type 2 diabetic individuals and results are controversial: Several reports have suggested a

more pronounced excess mortality in patients with type 1 compared with type 2 diabetes [5, 7–11], whereas a recent study from Sweden reported inverse findings [12]. Similarly, conflicting evidence exists regarding the influence of gender on the excess mortality in diabetic individuals: While some studies have revealed a higher excess mortality in diabetic women compared with their male counterparts [4, 10, 13–20], other reports have found a comparable risk in both genders [12, 21–23], and some have even observed inverse results [24, 25]. Such discrepancies may, at least partly, be explained by geographical differences as well as different underlying study populations or potential changes in mortality risk over time.

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The present study assessed the long-term mortality in a cohort of type 1 and type 2 diabetic patients in Switzerland over 30 years compared with the general population and according to gender. Separate analyses were performed for car-

diovascular and non-cardiovascular mortality. In addition, time changes in excess mortality of diabetic individuals between 1974 and 2005 were monitored.

## Materials and methods

### Patients

The present study is based on the Swiss participants of the "WHO Multinational Study of Vascular Disease in Diabetes", a study performed by 14 centres in 13 countries [26]. Details on the design, methods and recruitment of the study have been described before [26–30]. In brief, 533 patients aged between 35 and 54 years were recruited between February 1974 and May 1977 by 231 local Swiss practitioners according to a central protocol [26, 27]. Informed consent was required for all patients included. Patients were classified as having type 1 diabetes if insulin was needed for treatment within 1 year of diagnosis, otherwise they were attributed type 2 diabetes. At baseline, a standardised clinical examination was performed including a detailed questionnaire with information on diabetes diagnosis, the duration and treatment as well as on symptoms of vascular and cardiac disease, and blood samples for biochemical measurements were taken. All analyses were carried out in accordance with the declaration of Helsinki and the Swiss laws regarding data safety.

### Follow-up and outcome definition

The status (alive/dead) and date of death of each patient was ascertained as per January 1, 2006 based on data obtained from population registries. In deceased patients, the underlying cause of death was determined from a copy of the death certificate, hospital records, post-mortem reports (where available), and additional information given by the treating physicians. Causes of death were coded according to the International Classification of Disease (ICD-9 up to January 1, 1998, and ICD-10 thereafter). Outcomes were all-cause mortality, cardiovascular mortality (codes 390 to 459 and 798.1 in ICD-9, and I00 to I99 in ICD-10), and non-cardiovascular mortality (all ICD codes not covered in the category of cardiovascular mortality). In 17 patients (9 with type 1, 8 with type 2) the cause of death could not be assigned conclusively and these patients were included in the analyses of all-cause mortality exclusively.

### Statistical analysis

After checking for normality, continuous baseline characteristics between the two types of diabetes were

compared using Student's t-test. Non normally distributed variables were transformed prior to analysis. Pearson's chi-squared test was used for categorical variables. Kaplan-Meier survival analyses were separately performed in type 1 and type 2 diabetic patients. Differences according to sex within type of diabetes were assessed using the logrank test. Mortality rates for all-cause, cardiovascular, and non-cardiovascular mortality were calculated for the entire cohort and separately according to type of diabetes and sex. Since absolute mortality rates strongly depend on age and sex, indirect age- and sex-adjusted standardisation of mortality rates were performed by calculating the corresponding standardised mortality ratios (SMRs). The expected number of deaths in the cohort was computed by multiplying the sex-, year- and age-specific (in 1-year age bands for all cause mortality and in 5-year age bands for cardiovascular and non-cardiovascular mortality) person-years at risk within the cohort by corresponding mortality rates from the general population of Switzerland. Calculations of 95% confidence intervals were based on the assumption that the number of deaths followed a Poisson distribution [31]. Sex and age-specific all-cause mortality rates for the general Swiss population were obtained from the Human Mortality Database ([www.mortality.org](http://www.mortality.org)) and were available up to the year 2006. The corresponding rates for cardiovascular mortality were obtained from the Swiss Federal Statistical Office up to the year 2004. Rates for non-cardiovascular mortality were calculated as difference between all-cause and cardiovascular mortality rates. For the assessment of changes in mortality over study follow-up, annual SMRs were fitted separately for each type of diabetes using a multivariable Poisson regression model including sex, and linear and quadratic terms for calendar year (centered at 1990) as covariates. In a post-hoc analysis linear time-trends were assessed for observed increase or decrease in SMR in type 1 and type 2 diabetes by restricting the analyses to the year with the lowest up to the year with the highest SMR, or vice versa, and including calendar year as linear term as only covariate. All analyses were performed using Stata version 10.0 (Stata Corporation, College Station, TX, USA). A p-value <0.05 was considered statistically significant.

