Excess Mortality in Patients With Type 1 Diabetes Without Albuminuria—Separating the Contribution of Early and Late Risks

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OBJECTIVE

The current study investigated whether the risk of mortality in patients with type 1 diabetes without any signs of albuminuria is different than in the general population and matched control subjects without diabetes.

RESEARCH DESIGN AND METHODS

We studied a nationwide, population-based Finnish register of 10,737 patients diagnosed with type 1 diabetes during 1980–2005 and followed for 10 years and 2,544 adults with long-standing diabetes drawn from the Finnish Diabetic Nephropathy Study (FinnDiane). Mortality was compared with the general Finnish population and 6,655 control subjects without diabetes.

RESULTS

The standardized mortality ratio (SMR) was increased during the first 10 years after the diagnosis (2.58 [95% CI 2.07–3.18], $P < 0.001$). Mortality in adults with long-standing diabetes, but without albuminuria, was no different from that of the general population (1.02 [0.84–1.22], $P = 0.83$). However, it was higher compared with that of control subjects without diabetes (1.33 [1.06–1.66], $P = 0.01$). Excess mortality was largely due to acute diabetes complications and ischemic heart disease, which remained more than fourfold higher (mortality rate ratio 4.34 [2.49–7.57]) in adults with type 1 diabetes than in control subjects without diabetes, despite the absence of albuminuria. By contrast, deaths due to alcohol and drugs were reduced in adults with type 1 diabetes ($P = 0.007$), especially in men.

CONCLUSIONS

Excess mortality in type 1 diabetes is the result of its complications. Acute complications drive an increased SMR in the first years. In individuals who remain free of albuminuria, mortality due to ischemic heart disease is still four times higher, and acute complications also occur.

Despite significant improvements in management, type 1 diabetes remains associated with an increase in mortality relative to the age- and sex-matched general population (1,2). Acute complications of diabetes may initially account for this increased risk (3,4). However, with increasing duration of disease, the leading contributor to excess mortality is its vascular complications including diabetic kidney disease (DKD) and

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cardiovascular disease (CVD). Consequently, patients who subsequently remain free of complications may have little or no increased risk of mortality (1,2,5). For example, we have previously shown that excess mortality in the Finnish Diabetic Nephropathy Study (FinnDiane) cohort of adults with type 1 diabetes was confined to participants with persistently elevated albuminuria (denoting the presence of vascular complications) (1). By contrast, the mortality in individuals with a normal urinary albumin excretion rate (AER) was no different from that of the general Finnish population (1). Similarly, in the Pittsburgh Epidemiology of Diabetes Complications Study, the standardized mortality ratio (SMR) was not elevated in participants who remained free of complications (2). A Danish study also reported that mortality in patients with type 1 diabetes without nephropathy was only slightly increased compared with the background population (5).

By contrast, studies using registry data sets have reported that mortality remains significantly elevated, even in patients without chronic complications of diabetes (6–8). It is possible that these divergent findings may be driven by acute diabetes complications that predominantly occur early in the course of type 1 diabetes. In this article, we describe the increased SMR in 10,737 Finnish children (aged 0–14 years) in a large population-based cohort followed over their first 10 years after diagnosis. Another potential reason may be that the longer follow-up in registry studies (6–8) allows for the progressive accrual of chronic complications. To explore these hypotheses and better establish the residual mortality risk in adults with type 1 diabetes without albuminuria, we have extended our previous analysis of FinnDiane (1) a further 7 years, and in addition to comparison with the general population we incorporated age-, sex- and place of residence–matched control subjects without diabetes to avoid a diluting effect of patients with diabetes in the general population. Finally, if the mortality risk was the same in patients with type 1 diabetes as in the subjects without diabetes, then the distribution of causes of death would be equal to that in the population without diabetes and not diabetes related. To overcome this problem, we compared the cause-specific mortality of the people with type 1 diabetes with that of control subjects without diabetes.

