Long-term Mortality and End-Stage Renal Disease in a Type 1 Diabetes Population Diagnosed at Age 15–29 Years in Norway

DOI: 10.2337/dc16-1213

Vibeke Gagnum,[1,2] Lars C. Stene,[2,3] Torbjørn Leivestad,[4] Geir Joner,[1,2,5] and Torild Skrivarhaug[1,2,6]

OBJECTIVE

To study long-term mortality, causes of death, and end-stage renal disease (ESRD) in people diagnosed with type 1 diabetes at age 15–29 years.

RESEARCH DESIGN AND METHODS

This nationwide, population-based cohort with type 1 diabetes diagnosed during 1978–1982 (*n* = 719) was followed from diagnosis until death, emigration, or September 2013. Linkages to the Norwegian Cause of Death Registry and the Norwegian Renal Registry provided information on causes of death and whether ESRD was present. A clinical committee reviewed the causes of death. We calculated standardized mortality ratios (SMRs) for comparison with the background population.

RESULTS

During 30 years' follow-up, 4.6% of participants developed ESRD and 20.6% (*n* = 148; 106 men and 42 women) died. Cumulative mortality by years since diagnosis was 6.0% (95% CI 4.5–8.0) at 10 years, 12.2% (10.0–14.8) at 20 years, and 18.4% (15.8–21.5) at 30 years. The SMR was 4.4 (95% CI 3.7–5.1). Mean time from diagnosis of diabetes to ESRD was 23.6 years (range 14.2–33.5). Death was caused by chronic complications (32.2%), acute complications (20.5%), violent death (19.9%), or any other cause (27.4%). Death was related to alcohol in 15% of cases. SMR for alcohol-related death was 6.8 (95% CI 4.5–10.3), for cardiovascular death was 7.3 (5.4–10.0), and for violent death was 3.6 (2.3–5.3).

CONCLUSIONS

The cumulative incidence of ESRD was low in this cohort with type 1 diabetes followed for 30 years. Mortality was 4.4 times that of the general population, and more than 50% of all deaths were caused by acute or chronic complications. A relatively high proportion of deaths were related to alcohol.

Studies assessing causes of death in type 1 diabetes are most frequently conducted in individuals diagnosed during childhood (1–7) or without evaluating the effect of age at diagnosis (8,9). Reports on causes of death in cohorts of patients diagnosed during late adolescence or young adulthood, with long-term follow-up, are less frequent (10). This period in life is often referred to as "emerging adulthood" and is represented by several changes in life, increasing risk behaviors, and exploration of possible life directions (11). Young people move away from the care provided by their families. Transition from

[1]Division of Paediatric and Adolescent Medicine, Oslo University Hospital, Oslo, Norway
[2]Oslo Diabetes Research Centre, Oslo, Norway
[3]Division of Epidemiology, Norwegian Institute of Public Health, Oslo, Norway
[4]Norwegian Renal Registry, Department of Transplantation Medicine, Oslo University Hospital, Oslo, Norway
[5]Institute of Clinical Medicine, University of Oslo, Oslo, Norway
[6]Norwegian Childhood Diabetes Registry, Division of Paediatric and Adolescent Medicine, Oslo University Hospital, Oslo, Norway

Corresponding author: Vibeke Gagnum, vibeke.gagnum@ous-hf.no.

Received 6 June 2016 and accepted 1 October 2016.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc16-1213/-/DC1.

This study used data from the Norwegian Cause of Death Registry. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Norwegian Cause of Death Registry is intended nor should be inferred.

pediatric to adult health care frequently poses challenges (12). Adherence to treatment during this age is poor and the risk of acute diabetic complications is high (13–16). Mortality may differ between those with diabetes diagnosed during this period of life and those diagnosed during childhood. A large Finnish study focusing on mortality among early onset (0–14 years) and late-onset (15–29 years) type 1 diabetes reported deteriorating survival and an increasing proportion of deaths from acute diabetic complications in late-onset type 1 diabetes since the 1980s (10).

The aim of this study was to assess mortality, causes of death, and incidence of end-stage renal disease (ESRD) in a population-based, nationwide cohort diagnosed with type 1 diabetes during 1978–1982, at age 15–29 years, and followed to 2013. We linked high-quality nationwide registries to obtain the causes of death and the incidence of ESRD. A clinical committee reviewed the causes of death by evaluating clinical records. To our knowledge this is the only study with long-term follow-up among patients diagnosed in this age range and that uses a clinical review committee in addition to registry data.