## Results

### Study characteristics

The cohort consisted of 533 patients (225 with type 1, 308 with type 2 diabetes). During follow-up 35 patients (6.6%) left the country or were lost to follow-up and were censored accordingly, this calculated into 10349 person-years of follow up. Baseline characteristics are summarised in table 1.

### All-cause mortality

During the study period 352 subjects died (138 with type 1, 214 with type 2 diabetes) (table 2). This translated into an all-cause mortality which was 3.8-fold higher compared with the general Swiss population, when differences in age and sex were taken into account (SMR [95% CI] 3.8 [3.5–4.3]). Excess mortality was higher in type 1 (SMR 4.5 [3.8–5.3]) compared with type 2 diabetes (SMR 3.5 [3.1–4.0]),

**Table 1**

Baseline characteristics of the study population.

	All patients	Type 1 DM	Type 2 DM	p for difference Type 1 vs Type 2
<b>Demographic</b>				
Number of patients	533	225	308	
Men	278 (52.2%)	104 (46.2%)	174 (56.5%)	0.019
Age (years)	45.2 (6.2)	43.0 (6.10)	46.8 (5.8)	<0.001
<b>Clinical</b>				
Diabetes duration (years)	11.9 (8.4)	15.5 (9.7)	9.2 (6.0)	<0.001
Body mass index (kg/m <sup>2</sup> )	26.1 (5.2)	23.9 (4.2)	27.7 (5.3)	<0.001
Diastolic blood pressure (mm Hg)	87.6 (11.5)	85.5 (11.2)	89.1 (11.5)	<0.001
Systolic blood pressure (mm Hg)	139.0 (20.8)	136.1 (20.2)	141.1 (21.0)	0.007
Smoking status				0.75
Never	218 (40.9%)	88 (39.1%)	130 (42.2%)	
Former	138 (25.9%)	59 (26.2%)	79 (25.7%)	
Current	177 (33.2%)	78 (34.7%)	99 (32.1%)	
<b>Biochemical</b>				
Fasting glucose (mmol/l)	10.7 (5.3)	11.7 (6.5)	10.0 (4.1)	0.010
Total cholesterol (mmol/l)	6.4 (1.4)	6.2 (1.4)	6.6 (1.4)	<0.001
Triglycerides (mmol/l)	2.0 (2.3)	1.4 (1.2)	2.4 (2.7)	<0.001
Creatinine (µmol/l)	88.8 (35.2)	91.9 (43.3)	86.6 (27.4)	0.07
<b>Micro- and macrovascular disease</b>				
Hypertension	193 (36.2%)	68 (30.2%)	125 (40.6%)	0.014
Coronary heart disease	141 (26.5%)	45 (20.0%)	96 (31.2%)	0.004
Proteinuria	120 (22.8%)	49 (21.8%)	71 (23.4%)	0.71
Retinopathy	185 (34.7%)	117 (52.0%)	68 (22.1%)	<0.001
<b>Medication</b>				
Diet alone	27 (5.1%)	0 (0.0%)	27 (9.0%)	<0.001
Oral glucose-lowering drugs	215 (40.3%)	27 (12.0%)	188 (61.0%)	<0.001
Insulin	315 (59.0%)	225 (100.0%)	90 (29.2%)	<0.001
Lipid-lowering medication	19 (3.6%)	4 (1.8%)	15 (4.9%)	0.06
Antihypertensive medication	183 (34.3%)	55 (24.4%)	128 (41.6%)	0.07