RESEARCH DESIGN AND METHODS

Population-Based (Early) Diabetes Cohort

Mortality was evaluated in a population-based cohort of 10,737 children (aged 0–14 years) with newly diagnosed type 1 diabetes in Finland who were listed on the National Public Health Institute diabetes register, Central Drug Register, and Hospital Discharge Register in 1980–2005 as previously described (9). We excluded patients with type 2 diabetes and diabetes occurring secondary to other conditions, such as steroid use, Down syndrome, and congenital malformations of the pancreas. Patients were followed from the time of diagnosis until death or for 10 years—whichever was shorter. The study population (diagnosis years 1980–1999) overlaps with our previous mortality study (10). The time period of 10 years was selected to effectively exclude individuals suffering chronic complications of diabetes, which take >10 years to be significant enough to compromise survival. For each subject, mortality outcomes were compared with the age- and sex-matched Finnish population.

The FinnDiane (Late) Cohort

FinnDiane is an ongoing, nationwide, multicenter study initiated to identify genetic and environmental risk factors for diabetes complications, with special emphasis on diabetic nephropathy in patients with type 1 diabetes.

A detailed description of the FinnDiane recruitment protocol has previously been published (11). Briefly, adult (≥18 years of age) patients with type 1 diabetes from 5 university and 16 central hospitals, 33 district hospitals, and 26 primary health care centers across Finland were asked to participate, and the participation rate was 78%. Type 1 diabetes was defined as age at onset of diabetes <40 years and insulin treatment initiated within 1 year of diagnosis. The study protocol is in accordance with the principles of the Declaration of Helsinki as revised in 2000 and was approved by the ethics committee of the Helsinki and Uusimaa Hospital District (FinnDiane) and the ethics committee of the National Institute for Health and Welfare (the early diabetes cohort). Written informed consents were obtained from each FinnDiane patient.

The baseline visit occurred between the years 1994 and 2008, at which time participants underwent a thorough clinical examination and blood and urine samples were collected. Information on the presence of diabetes complications including CVD was obtained from the medical files by the attending physician using a standardized questionnaire. Patients filled in questionnaires regarding their lifestyle, including their smoking habits, alcohol consumption, and socioeconomic and employment statuses.

Normal urinary albumin excretion was defined by AER persistently <20 μg/min or <30 mg/24 h or an albumin-to-creatinine ratio <2.5/3.5 mg/mmol. For this study, participants with normal urinary albumin excretion both at baseline and during follow-up (n = 2,544) were selected from the total cohort of FinnDiane participants with type 1 diabetes (n = 4,772). Patients who progressed during follow-up from normo- to microalbuminuria or even higher levels of albuminuria were excluded from the study (n = 294). Progression status was assessed at the follow-up visits, as well as by reviewing the medical files. AER is measured annually at the regular visits to the diabetes clinic. The median number of measurements of AER was 14 (interquartile range [IQR] 12–15). Only 9.2% of the patients did not provide any updated data on renal status after baseline. Participants were followed from their first baseline visit until the end of the calendar year 2014 or death. During the follow-up, series of estimated glomerular filtration rate (estimated using the Chronic Kidney Disease–Epidemiology Collaboration [CKD-EPI] equation) values were also collected. There were 67 decliners and 2,477 non-decliners according to the definition of Krolewski et al. (12) using a ≥3.3% annual loss of kidney function for decliners.

For each FinnDiane patient, mortality outcomes were compared with *1*) the age- and sex- matched general population or *2*) three control individuals selected from the Population Register Centre, matched for sex, age, and the place of residence in the year of diagnosis of diabetes in the FinnDiane patient. Any individuals with entitlement to special reimbursement for the costs of diabetes drugs (n = 593) were excluded from this control group. After this exclusion, there remained 6,655 subjects without diabetes in the control group. Follow-up in the control subjects was started on the same day as the follow-up in the case subject and continued until the end of the calendar year 2014 or death.