RESEARCH DESIGN AND METHODS

Subjects and Study Design

The cohort was population-based and national, comprising individuals diagnosed with type 1 diabetes between 15 and 29 years of age, in 1978–1982 (n = 719). The cohort was collected retrospectively in 1988–1990 by contacting all medical and pediatric departments in Norway, and through the nationwide National Insurance Institution. The ascertainment of the cohort, based on two independent sources, was estimated to 87.8% (17). The cases were classified as type 1 diabetes according to EURODIAB criteria (18). The cohort represented a homogenous population, comprising almost exclusively ethnic Norwegians with good access to a public health care system (19). The cohort consisted of 784 cases in 1991 but was reduced during a cleaning process to 719 cases in this study. Duplicates were deleted (n = 30) and cases that were not identifiable in the National Population Registry (n = 7), did not consent to be in the diabetes registry (n = 3), did not have type 1 diabetes (n = 11), or had an incorrect original date of diagnosis (n = 14) were removed. The follow-up period for each patient was calculated from the date of the first insulin injection to the date of death, emigration, or 30 September 2013. Survival and emigration status were determined by linking the study cohort to the National Population Registry using participants' unique national personal identification numbers.

Causes of Death

We obtained causes of death by linking to the Norwegian Cause of Death Registry. This national registry bases its information on death certificates and autopsy reports. In Norway doctors are required to complete death certificates. In 1986 round 18% of all people who died in Norway were autopsied, decreasing to only 8.3% in 2010 (20). To assess excess mortality compared with the general population in Norway, we calculated cause-specific standardized mortality ratios (SMRs) based on the ICD-10 code for the underlying cause of death (violent death, including accidents and intoxications [V01–V99, W00–X59, X4n, F10.0–F19.0], suicides [X60–X84], cancer [C00–C97], cardiovascular disease [CVD; I00–I99], ischemic heart disease [I20–I25], and cerebrovascular disease [I60–I69]). If the underlying cause of death was "diabetes" (E10.0–E10.9, except E10.5, which was classified as cardiovascular death), we examined the other ICD codes listed on the death certificate since we know that "diabetes" might reflect both acute and a variety of long-term complications. If an ICD code indicating cardiovascular death was identified anywhere on the death certificate, the case was defined as cardiovascular death. If no other causes (ICD codes) were listed, the case was excluded from the SMR analysis. SMRs for acute diabetic complications were not estimated because death due to hypoglycemia and diabetic ketoacidosis (DKA) occurs almost exclusively in individuals with type 1 diabetes. We calculated SMRs for alcohol-related deaths (ICD-10 codes E24.4, F10.0, F10.2, F10.4, F10.7, G31.2, G62.1, G72.1, I42.6, K29.2, K70, K86.0, Q86.0, X45, X65, Y15) in two ways: based on the underlying cause of death and based on all ICD codes listed on the death certificate. During the period of this study, the ICD codes in use were either ICD-8, ICD-9, or ICD-10. All codes were translated into ICD-10 codes.

A clinical committee comprising two diabetologists (V.G., T.S.) reviewed the causes of death in detail by considering all death certificates, medical journals, autopsy reports, and police reports available. We obtained the medical records by contacting regional and local hospitals, the doctors signing the death certificates, or the general practitioners. The review committee grouped the causes of death as follows:

1. Acute complications: include DKA and hypoglycemia. DKA was diagnosed by autopsy or in the hospital before death occurred. Death was attributed to hypoglycemia if blood glucose near time of death indicated hypoglycemia or if it was implied by other circumstances and signs.
2. Chronic complications: include deaths from renal failure and all cardiovascular deaths, subdivided as death from ischemic heart disease, cerebrovascular disease and all other CVDs, and other diabetes complications. Cases were classified as renal death if renal disease was considered the primary/immediate cause of death.
3. Violent death: subdivided as fatal accidents, intoxications, and suicides.
4. Other, non-diabetes-related deaths: all other causes of death, including infections not related to diabetes, any form of cancer, and sudden, unexplained deaths. The committee looked for cases of "dead-in-bed," defined as individuals without a history of long-term complications, observed to be in good health the day before, but found dead in an undisturbed bed and for whom the autopsy was not informative (21). We tried to identify factors that might have contributed to death. A particular focus was on deaths related to alcohol or drug abuse, defined by ICD-10 codes in accordance with the definition used by the Norwegian Institute of Public Health (20). The committee also classified the causes of death in relation to diabetes: "diabetes-related deaths" (diabetes caused or was a major contributor to death) or "non-diabetes-related deaths" (death was not related to diabetes or the relation was uncertain).

The Norwegian Regional Committee for Research Ethics approved the study protocol (reference no. 2012/1939). The

director of public prosecutions gave permission to review the forensic autopsy reports, including police reports.