$p = 0.032$ , table 2). In type 1 diabetes absolute mortality rates tended to be higher in men than in women: 35.5/1000 person-years (95% CI 28.1–45.0/1000) versus 26.6/1000 person-years (21.0–33.6/1000) (table 2) although the difference did not reach the level of significance ( $p$ -value from log-rank test 0.06, fig. 1a). In type 2 diabetes absolute mortality rates were comparable between men and women: 38.3/1000 person-years (32.1–45.8/1000) versus 35.1/1000 person-years (28.6–43.0/1000) (table 2, fig. 1b). The SMRs for the entire follow-up were significantly higher in women compared with men in type 1 (SMR 5.4 [4.3–6.8] vs 3.8 [3.0–4.8],  $p = 0.020$ ) and type 2 diabetes (SMR 4.7 [3.9–5.8] vs 3.0 [2.5–3.5],  $p < 0.001$ ) (table 2).

### Cardiovascular mortality

Cardiovascular death occurred in 169 patients (60 with type 1, 109 with type 2 diabetes). When compared with the general population, type 1 and type 2 diabetic patients revealed an increased risk for cardiovascular mortality (SMR [95% CI] 5.6 [4.8–6.6], table 2) but SMRs did not significantly differ between the two types of diabetes. There was no significant gender difference in the observed absolute mortality rates for both types of diabetes (table 2, fig. 1c and 1d). However, women had significantly higher cardiovascular SMRs compared

with their male counterparts in both types of diabetes: In type 1 diabetes SMRs were 9.5 (6.6–13.8) versus 5.2 (3.6–7.4,  $p$  for difference 0.004); in type 2 diabetes the corresponding values were 7.2 (5.3–9.8) versus 4.4 (3.4–5.6,  $p$  for difference 0.005) (table 2).

### Non-cardiovascular mortality

Death due to non-cardiovascular causes was recorded in 166 patients (69 with type 1, 97 with type 2 diabetes). Both, type 1 and type 2 diabetic patients, showed an increased risk to die from non-cardiovascular causes compared with the general population (SMR [95% CI] 2.7 [2.3–3.1], table 2) and SMRs did again not differ between type 1 and type 2 diabetes. The absolute risk to die from non-cardiovascular causes was comparable between men and women within both types of diabetes (table 2, fig. 1e and 1f). While in type 1 diabetes SMRs for men and women were comparable, there was a strong trend towards a higher SMR in type 2 diabetic women compared with men (3.1 [2.3–4.2] vs 2.1 [1.6–2.7],  $p$  for difference 0.052, table 2).

### Time trends of mortality

In type 1 diabetes, the annual SMRs for all-cause mortality were stable up to 1984 but constantly decreased afterwards (fig. 2a,  $p$  for trend

0.004). In type 2 diabetes, there was an increase in SMRs between 1974 and 1988 (p for trend 0.002) and a constant decrease thereafter (p for trend 0.002, fig. 2b). Similarly, SMRs for cardiovascular mortality steadily decreased after 1984 in type 1 (p for linear trend 0.021, fig. 2c) and after 1985 in

type 2 diabetic patients (p for linear trend 0.013, fig. 2d). SMRs for non-cardiovascular mortality showed a comparable decline after 1984 and 1987, in type 1 and type 2 diabetic patients, respectively (p for linear trend 0.001 in both types of diabetes, fig. 2e and 2f).