Ascertainment of Outcomes

The data were linked with the Finnish Cause of Death Register, and all death certificates of patients with diabetes were assessed. The reliability of the Finnish cause of death registers has been found to be high (13). Causes of death were classified based on the underlying cause of death using the ICD-10 as follows: ischemic heart disease (IHD) (I20–I25); cerebrovascular disease (I60–I69); other vascular disease (I00–I19, I26–I59, and I61–I99); cancer (C00–C97); acute diabetes complications hypo- and hyperglycemia and diabetic ketoacidosis (E100 and E101); fatal infections (mainly, pneumonia [J18], meningitis [A39], and pulmonary disease with infection [J440]); diseases of the nervous system (Alzheimer disease [G30 and F00], vascular dementia [F01], Parkinson disease [G20], epilepsy [G40], amyotrophic lateral sclerosis [G122], degeneration of nervous system [G31], and multiple sclerosis [G35]); risk-taking behavior deaths including suicides (X60–X84 and Y87), violent deaths (X85–Y09, Y16–Y84, and Y88–Y89), and drug- and alcohol-related deaths (poisonings and accidents due to alcohol or drugs [X41–X45], alcohol-induced chronic pancreatitis [K86], and alcoholic liver disease [K70]); and other causes. In a few cases, the classification had changed. If an accident was due to an acute diabetes complication, then the accident was classified as an acute diabetes complication. If an acute diabetes complication was due to alcohol or drugs, then the diabetes complication was classified as an alcohol/drug-related death. Data on hospitalizations due to acute diabetes episodes in the FinnDiane and the early-stage diabetes group were identified by linking the data with the Finnish Care Register for Health Care.

Statistical Methods

Crude mortality rates were calculated per 10,000 person-years with 95% Poisson confidence intervals. For modeling of the prognostic variables related to mortality, Cox regression analyses were conducted. Cumulative mortality was estimated by Kaplan-Meier survival analyses, and the log-rank test was used to test for between-group differences.

SMRs were calculated as the ratio of the number of observed and expected deaths in the age- and sex-matched Finnish general population, calculated by multiplying the number of person-years at risk by sex-, age-, and calendar year–specific mortality rates in the Finnish background population (Statistics Finland). The data were split into time at risk for each sex, 1-year age-groups, and calendar year groups. Mortality ratios for the FinnDiane cohort were also expressed as a ratio versus matched control subjects without diabetes. Statistical analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC).

RESULTS

Population-Based (Early) Diabetes Cohort

A total of 10,737 children with type 1 diabetes from the Finnish population were followed from diagnosis, including 5,816 boys and 4,921 girls with a median age of 18.3 years (IQR 14.8–21.5) and median age at onset of 8.3 years (IQR 4.9–11.5). The baseline characteristics of this cohort have previously been described (9). In this cohort, in the 10 years after diagnosis there were 84 deaths, equating to a mortality rate of 7.85 (95% CI 6.26–9.72) per 10,000 person-years. When compared with that of the age- and sex-matched Finnish population, the SMR was 2.58 (95% CI 2.07–3.18). The excess risk was similar for boys and girls. In addition, the SMR was increased regardless of the age at onset or the year of diagnosis of diabetes (Table 1). The main cause of death was acute diabetes complications (Fig. 1*A*).

The FinnDiane (Late) Cohort

Adults with type 1 diabetes without albuminuria (n = 2,544) from the FinnDiane cohort had a median age of 36.3 years (IQR 27.1–46.7) and a median duration of diabetes of 16.2 years (8.3–26.0) at baseline. Baseline characteristics are shown in Table 2. Over a median follow-up of 14.0 years (IQR 12.1–15.7) there were 117 deaths, equating to a mortality rate of 33.9 deaths per 10,000 person-years (95% CI 28.0–40.6). The main cause of death was CVD (Fig. 1*B*). With use of the total Finnish general population as reference, the expected number of deaths in FinnDiane was 114 compared with the 117 observed deaths, resulting in a nonsignificant SMR of