End-Stage Renal Disease

To estimate the cumulative incidence of ESRD caused by diabetic nephropathy, we linked to the Norwegian Renal Registry; this registry includes data on all patients in Norway receiving renal replacement therapy for chronic renal failure since 1980 and has high degree of ascertainment (22). We also assessed cumulative mortality among individuals with ESRD.

Data Analysis

We used Stata software version 13 (StataCorp LP, College Station, TX) for data handling and analyses. We estimated the cumulative mortality by years from diagnosis of type 1 diabetes using Kaplan-Meier analysis. Differences between curves were tested by the log-rank test. We also used years since diagnosis as the time scale in Cox regression models to estimate unadjusted and adjusted hazard ratios (HRs) for the association between mortality, sex, and ESRD. ESRD was handled as a time-varying covariate. The variables were included simultaneously in the regression model. We assessed cumulative incidence of ESRD by years from diagnosis of type 1 diabetes using Kaplan-Meier analysis; we also analyzed the data when considering death as a competing risk (stcompet and stcrreg functions in Stata). SMRs were calculated, based on age attained and sex, as a ratio of the observed to the expected number of deaths. All-cause mortality rates in one calendar year and age groups for each sex were obtained from Statistics Norway, and cause-specific mortality rates in 5-year periods and age groups for each sex were obtained from the Norwegian Cause of Death Registry. Mortality rates among the general population were obtained for the period 1978–2012. Each patient contributed to the total person-years the time they spent within each age band and calendar period. A significance level of 5% was used in all analyses.

RESULTS

All-Cause Mortality

Among the cohort of 719 individuals, 20.6% (n = 148; 25.4% of men and 13.9% of women) died during a mean follow-up of 29.6 years (Table 1). The overall mortality rate was 6.96 per 1,000 person-years; the risk of mortality in women was about half that of men (HR 0.5; 95% CI 0.4–0.8; $P < 0.001$). Cumulative mortality by years since diagnosis was 6.0% (95% CI 4.5–8.0) at 10 years, 12.2% (95% CI 10.0–14.8) at 20 years, and 18.4% (95% CI 15.8–21.5) at 30 years (Supplementary Fig. 1). Mortality was between four and five times higher than in the general population (SMR 4.4; 95% CI 3.7–5.1). The excess mortality was similar for men (SMR 4.5; 95% CI 3.8–5.5) and women (SMR 3.9; 95% CI 2.9–5.3). SMR was higher in the lower age bands—6.7 (95% CI 3.9–11.5) at 15–24 years and 7.3 (95% CI 5.2–10.1) at 25–34 years—compared with the higher age bands: 3.7 (95% CI 2.7–4.9) at 45–54 years and 3.9 (95% CI 2.6–5.8) at 55–65 years (Supplementary Fig. 2). The Cox regression model showed that the risk of death increased significantly by age at diagnosis (HR 1.1; 95% CI 1.1–1.2; $P < 0.001$) and was eight to nine times higher if ESRD was present (HR 8.7; 95% CI 4.8–15.5; $P < 0.0001$).

Table 1—Demographic characteristics of 719 individuals with type 1 diabetes, diagnosed at age 15–29 years, in Norway, 1978–1982

	Total	Men	Women
Participants	719 (100)	417 (58.0)	302 (42.0)
Age at diagnosis (years)	22.4 (15.0–29.9)	22.5 (15.1–29.9)	22.4 (15.0–29.9)
Duration of diabetes (years)	29.6 (0.05–35.8)	28.6 (0.15–35.8)	31.0 (0.05–35.8)
Age at end of follow-up (years)	52.0 (17.1–64.9)	51.0 (17.1–64.9)	53.4 (17.8–64.6)
Follow-up (person-years)	21,271.7	11,913.2	9,358.5
Mortality			
Dead*	148 (20.6)	106 (25.4)	42 (13.9)
Emigrated	15 (2.1)	9 (2.2)	6 (2.0)
Mortality rate (per 1,000 person-years)	6.96 (5.90–8.15)	8.90 (7.32–10.72)	4.49 (3.28–6.01)
ESRD			
Participants who developed ESRD	33 (4.6)	22 (5.3)	11 (3.6)
Incidence rates of ESRD (per 1,000 person-years)	1.57 (1.11–2.20)	1.87 (1.23–2.84)	1.18 (0.65–2.14)
Time from diagnosis of diabetes to ESRD (years)	23.6 (14.2–33.5)	23.4 (14.2–33.5)	24.0 (16.9–31.5)
Deceased participants who had ESRD	14 (9.5)	8 (7.5)	6 (14.3)

Data are n (%) or mean (range), unless otherwise indicated. *Mean HbA_{1c} was 9.00% (77 mmol/mol), but HbA_{1c} was available in only 26.0% (n = 38) of the deceased and is probably not representative of the cohort.