## Discussion

Based on 30 years of follow-up investigations, this study confirms that long-term mortality was substantially higher in diabetic patients compared with the general Swiss population. Although this finding is in line with previous reports from other European countries [4-6, 8, 10, 12, 13, 15, 16, 19,

21-24, 32, 33], Northern and Southern America [20, 34-36], New Zealand/Australia [37-39], and Asia [14, 17, 40], SMRs in the present study may appear comparably high. Earlier studies have reported SMRs for diabetic patients ranging between 1.2 and 2.4 [6, 10, 12, 16, 32] while in the

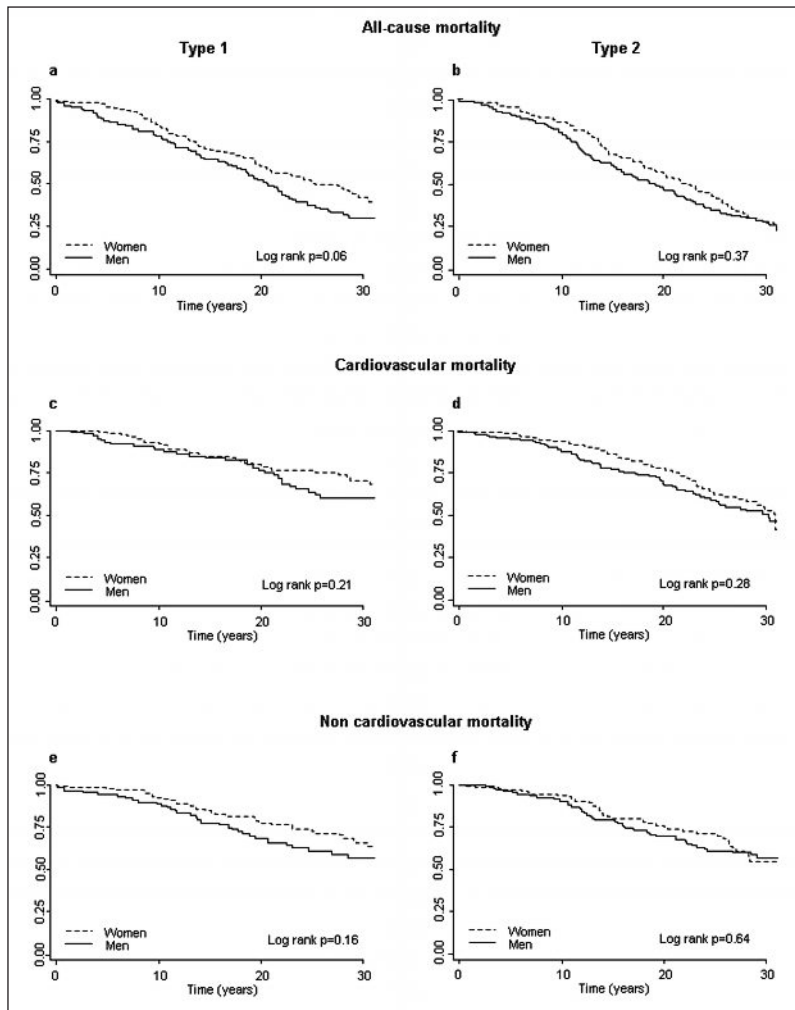
**Table 2**

Person-years, observed and expected deaths, standardised mortality ratios (SMR) and 95% confidence interval.