Table 1—Characteristics of the children and young Finnish adults with type 1 diabetes and their observed mortality in the 10 years after diagnosis

Variable	Number of patients	Observed number of deaths	Person-years	Mortality per 10,000 person-years	Expected number of deaths	SMR (95% CI)
Sex						
Men	5,816	53	57,960	9.14	23.51	2.25 (1.71–2.93)
Women	4,921	31	49,032	6.32	9.03	3.32 (2.28–4.68)
No. of hospitalizations for acute diabetes complication						
0	8,595	60	85,621	7.00	26.32	2.24 (1.72–2.87)
1	1,402	14	13,989	10.00	4.00	3.50 (1.99–5.73)
2–3	560	4	5,581	7.17	1.63	2.45 (0.78–5.92)
≥4	181	6	1,800	33.3	0.58	10.30 (4.17–21.42)
Age at onset of diabetes (years)						
0–4	2,784	7	27,748	2.52	4.30	1.63 (0.71–3.23)
5–9	3,969	22	39,573	5.56	8.35	2.63 (1.69–3.92)
10–14	3,984	55	39,652	13.9	19.87	2.72 (2.06–3.52)
Year of diagnosis						
1980–1989	3,298	27	32,845	8.22	12.84	2.03 (1.35–2.93)
1990–1999	4,253	33	42,400	7.78	12.31	2.68 (1.88–3.72)
2000–2005	3,186	24	31,748	7.56	7.39	3.25 (2.13–4.76)