Causes of Death

In two cases the cause of death was missing from the Norwegian Cause of Death Registry. According to that registry, of the remaining 146 cases the underlying cause of death was diabetes in 57 individuals (39.0%), circulatory in 22 (15.1%), cancer in 18 (12.3%), accidents or intoxications in 20 (13.7%), suicide in 8 (5.5%), and any other cause in 21 (14.4%) (Supplementary Fig. 3). In addition, diabetes contributed to death in 29.5% (n = 43) and CVD contributed to death in 10.9% (n = 29) of the 146 cases. Diabetes was mentioned on the death certificate for 68.2% of the cohort but for only 30.0% of the violent deaths. An autopsy was performed in 51%.

The clinical committee reviewed death certificates in all cases, medical records in 82%, medical autopsy reports in 19%, forensic autopsy reports in 32%, and police reports in 27%. Among those who died in a hospital (n = 59), medical records from terminal admission were available in 56 cases. Among those who did not die in a hospital (n = 87) an autopsy was performed in 50 cases and medical records were obtained in 63 cases. The medical records were either from previous visits or admissions to the hospital (n = 19), clinical notes by the doctor who certified death and wrote the death certificate (n = 4), or a combination of the two (n = 40). All autopsy reports were available. In 5% (n = 8; six cancers, one accident, and one case of meningitis), the only source of information was the death certificate; in all these cases, however, the death certificate was considered to be of high quality and additional information was not necessary. The clinical committee reclassified the cause of

death in 71 cases. All cases with diabetes listed as the underlying cause of death were reclassified (n = 57): 33.3% (n = 19) to DKA, 14.0% (n = 8) to hypoglycemia, 33.3% to chronic complications (CVD, n = 16; renal death, n = 3), 1.8% (n = 1) to suicide, 1.8% (n = 1) to cancer, and 15.8% (n = 9) either to other causes not related to diabetes or to sudden, unexplained deaths. Among the 57 cases with diabetes as the underlying cause of death, the ICD-10 code E10.9 (diabetes without complications) was used without any additional codes in 11 cases; 10 of these were classified as acute complications when reviewed by the clinical committee. The clinical committee classified death as caused by hypoglycemia in an additional two cases; one was originally noted with CVD on the death certificate, the other with violent death. One male fulfilled the criteria of dead-in-bed; he also had epilepsy. Cause-specific mortality rates are presented in Supplementary Table 1.

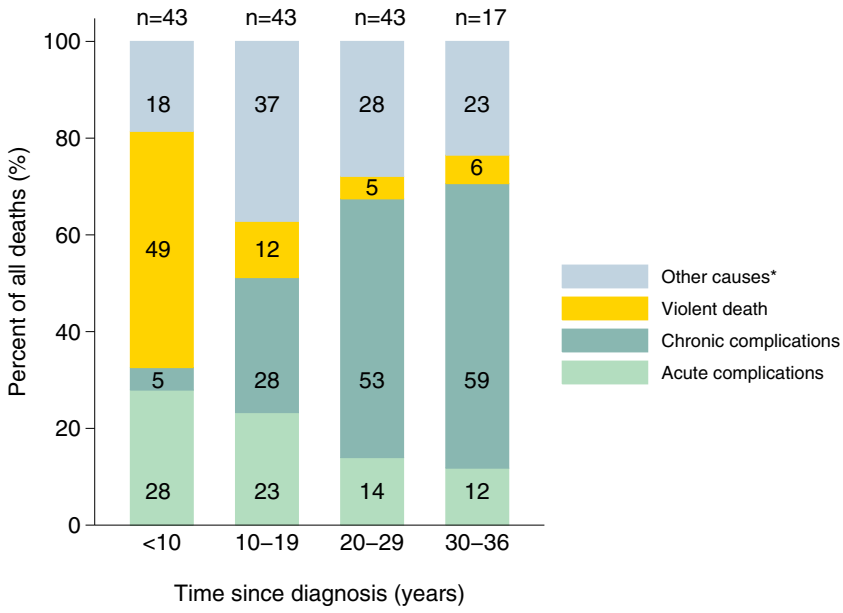

Figure 1—Causes of death by years since diagnosis of diabetes in 146 individuals with type 1 diabetes diagnosed between 15 and 29 years of age, assessed by a clinical review committee. Percentages are displayed in the bar diagram. Age at death ranged from 17 to 63 years. *"Other causes" include death by cancer and sudden, unexplained deaths.