Mortality	Classification	Person-years	Number of deaths		Observed mortality rate (per 1000 py)	SMR (95% CI)
			Observed	Expected		
All-cause	Type 1					
	Women	2599	69	12.8	26.6 (21.0-33.6)	5.4 (4.3-6.8) <sup>a</sup>
	Men	1943	69	18.2	35.5 (28.1-45.0)	3.8 (3.0-4.8)
	All	4542	138	31.0	30.4 (25.7-35.9)	4.5 (3.8-5.3) <sup>c</sup>
	Type 2					
	Women	2625	92	19.5	35.1 (28.6-43.0)	4.7 (3.9-5.8) <sup>c</sup>
	Men	3183	122	41.4	38.3 (32.1-45.8)	3.0 (2.5-3.5)
	All	5807	214	60.8	36.9 (32.2-42.1)	3.5 (3.1-4.0)
	Type 1 and 2					
	Women	5224	161	32.3	30.8 (26.4-36.0)	5.0 (4.3-5.8) <sup>c</sup>
	Men	5125	191	59.6	37.3 (32.3-42.9)	3.2 (2.8-3.7)
	All	10349	352	91.8	34.0 (30.6-37.8)	3.8 (3.5-4.3)
Cardiovascular	Type 1					
	Women	2554	28	2.9	11.0 (7.6-15.9)	9.5 (6.6-13.8) <sup>b</sup>
	Men	1914	30	5.8	15.7 (11.0-22.4)	5.2 (3.6-7.4)
	All	4467	58	8.8	13.0 (10.0-16.8)	6.6 (5.1-8.6)
	Type 2					
	Women	2591	40	5.6	15.4 (11.3-21.1)	7.2 (5.3-9.8) <sup>b</sup>
	Men	3139	62	14.2	19.8 (15.4-25.3)	4.4 (3.4-5.6)
	All	5730	102	19.7	17.8 (14.7-21.6)	5.2 (4.3-6.3)
	Type 1 and 2					
	Women	5145	68	8.5	13.2 (10.4-16.8)	8.0 (6.3-10.2) <sup>c</sup>
	Men	5052	92	20.0	18.2 (14.9-22.3)	4.6 (3.8-5.7)
	All	10197	160	28.5	15.7 (13.4-18.3)	5.6 (4.8-6.6)
Non-cardiovascular	Type 1					
	Women	2554	31	9.4	12.1 (8.5-17.3)	3.3 (2.3-4.7)
	Men	1914	35	12.1	18.3 (13.1-25.5)	2.9 (2.1-4.0)
	All	4467	66	21.5	14.8 (11.6-18.8)	3.1 (2.4-3.9)
	Type 2					
	Women	2591	42	13.7	16.2 (12.0-21.9)	3.1 (2.3-4.2) <sup>d</sup>
	Men	3139	55	26.4	17.5 (13.5-22.8)	2.1 (1.6-2.7)
	All	5730	97	40.0	16.9 (13.9-20.7)	2.4 (2.0-3.0)
	Type 1 and 2					
	Women	5145	73	23.1	14.2 (11.3-17.9)	3.2 (2.5-4.0) <sup>a</sup>
	Men	5052	90	38.5	17.8 (14.5-21.9)	2.3 (1.9-2.9)
	All	10197	163	61.6	16.0 (13.7-18.6)	2.7 (2.3-3.1)

Note that follow-up was from 1974-2005 for overall mortality and from 1974-2004 for cardiovascular and non cardiovascular mortality; p-levels for difference between men and women: <sup>a</sup> <0.05, <sup>b</sup> <0.01, <sup>c</sup> <0.001, <sup>d</sup> 0.052; <sup>e</sup> p for difference between type 1 and type 2 diabetes <0.05.