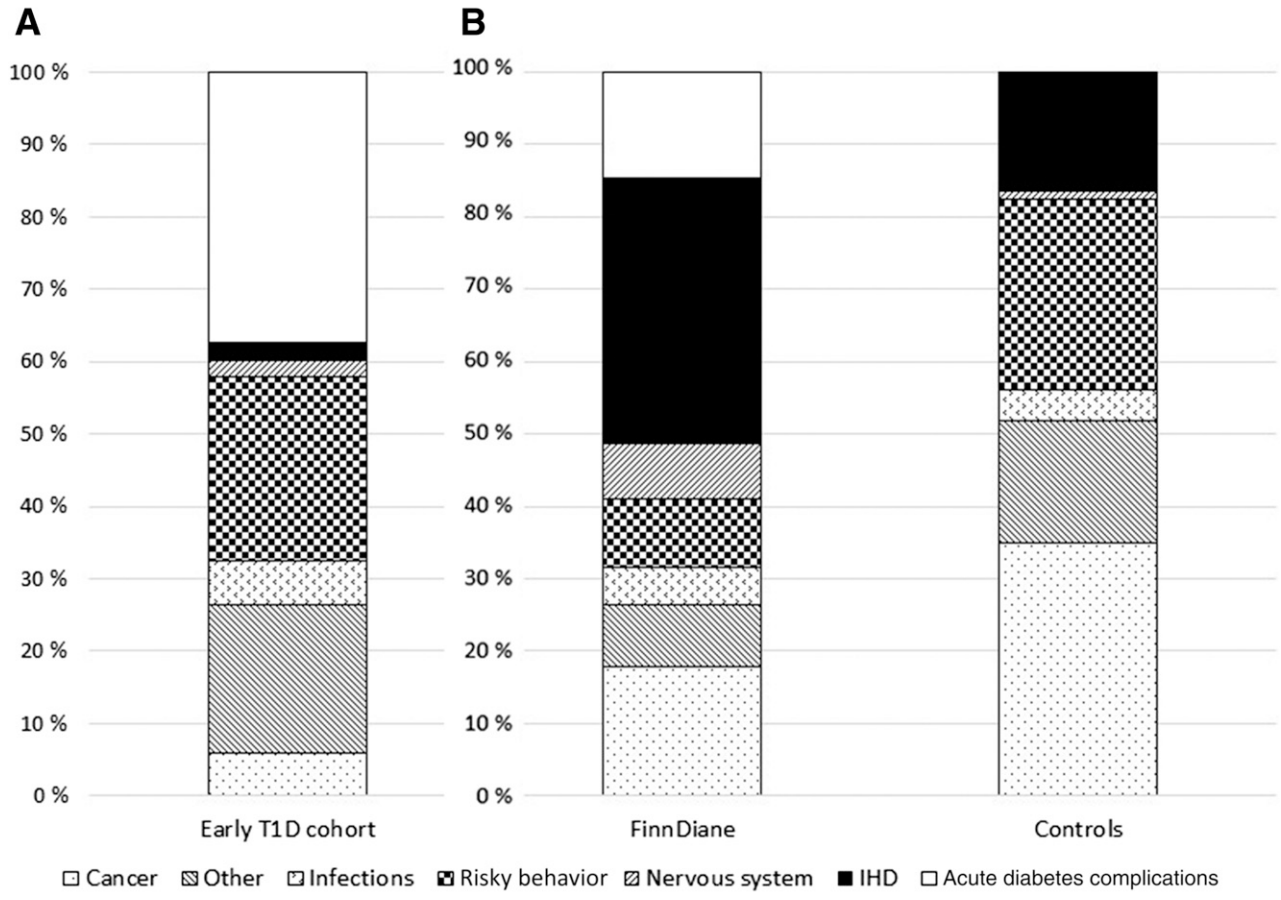

Figure 1—The proportion of causes of death in early-stage type 1 diabetes (T1D) during the first 10 years of diabetes (*A*) and in FinnDiane patients with normoalbuminuric type 1 diabetes and control individuals (without diabetes) for FinnDiane patients (*B*).

1.02 (95% CI 0.84–1.22). However, with use of control subjects without diabetes as the reference, the mortality rate ratio was 1.33 (95% CI 1.06–1.66, $P = 0.01$) (Table 3). Notably, this excess mortality in women became apparent only after >7 years of follow-up in the study (Supplementary Fig. 1*A*), and the mortality rate ratio was significant (1.59 [95% CI 1.10–2.30]) only in women (Supplementary Fig. 1*B*)—not in men (1.18 [95% CI 0.90–1.57]) (Supplementary Fig. 1*C*). Exclusion of the 67 decliners did not change the mortality rate ratio (1.28 [1.02–1.60]).

FinnDiane participants who died were more likely to be male, older, have a longer duration of diabetes, and later age of diabetes onset (Table 2). Notably, none of the conventional variables associated with complications (e.g., HbA_{1c}, hypertension, smoking, lipid levels, or AER) were associated with all-cause mortality in this cohort of patients without albuminuria. However, mortality was also independently associated with alcohol intake, employment status, and previous hospitalization due to acute diabetes complications (Supplementary Table 1).

The most frequent cause of death in the FinnDiane cohort was IHD (Fig. 1*B* and Table 3), largely driven by events in patients with long-standing diabetes and/or previously established CVD (Supplementary Fig. 2*A*). The mortality rate ratio for IHD was 4.34 (95% CI 2.49–7.57, $P < 0.0001$). There remained a number of deaths due to acute complications of diabetes, including ketoacidosis and hypoglycemia. This was most significant in patients with a shorter duration of diabetes but still apparent in those with long-standing diabetes (Supplementary Fig. 2*B*). Notably, deaths due to "risk-taking behavior" were lower in adults with type 1 diabetes compared with matched individuals without diabetes: mortality rate ratio was 0.42 (95% CI 0.22–0.79, $P = 0.006$) (Fig. 1*B* and Table 3). This was largely driven by the 80% reduction (95% CI 0.06–0.66) in deaths due to alcohol and drugs in males with type 1 diabetes (Table 3). No reduction was observed in female patients (rate ratio 0.90 [95% CI 0.18–4.44]), although the absolute event rate was already more than seven times lower in Finnish women than in men.