Diabetic Complications

In 60% (88/146) of the cases the review committee considered death to be related to diabetes, whereas in 40% (58/146) the cause was unrelated to diabetes or had an unknown relation to diabetes. According to the clinical committee, acute complications caused death in 20.5% (30/146) of the cases; 20 individuals died as a result of DKA and 10 from hypoglycemia. Among deaths attributed to DKA, an autopsy was performed in 15 cases and hospital records from terminal admission were available in 5 cases. The proportion of deaths due to acute complications was lower in the higher age bands (Fig. 1). The risk of death due to acute complications was lower in women compared with men (borderline significant; HR 0.47; 95% CI 0.21–1.02; Supplementary Table 1). Chronic complications caused the largest proportion of deaths (47/146; 32.2%) and increased with increasing duration of diabetes (Fig. 1). Among individuals dying as a result of chronic complications (n = 47), CVD caused death in 94% (n = 44) and renal failure in 6% (n = 3). ESRD contributed to death in 22.7% (10/44) of those dying from CVD. Cardiovascular death occurred at mortality rates seven times higher than those in the general population (Table 2). ESRD caused or contributed to death in 13 of 14 cases, when present. The mortality rate for renal death was 0.14 (95% CI 0.05–0.43) per 1,000 person-years (Supplementary Table 1). However, if including all 13 cases in which renal disease was the immediate or contributing cause of death, the mortality rates were 0.61 (95% CI 0.34–1.02) per 1,000 person-years (0.58 [95% CI 0.26–1.16] in men and 0.64 [95% CI 0.26–1.33] in women). Among individuals with ESRD (n = 14), 71.4% (n = 10) died of CVD, 21.4% (n = 3) from renal failure, and 7.1% (n = 1) from cancer. The three individuals dying because of renal failure all had CVD, although CVD did not contribute to death.

Violence (intoxications, accidents, and suicides) was the leading cause of death before 10 years' duration of diabetes; thereafter it was only a minor cause (Fig. 1). Insulin was used in two of seven suicides. The risk of violent death was significantly lower among women compared with men (HR 0.05; 95% CI 0.01–0.35; Supplementary Table 1). Only one woman died due to violence. Mortality rates were significantly elevated compared with the general population. (Table 2).

Alcohol-Related Death

According to the available medical records and autopsy reports, about 20% (29/146) of the deceased misused alcohol. In 15% (22/146) alcohol-related ICD-10 codes were listed on the death certificate (18% [19/106] of men and 8% [3/40] of women). In 10 cases the cause of death was uncertain but considered to be related to alcohol or diabetes; otherwise the cause of death was DKA (n = 5), hypoglycemia (n = 1), suicide (n = 2), alcoholic liver cirrhosis (n = 3), or renal failure (n = 1). An autopsy had been performed in 13 cases. The SMR for alcohol-related death was high when considering the underlying cause of death (5.0; 95% CI 2.5–10.0), and even higher when considering all alcohol-related ICD-10 codes listed on the death certificate (6.8; 95% CI 4.5–10.3). The cause of death was associated with alcohol in 21.8% (19/87) of those who died with less than 20 years' diabetes duration. Drug abuse was noted on the death certificate in only two cases.

End-Stage Renal Disease

During follow-up, 33 individuals (4.6%; 22 men and 11 women) developed ESRD as a result of diabetic nephropathy. Mean time from diagnosis of diabetes to ESRD was 23.6 years (range 14.2–33.5 years). Cumulative incidence of ESRD by years since diagnosis of diabetes was 1.4% (95% CI 0.7–2.7) at 20 years and 4.8% (95% CI 3.4–6.9) at 30 years. There was no significant difference between men and women (Fig. 2). The Kaplan-Meier estimate and the model handling death as a competing risk gave very similar results (data not shown). Incidence of ESRD by years after diagnosis of type 1 diabetes was 2.91 per 1,000 person-years (95% CI

Table 2—Standardized mortality ratios for underlying cause of death by sex in 719 individuals with type 1 diabetes, diagnosed between 15 and 29 years of age, followed until September 2013