**Figure 1**

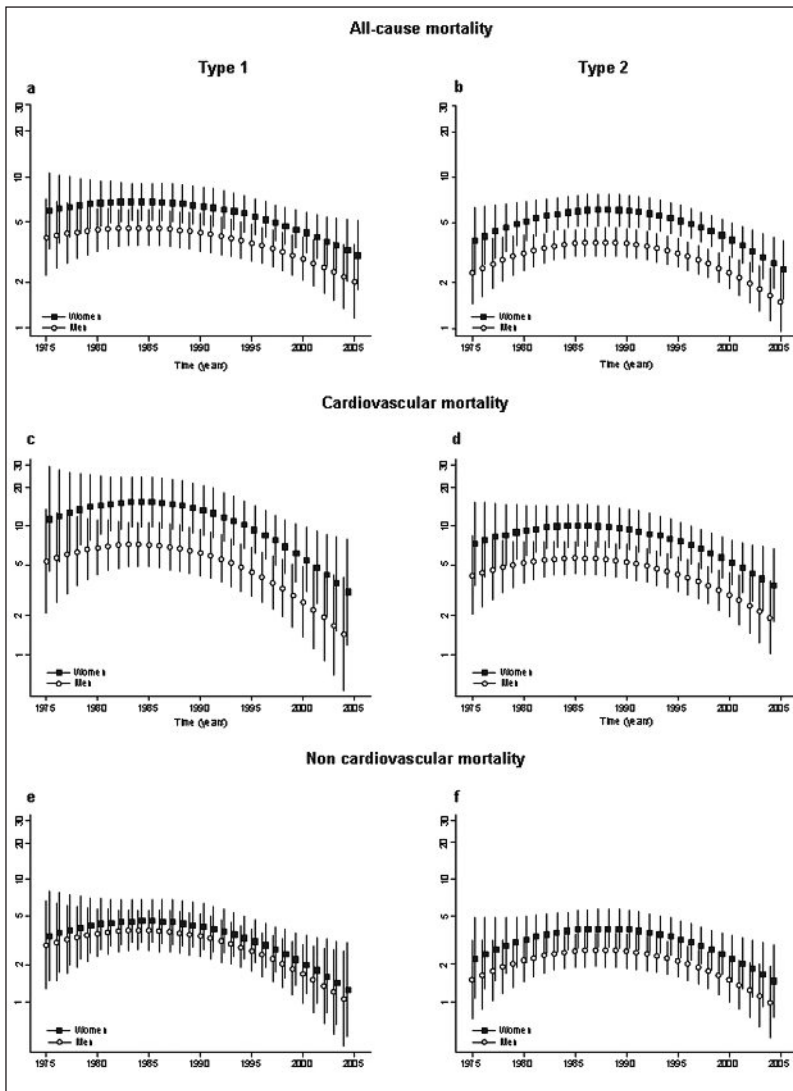
Kaplan-Meier estimation of survival probabilities according to type of diabetes and sex for all-cause mortality (Panels a and b), cardiovascular mortality (Panels c and d), and non-cardiovascular mortality (Panels e and f).

present analysis the overall SMR was 3.8. Such discrepancies may either be due to differences in absolute mortality rates in the cohort or, alternatively, differences in the underlying mortality in the reference population. It is noteworthy that absolute mortality rates in a comparable population of adult diabetic patients in the UK were similar to those in the present study (about 34/1000 person-years in both studies) [10]. Conversely, absolute mortality rates in a cohort of type 2 diabetic patients from Italy were reported to be substantially higher (around 49/1000 person-years compared with 37/1000 person-years in the present study) despite lower SMRs in that study [6]. It has been previously shown that Switzerland has a comparably low mortality in the general population [41, 42], which may at least partly explain the higher SMRs in the present analysis. This may even be more relevant with respect to SMRs for cardiovascular mortality since it has been reported that Switzerland bears one of the lowest cardiovascular mortality rates in Europe [43]. In addition, differences in the age structure of the diverse cohorts may have influenced SMRs, as it is known that the excess mortality of diabetic patients becomes smaller with increasing age [5, 9, 14, 21, 22, 37].

The results regarding differences according to gender and type of diabetes merit closer consideration: Although absolute mortality rates did not differ between women and men, women had a significantly higher excess mortality compared with men for both types of diabetes and this difference was most pronounced for cardiovascular mortality. These findings not only confirm those of earlier reports [4, 10, 13–20] suggesting that cardiovascular risk may disproportionately increase in women with type 2 diabetes [44]. Furthermore, in accordance with recent publications [4, 13] the present study provides additional evidence that similar mechanisms also may hold true for women with type 1 diabetes. In addition to the loss of the inherent protective endocrine status in diabetic women [44], it has been shown that women with diabetes and cardiovascular disease generally have poorer control of important modifiable risk factors compared with men and, for instance, are offered lipid-lowering treatment less frequently [45]. While in the present study lipid values were similar in men and women with both types of diabetes, women with type 2 diabetes had a higher systolic blood pressure at baseline than their male counterparts (data not shown). Conversely, a higher proportion of smokers was found among men in both types of diabetes. While the difference in smoking status may contribute to the increased absolute mortality in type 1 diabetic men, it has to remain speculative whether in type 2 diabetes the increased proportion of smokers in men is at least partly counterbalanced by the increased prevalence of hypertension in women.