CONCLUSIONS

The chief determinant of excess mortality in patients with type 1 diabetes is its complications. In the first 10 years of type 1 diabetes, the acute complications of diabetes dominate and result in excess mortality—more than twice that observed in the age- and sex-matched general population. This early excess explains why registry studies following patients with type 1 diabetes from diagnosis have consistently reported reduced life expectancy, even in patients free of chronic complications of diabetes (6–8). By contrast, studies of chronic complications, like FinnDiane and the Pittsburgh Epidemiology of Diabetes Complications Study (1,2), have followed participants with, usually, >10 years of type 1 diabetes at baseline. In these patients, the presence or absence of chronic complications of

Table 2—Baseline clinical characteristics of adults with type 1 diabetes without albuminuria from the FinnDiane cohort study, stratified according to mortality

	Alive (n = 2,427)	Deceased (n = 117)	P
Male sex	47.2	62.2	0.001
Age (years)	34.8 (26.1–44.1)	50.3 (39.52–56.3)	<0.0001
Age at onset of diabetes (years)	16.5 (10.65–25.28)	20.6 (12.8–30.2)	0.0006
Duration of diabetes (years)	16.2 (8.65–25.40)	27.3 (18.6–38.6)	<0.0001
BMI (kg/m^2)	24.8 ± 3.3	26.0 ± 3.7	0.41
eGDR (mg/kg/min)	8.8 ± 2.3	7.9 ± 2.2	0.16
HbA_{1c} (%)	8.2 ± 1.4	8.1 ± 1.3	0.97
HbA_{1c} (mmol/mol)	65.7 ± 15.0	64.5 ± 14.7	
Hypertension†	61.5	79.5	0.27
Systolic blood pressure (mmHg)	129.0 ± 15.4	137.3 ± 15.7	0.22*
Diastolic blood pressure (mmHg)	77.9 ± 9.1	76.5 ± 9.5	0.004*
Antihypertension drugs	17.6	38.5	0.13*
Lipid-lowering drugs	6.7	19.7	0.13*
Total cholesterol (mg/dL)	185.3 ± 34.7	189.2 ± 34.7	0.71*
LDL (mg/dL)	112.0 ± 30.9	115.8 ± 30.9	0.47*
HDL cholesterol (mg/dL)	54.1 ± 15.4	54.1 ± 15.4	0.64*
Triglycerides (mg/dL)	34.7 (27.0–50.2)	38.6 (30.9–50.2)	0.07*
eGFR (mL/min/1.73 m^2)	98.8 ± 19.0	89.68 ± 18.7	0.55*
Smoking status			
Ever smokers	40.7	58.0	0.0003
Current smokers	22.8	30.4	0.0001
Amount of alcohol (g/week)	48 ± 70.6	91 ± 113	<0.0001
Employment status			<0.0001
Unemployed	12.2	24.8	
Unable to work	4.8	22.2	
Employed	61.8	41.0	
Not known	16.9	12.0	
No. of hospitalizations for acute diabetes complication			0.0006
0	71.2	58.1	
1	15.4	17.1	
2–3	9.7	14.5	
≥4	3.7	10.3	
Laser-treated diabetic retinopathy	11.8	33.3	0.0002*
CVD event‡	8.0	25.6	<0.0001*

Data are expressed as mean ± SD, median (IQR), or percent. P value refers to ANOVA, Kruskal-Wallis test, or χ^2 test. eGDR, estimated glucose disposal rate; eGFR, estimated glomerular filtration rate (estimated using the CKD-EPI equation). *Denotes adjustment for age. †Blood pressure ≥130/80 mmHg or use of antihypertension medication. ‡Includes myocardial infarction, coronary revascularization, and stroke (events until the end of 2014). To convert cholesterol to millimoles per liter, multiply values by 0.0259.

diabetes is critical for survival. In particular, the presence and severity of albuminuria (as a marker of vascular burden) is strongly associated with mortality outcomes in type 1 diabetes (1). However, the FinnDiane normoalbuminuric patients showed increased all-cause mortality compared with the control subjects without diabetes in contrast to when the comparison was made with the Finnish general population, as in our previous publication (1). Two crucial causes behind the excess mortality were acute diabetes complications and IHD.