Cause of death, by sex	Observed deaths (*n*)	Expected deaths (*n*)	SMR	95% CI
CVD				
Male	28	4.40	6.4	4.4–9.2
Female	13	1.18	11.0	6.4–18.9
Ischemic heart disease				
Male	21	2.60	8.0	5.2–12.3
Female	10	0.40	22.7	12.2–42.2
Cerebrovascular disease				
Male	3	0.69	4.4	1.4–13.5
Female	0	0.42	—	—
Alcohol-related*				
Male	19	2.70	7.0	4.5–11.1
Female	3	0.55	5.5	1.8–16.9
Suicide				
Male	7	2.52	2.8	1.3–5.8
Female	0	0.76	—	—
Violent (intoxication and accidents)				
Male	21	5.91	3.6	2.3–5.3
Female	0	1.27	—	—
Cancer				
Male	9	5.48	1.6	0.9–3.2
Female	9	5.35	1.7	0.9–3.2
Renal death				
Male	2	0.03	58.1	28.4–232.3
Female	2	0.02	108.0	27.0–431.9

*SMR for alcohol-related death was based on all ICD-10 codes listed on the death certificate.

1.83–4.62) at 15–24 years and 3.05 per 1,000 person-years (95% CI 1.80–5.14) at 25–34 years. In total, 51% (95% CI 33–72) died within 10 years after diagnosis of ESRD (Supplementary Fig. 4).

CONCLUSIONS

This study highlights three important findings. First, among individuals who were diagnosed with type 1 diabetes in late adolescence and early adulthood and had good access to health care, and who were followed for 30 years, mortality was four to five times that of the general population. Second, 15% of all deaths were associated with alcohol, and the SMR for alcohol-related deaths was 6.8. Third, there was a relatively low cumulative incidence of ESRD (4.8%) 30 years after the diagnosis of diabetes.

We report mortality higher than those from a large, population-based study from Finland that found cumulative mortality around 6% at 20 years' and 15% at 30 years' duration of diabetes among a population with age at onset and year of diagnosis similar to those in our cohort (10). The corresponding numbers in our cohort were 12% and 18%, respectively; the discrepancy was particularly high at 20 years. The SMR in the Finnish cohort was lower than that in our cohort (2.6–3.0 vs. 3.7–5.1), and those authors reported the SMR to be lower in late-onset diabetes (at age 15–29 years) compared with early onset diabetes (at age <15 years). This was not the case in Norway; the SMR we report in this study was comparable to or higher than what was recently published in a study of childhood-onset diabetes (3.1–4.0 vs. 3.7–5.1) (23). The differences between the Norwegian and Finnish data are difficult to explain since both reports are from countries with good access to health care and a high incidence of type 1 diabetes. A recent study using the DCCT/Epidemiology of Diabetes Interventions and Complications (EDIC) cohort reported mortality in the intensively treated group to be similar to that of the general population (SMR 0.67–1.16), whereas in the conventionally treated group the SMR was 1.05–1.16 (24). However, these results are not comparable to those from our cohort because the participants in the DCCT were enrolled in a randomized clinical trial that required adherence to specific treatment and therefore included highly motivated patients. Also, the selection criteria for DCCT excluded those with hypertension, severe dyslipidemia, or other serious comorbidities and included individuals with diabetes duration of 1–15 years, thereby reducing the potentially high mortality of the first years with diabetes.

We found that SMRs in the younger age bands were higher than those in the older age bands (Supplementary Fig. 2), and the high mortality at 20 years with diabetes was mainly caused by violent death and acute complications (55%). This leads us to speculate about increased risk behavior in young adults with type 1 diabetes. SMRs for violent death and suicide—around 3.0 for both causes—support this hypothesis. A large Swedish study reported fewer protective factors and more risk behavior among adolescents (aged 15–17 years) with chronic conditions compared with their healthy peers (25). High risk of violent death in individuals with type 1 diabetes was also demonstrated in a recent review article: 2.5 (95% CI 1.7–3.9) in women and 1.8 (95% CI 1.3–2.5) in men (26). However, the review article included studies using an age of 0–30 years at diagnosis.

We note that mortality associated with alcohol was about five to seven times higher in the cohort with type 1 diabetes compared with the general population in Norway. It is known that alcohol consumption is underreported on death certificates (27). However, underreporting probably occurs for both people with and people without diabetes, and would therefore not affect the SMR. A couple of mortality studies have shown abuse of drugs or alcohol among cohorts with type 1 diabetes, but neither provided long-term follow-up nor compared those cohorts with the general population (28,29). The SMR for alcohol-associated deaths has, to our knowledge, only been published in a Finnish study demonstrating that alcohol- and drug-related deaths accounted for 39% of deaths at 20 years' duration among patients diagnosed between 1985 and 1989. However, that study reported an SMR for alcohol-related deaths lower than what we found (1.5; 95% CI 1.2–2.7) (10).