So far, only few studies have directly compared the mortality of patients with type 1 and type 2 diabetes within one single study framework. The finding of higher SMRs in patients with type 1 diabetes is in accordance with several recent studies [5, 7, 9, 11, 19, 20]. Interestingly, inverse findings were reported from a large Swedish study where type 2 diabetic patients revealed higher SMRs compared with their type 1 diabetic counterparts [12]. A potential explanation for this conflicting evidence could be found in the comparably young age of the patients in the Swedish study, and the fact that the follow-up of these patients was from the diagnosis of diabetes onwards, over a shorter period between 1983 and 1999 [12].

Excess mortality consistently declined in both types of diabetes and both genders over the past two decades. A similar decline in SMRs has also been reported in a recent cohort study in Sweden over 20 years of follow-up [9] as well as in a report from the Danish National Diabetes Register, although the latter did not differentiate between type 1 and type 2 diabetes [21]. In the present study, the changes in SMRs over time are likely to be due to several reasons: Firstly, a slight excess mortality due to comparably young individuals was observed in the first years which could potentially be responsible for the initial increase in



**Figure 2**  
Fitted SMRs according to type of diabetes and sex for all-cause mortality (Panels a and b), cardiovascular mortality (Panels c and d), and non-cardiovascular mortality (Panels e and f). SMRs were modelled using a Poisson-regression model including sex and the calendar year (centered at 1990) as linear and quadratic term.

SMRs, especially in type 2 diabetes. Secondly, a selection of healthier individuals over the study time cannot fully be ruled out. However, a careful assessment of expected and observed mortality rates in age-specific strata over time made a relevant selection bias unlikely (data available on request). As a consequence, it is likely that the observed decline in SMRs over the last two decades in both types of diabetes reflects a true effect of improved treatment guidelines and strategies. While the results of the large Diabetes Control and Complications Trial (DCCT) were made public only in 1993 [46], a number of randomised controlled trials already suggested a beneficial effect of intensified glycaemic control in type 1 diabetes in the previous years [47–52]. In type 2 diabetes, the results of the University Group Diabetes Program (UGDP) study [53], though controversial, may have influenced therapeutic strategies before the publication of the landmark Veterans Affairs (VA) trial and the United Kingdom Prospective Study (UKPDS) [54, 55]. In addition, treatment options to tackle concomitant cardiovascular risk factors (for example statins or anti-

hypertensive drugs) have steadily increased over the last years and environmental factors (dietary changes for example) may have further reduced excess mortality [56–58].

The strength of the present study lies in a comparably long follow-up of a well-defined cohort [26, 27] including both types of diabetes. The study had a low drop-out rate and evaluated pre-specified endpoints. Still, there are some limitations to be acknowledged: Firstly, the design of the study did not allow to repetitively collect information on specific treatment modalities or clinical or biochemical parameters (HbA1c for example) during follow-up. Therefore, the interpretation of the observed time trends in mortality has to remain limited and to some extent speculative, despite careful assessment to avoid potential bias. Secondly, the absolute number of patients in the current study was comparably small and a careful follow-up may only partly offset this shortcoming. In addition, despite the fact that recruitment was done by local practitioners in various regions of Switzerland and according to an internationally approved central protocol, a potential selection bias can not be fully ruled out. Thirdly, the underlying cause of death was generally determined from a copy of the death certificate, which is a comparatively unreliable source of information. Despite all efforts to collect comprehensive data from hospital records, post-mortem reports, and by the treating physicians, the cause of death may have been misclassified in some cases. Finally, the general population of Switzerland (including diabetic and non-diabetic individuals) was used as the reference to calculate SMRs and this may have resulted in underestimation of the excess risk for diabetic patients.

In summary, the present long-term follow-up study revealed an increased mortality of diabetic patients compared with the general Swiss population. Excess mortality was highest for cardiovascular disease in both types of diabetes. Of concern, women with both types of diabetes showed a significantly higher excess mortality compared with men for both types of diabetes and this was essentially attributable to an excess in cardiovascular mortality. The constant decline of excess mortality in both types of diabetes and in both genders over the past two decades indicates a beneficial impact of improved treatment strategies. However, the present results also suggest that further efforts to outweigh persistent gender-specific differences in diabetic patients may still be required.

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