Despite major improvements in the delivery of diabetes care and other technological advances, acute complications remain a major cause of death both in children and in adults with type 1 diabetes. Indeed, the proportion of deaths due to acute events has not changed significantly over the last 30 years. The proportion of deaths due to acute diabetes complications reported here in the Finnish early diabetes cohort (36%) is very similar to that previously reported in other Nordic countries (8,14). Similarly, the proportion of deaths due to acute complications in the FinnDiane group was 14%, which is also consistent with rates observed in other recent cohort studies in adults with type 1 diabetes (14). Even in patients with long-standing diabetes (>20 years), the risk of death due to hypoglycemia or ketoacidosis remains a constant companion. It is important to note that these events were partly predictable, with most of the deaths occurring in the first 10 years after diagnosis and in individuals with a prior history of hospitalization for acute complications. If it were possible to eliminate all deaths from acute events, the observed mortality rate would have been no different from the general population in the early cohort.

It is well-known that CVD is strongly associated with DKD (15). However, in the current study, mortality from IHD remained higher in adults with type 1 diabetes without albuminuria compared with matched control subjects in both men and women. This is concordant with other recent studies also reporting

Table 3—Underlying cause of death, crude mortality, and mortality rate ratio in adults with type 1 diabetes without albuminuria from the FinnDiane cohort

Causes of death	Deaths in FinnDiane	Deaths in control subjects without diabetes	Mortality rate in FinnDiane per 10,000 person-years	Mortality rate in control subjects without diabetes per 10,000 person-years	Mortality rate ratio (95% CI) between FinnDiane and control subjects without diabetes	*P*
All causes, all	117 (100)	232 (100)	33.89	25.53	1.33 (1.06–1.66)	0.01
Women	45	76	24.85	15.59	1.59 (1.10–2.30)	0.01
Men	72	156	43.89	37.05	1.18 (0.90–1.57)	0.23
Cancer	21 (18.0)	81 (34.9)	6.08	8.9	0.68 (0.42–1.10)	0.11
IHD, all	33 (28.2)	20 (8.6)	9.56	2.2	4.34 (2.49–7.57)	<0.0001
Women	13	6	7.18	1.23	5.83 (2.22–15.35)	<0.0001
Men	20	14	12.2	3.33	3.66 (1.85–7.25)	<0.0001
Cerebrovascular disease	6 (5.1)	8 (3.5)	1.74	0.88	1.97 (0.68–5.69)	0.20
Other circulatory	4 (3.4)	10 (4.3)	1.16	1.10	1.05 (0.33–3.36)	0.93
Infections	6 (5.1)	10 (4.3)	1.74	1.10	1.58 (0.57–4.34)	0.37
Diseases of the nervous system	9 (7.7)	3 (1.3)	2.61	0.33	7.89 (2.14–29.16)	0.0002
Accidents	5 (4.3)	13 (5.6)	1.45	1.43	1.01 (0.36–2.84)	0.98
Suicides*	5 (4.3)	17 (7.3)	1.45	1.87	0.77 (0.29–2.10)	0.61
Alcohol and drug related, all*	5 (4.3)	44 (19.0)	1.45	4.84	0.30 (0.12–0.75)	0.007
Women	2	6	1.10	1.23	0.90 (0.18–4.40)	0.89
Men	3	38	1.83	9.03	0.20 (0.06–0.66)	0.003
Violent*	1 (0.85)	8 (3.5)	0.29	0.88	0.33 (0.04–2.63)	0.27
Acute diabetes complication	16 (13.7)*	—	4.63	—	—	—
Chronic diabetes complications	1 (0.8)	—	0.29	—	—	—
Other causes	4 (3.4)	18 (7.8)	1.16	1.98	—	—

Data are *n* or *n* (%) unless otherwise indicated. *Risk-taking behavior deaths.

increased mortality from CVD in patients with type 1 diabetes in the absence of DKD (7,8) and reinforces the need for aggressive cardiovascular risk reduction even in patients without signs of microvascular disease. However, it is important to note that the risk of death from CVD, though significant, is still at least 10-fold lower than observed in patients with albuminuria (1).