Finland and Norway are appropriate to compare because they share important

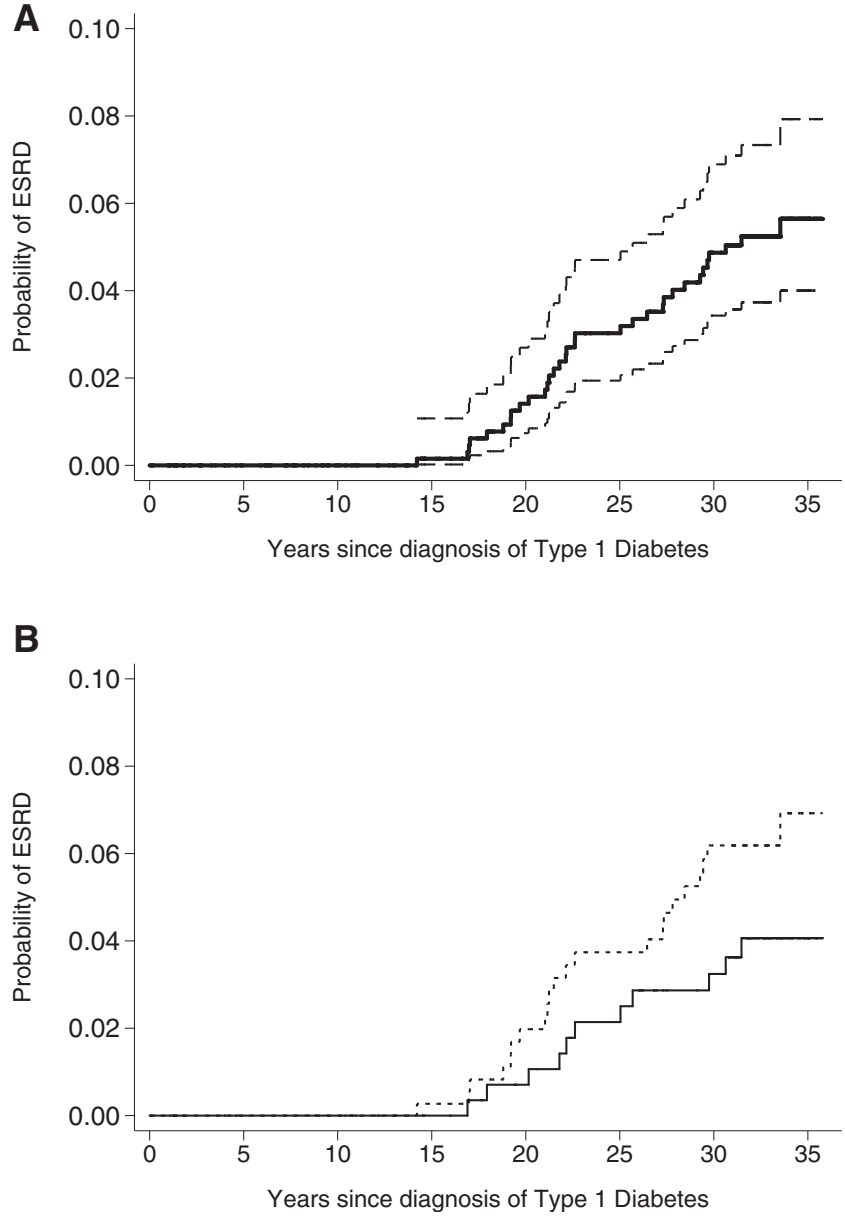

Figure 2—Cumulative incidence of ESRD in 719 individuals with type 1 diabetes diagnosed at 15–29 years of age, with 95% CIs (*A*) and by sex (*B*) ($P = 0.17$). In *B*, the dashed line represents men and the solid line, women.

population and welfare characteristics. There are, however, significant differences in drinking levels and alcohol-related mortality: the Finnish population consumes more alcohol and the Norwegian population consumes less. The mortality rates for deaths related to alcohol are about three to four times higher in Finland than in Norway (30). The alcohol-related mortality rate for individuals with type 1 diabetes diagnosed between 1980 and 1984 in Finland is reported to be 9.8 per 10,000 person-years (95% CI 6.1–15) (10); the corresponding rate in our population is similar at 10.3 per 10,000 person-years (95% CI 6.6–15.4). The markedly higher SMR in our cohort can probably be explained by the lower mortality rates for alcohol-related mortality in the general population. However, our study shows that people with type 1 diabetes also have a much higher risk of alcohol-related death in a country with substantially lower alcohol consumption and lower mortality related to alcohol. Alcohol consumption impairs cognitive processes such as memory, attention, and planning, which are essential for people with type 1 diabetes (31). It is also a marker for poorer adherence to diabetes self-management and glycemic control (32,33). Our study indicates that diabetes is a major hazard for people with a low ability for self-care. Deaths associated with alcohol may also be a marker for other, nonbeneficial health-related behaviors. This warrants attention from clinicians to people at risk for alcohol abuse.