Alcohol- and drug-related deaths were substantially lower in patients with type 1 diabetes compared with the age-, sex-, and region-matched control subjects. Our previous population-based study that did not require participation showed that the proportion of alcohol-related deaths and suicides was remarkable (~30%) and comparable with that of control subjects without diabetes in this study (10). The reduction in the current study substantially offset the increased deaths due to IHD and acute diabetes complications in this cohort. Even though alcohol consumption remained associated with all-cause mortality in this cohort, the overall alcohol intake documented here was less than that documented in the Finnish general population (16). This may reflect a selection bias, such that FinnDiane participants were all volunteers. Even though participation rates in FinnDiane were high (78%), it is possible that the health behaviors of participants were different from those of the general population or control subjects selected anonymously from registry data. Nonparticipation in health studies is associated with poorer health, stress, and lower socioeconomic status (17,18), which are in turn associated with increased risk of premature mortality. It can be speculated that with inclusion of patients with risk-taking behavior, the mortality rate in patients with diabetes would be even higher and, consequently, the SMR would also be significantly higher compared with the general population.

Selection of patients who despite long-standing diabetes remained free of albuminuria may also have included individuals more accepting of general health messages and less prone to depression and nihilism arising from treatment failure. This kind of selection is seen in the DCCT/EDIC (Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications) study, where mortality in patients with type 1 diabetes was not increased compared with the U.S. general population (19). The researchers acknowledged that study population had a high socioeconomic status and high likelihood of compliance with the treatment protocol.

When we consider the generalizability of SMR findings from this study as well as any study, we have to carefully take into account the assembly of the study population and the strengths and limitations and therefore the consequences of the comparison group that is used. In this study, we used two different analytical approaches, comparing data on mortality in adults without albuminuria in FinnDiane with data from the age- and sex-matched general population as well as age-, sex-, and region-matched control subjects without diabetes. Only the latter demonstrated that adults without albuminuria had a modest but significant increase in all-cause mortality. Comparisons with the general population, rather than matched control subjects, may overestimate expected mortality, diluting the SMR estimate, as in the general population ~10% of adults have diabetes (20,21). Indeed, when we included individuals with diabetes in the control subjects, the mortality rate ratio was 1.20 instead of 1.33. The discrepancy between the estimates when the reference was the general population or the control subjects without

diabetes can be explained by the presence of patients with diabetes in the general population as well as the likelihood of participation in a study.

One strength of this study is the large number of patients studied over long periods of time, extending our previous observations in adults with long-standing diabetes (1) by >7 years. Notably, time-to-event analyses revealed that the cumulative mortality only became significantly different 10 years after enrollment. This may partly explain why our initial 7-year follow-up study did not show any excess mortality in adults without albuminuria (1). Why excess mortality was specifically observed in female patients but not males is unclear, although previous studies have reported the attenuation of sex-associated protection against CVD in women with diabetes (22). It is also possible that fewer deaths due to excess alcohol consumption and drugs in men with diabetes substantially offset other causes of deaths, resulting in a mortality rate in men not different from that in matched control subjects. Women, on the other hand, already have a much lower rate of death due to alcohol or drugs, meaning that an increase in IHD deaths was significant and apparent earlier in women. Longer follow-up may be required before the clear increased risk of cardiovascular death observed in men also ultimately results in significantly increased all-cause mortality.

In conclusion, these findings reinforce the importance of early strategies for preventing, slowing, arresting, or reversing all diabetes complications. Hypoglycemia and ketoacidosis remain major barriers both in early and advanced diabetes—in childhood and in adulthood. In long-term diabetes, avoiding chronic complications may be associated with mortality rates comparable with those of the general population; although death from IHD remains increased, this is offset by reduced risk-taking behavior, especially in men.

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