The presence of renal disease is known to be the major predictor of mortality in type 1 diabetes (34). In line with this, we found that the risk of death associated with ESRD was high (HR 8.7). Renal death is low in our study compared with several others, even when including the whole contribution of ESRD (2,35). In accordance with this, we report a low cumulative incidence of ESRD (4.8% at 30 years). A Finnish study reported a cumulative incidence of ESRD of about 6% in women and 8% in men among patients aged 15–30 years at the onset of diabetes and followed for 30 years (36). In the U.S. the cumulative incidence is reported to be 9.3% at 25 years (37); however, Sweden has reported results comparable to our numbers: 3.2–5.3% at 30 years (38). The average incidence of ESRD in Finland among individuals between 20 and 30 years after their diagnosis of type 1 diabetes (diagnosed in 1965–1979) was 7.3 and 5.5 per 1,000 person-years for men and women, respectively (36). We report lower rates at 4.4 and 2.6 per 1,000 person-years, respectively. It has previously been published that the incidence of diabetic nephropathy in Norway is low—7.8% among a population with a duration of type 1 diabetes between 19 and 30 years—compared with its incidence in other countries (39).

A major strength of this study is being based on a cohort with type 1 diabetes that is national, is population-based, and has high ascertainment (17). Registry linkage via individuals' unique national personal identification numbers gave survival information on all patients. Cohort studies following patients from diagnosis are preferable to studies based on cause of death registries alone because we know that diabetes is underreported on death certificates (40); also, differentiation between type 1 and type 2 diabetes is rarely reliable. We present what is to our knowledge the only study with long-term follow-up of patients diagnosed during late adolescence or young adulthood and using a clinical review committee in

addition to registry data; however, short-term mortality has been assessed in similar ways in a few studies (28,29,41). Registry data are based on death certificates written by physicians, often with limited access to clinical data. Our study suggests the underestimation of specific causes of death that are of particular importance to individuals with diabetes, such as acute complications and CVD, when using death certificates as the only source of information. Other studies have also underscored the problem with the insufficient reliability of causes of death in type 1 diabetes when only considering death certificates (39,42,43).

An important limitation of this study is that we did not have complete information on HbA_{1c} or smoking status, among other risk factors. Another limitation is the relatively small cohort, which might influence the statistical power and give less precise estimates.

In conclusion, the high mortality reported in this cohort with an onset of diabetes in late adolescence and young adulthood draws attention to people diagnosed during a vulnerable period of life. Both acute and chronic complications cause substantial premature mortality, implying a continuous need for improved diabetes care. Our study suggests that increased awareness of alcohol-related death should be encouraged in clinics providing health care to this group of patients.

Acknowledgments. The authors acknowledge Professor Trond G. Jenssen, Department of Transplant Medicine, Oslo University Hospital; and Dr. Line M. Berteussen, Department of Forensic Pathology and Clinical Forensic Medicine, Norwegian Institute of Public Health, for sharing their experiences regarding the clinical review committee. The authors thank all the hospitals in all the Norway Regional Health Authorities that gathered clinical information about the deceased individuals included in this study: the South-Eastern Norway Regional Health Authority, the Western Norway Regional Health Authority, the Central Norway Regional Health Authority, and the Northern Norway Regional Health Authority. The authors also thank the following departments of pathology: Division of Forensic Sciences, Norwegian Institute of Public Health; Gade Laboratory of Pathology, University of Bergen; Department of Pathology, Stavanger University Hospital; Department of Pathology and Medical Genetics, St. Olavs University Hospital; Department of Pathology, University Hospital of Tromsø. The Norwegian Cause of Death Registry contributed data based on death certificates. The authors thank all the members of the Norwegian Childhood Diabetes Study Group for their contribution and, finally, the patients who contributed their data.

Funding. The South-Eastern Norway Regional Health Authority funded the study.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. V.G. wrote the manuscript and collected, organized, and analyzed the data. V.G. and T.S. comprised the clinical committee. L.C.S. supervised the data analysis. T.L. helped with data collection. G.J. initiated the study and collected data. T.S. developed the study concept, initiated the study, collected data, and supervised the study. All authors interpreted the results and contributed to the discussion, and critically reviewed and approved the final version of the manuscript. T.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented at the 52nd European Association for the Study of Diabetes (EASD) Annual Meeting, Munich, Germany, 13–16 September 2016

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