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Causes of death in childhood-onset Type 1 diabetes: long-term follow-up

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Abstract

Aims To assess the causes of death and cause-specific standardized mortality ratios in two nationwide, population-based cohorts diagnosed with Type 1 diabetes during the periods 1973–1982 and 1989–2012, and to evaluate changes in causes of death during the follow-up period.

Methods People with Type 1 diabetes who were aged < 15 years at diagnosis were identified in the Norwegian Childhood Diabetes Registry and followed from diagnosis until death, emigration or September 2013 (n = 7871). We assessed causes of death by linking data to the nationwide Cause of Death Registry and through a review committee that evaluated medical records, autopsy reports and death certificates.

Results During a mean (range) follow-up of 16.8 (0–40.7) years, 241 individuals (3.1%) died, representing 132 143 person-years. The leading cause of death before the age of 30 years was acute complications (41/119, 34.5%). After the age of 30 years cardiovascular disease was predominant (41/122, 33.6%), although death attributable to acute complications was still important in this age group (22/122, 18.0%). A total of 5% of deaths were caused by 'dead-in-bed' syndrome. The standardized mortality ratio was elevated for cardiovascular disease [11.9 (95% CI 8.6–16.4)] and violent death [1.7 (95% CI 1.3–2.1)] in both sexes combined, but was elevated for suicide only in women [2.5 (95% CI 1.2–5.3)]. The risk of death from acute complications was approximately half in women compared with men [hazard ratio 0.43 (95% CI 0.25–0.76)], and did not change with more recent year of diagnosis [hazard ratio 1.02 (0.98–1.05)].

Conclusions There was no change in mortality attributable to acute complications during the study period. To reduce premature mortality in people with childhood-onset diabetes focus should be on prevention of acute complications. Male gender implied increased risk.

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Introduction

Mortality in individuals with Type 1 diabetes is higher than in the general population [1–5]. Causes of death in children and young adults are mainly related to acute diabetic complications, while in adulthood the main cause of death is related to long-term complications [2,5–9]. To provide a greater understanding of mortality in Type 1 diabetes, it is important to examine the causes of death in newer cohorts.

Diabetes is under-reported on death certificates, therefore, cohort studies are the best way to assess causes of death among individuals with diabetes [10]; however, studies with long-term follow-up in cohorts with childhood-onset diabetes, reporting changes in cause-specific mortality over recent decades are relatively rare [2,8]. Several studies assessing causes of death in Type 1 diabetes base their conclusions exclusively on data from health registries [1,3,9]. Few recent studies have addressed cause-specific mortality in Type 1 diabetes based on clinical information in addition to register data [7,8,11]. Considering register data alone might lead to underestimation of certain causes of death. Additionally, coding practice in cause-of-death registries has changed over time [12,13], this complicates comparison over time and between studies.

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What's new?

- This nationwide, population-based study is a long-term follow-up of two cohorts, diagnosed with childhood-onset Type 1 diabetes in 1973–1982 and 1989–2012 [mean (range) follow-up 16.8 (0–40.7) years].
- The study addresses cause-specific mortality based on clinical information in addition to high-quality register data.
- The leading cause of death before the age of 30 years was acute complications; after the age of 30 years cardiovascular death was predominant.
- In spite of improved diabetes care during the study period we report no change in mortality attributable to acute complications.
- Our results indicate a need to improve diabetes management and psychosocial care to prevent premature mortality.

The present study has one of the longest follow-up periods in a cohort with childhood-onset Type 1 diabetes (up to 40.7 years). It reports causes of death in a large nationwide, population-based cohort of 7871 individuals with childhood-onset Type 1 diabetes, diagnosed during 1973–2012 and followed up until 2013. We have shown earlier that all-cause mortality in this cohort was elevated 3.6 times compared with the general population in Norway [4]. We aimed to present in detail the causes of death based on a review committee evaluating clinical data in addition to register data. We evaluated cause-specific mortality by sex and over period of follow-up. Furthermore, we estimated the standardized mortality ratio (SMR) for causes of death.

Patients and methods

Subjects and study design

The study was based on data from the Norwegian Childhood Diabetes Registry (NCDR), a population-based, nationwide registry including all new-onset cases of childhood-onset (age < 15 years) diabetes in Norway [14,15]. The study population consisted of two nationwide cohorts diagnosed during 1973–1982 and 1989–2012 (n = 7871). Data on individuals diagnosed during 1973–1982 were collected retrospectively [14]. Since 1989, all new cases have been registered prospectively in the NCDR. We excluded individuals with genetically verified monogenic diabetes, those diagnosed before 6 months of age and those with known Type 2 diabetes. Among the deceased, six individuals were excluded because they did not have Type 1 diabetes, these cases were all diagnosed in 1973–1982. This left a fairly homogenous study population of 7871 almost exclusively ethnic Norwegians with Type 1 diabetes [16]. Survival or emigration status was determined as of 30 September 2013, by linking the NCDR database to the National Population Register. Mortality in individuals diagnosed during the period 1973–1982 and followed up to 2002 has been described previously [7,17]. As part of the present study, the same cohort was followed for a further 10.7 years (mean duration of follow-up 34.1 years). In the present study a clinical review committee evaluated all deaths using an identical procedure to establish the causes of death, independently of earlier published data.

Classification of the causes of death

We obtained the causes of death from the nationwide Norwegian Cause of Death Registry. This registry is based on information from death certificates and contains data concerning the underlying, immediate, intermediate and contributing causes of death. We compared mortality with the general population by calculating the SMR. Causes of death were grouped by the underlying cause of death [International Classification of Disease (ICD) codes]. All ICD-codes (ICD-8 and ICD-9) were translated into ICD-10 codes. An important issue in mortality studies of Type 1 diabetes is the fact that 'diabetes' may be registered as the underlying cause of death, while the immediate cause of death is more specific [12,13]. To limit the underestimation of certain causes of death, we examined both the immediate and contributing causes of death in cases where the underlying cause of death was diabetes-related (E10, E14).

A clinical review committee, consisting of two paediatric diabetologists (V.G. and T.S.), one nephrologist (T.G.J.) and one forensic pathologist (L.M.B.), agreed on the causes of death by evaluating all available information regarding the deceased. We obtained and considered 122 of 123 autopsy reports, 98 forensic autopsy reports, all including police reports, and 24 medical autopsy reports. We had access to medical records from primary or secondary care for 171 (71.0%) cases. In eight patients the only source of information was the death certificate; in seven of these cases the review committee decided that the information on the death certificates was sufficient to conclude on the cause of death (six accidents and one suicide). In one case, death was sudden and unexplained.

The causes of death were grouped as follows:

(1) Acute diabetic complications: including diabetic ketoacidosis (DKA) and hypoglycaemia. DKA was either diagnosed by autopsy or in hospital before death occurred. Death from hypoglycaemia was divided into two groups by degree of certainty after evaluating the clinical information available: death from hypoglycaemia (blood sugars near time of death available) and death probably attributable to hypoglycaemia.

(2) Cardiovascular deaths: including death from all cardiovascular disease (CVD).

(3) Renal death: including all deaths from renal failure.

(4) Other diabetes-related deaths: including death from diabetes-related infections and other diabetes-related complications that were not classified as acute complications, CVD or renal disease.

(5) Violent death: including fatal accidents, intoxications and suicide. Violent deaths related to diabetes were grouped as 'other diabetes-related deaths' when presenting data in relation to diabetes.

(6) Other causes: all other causes of death, including infections not related to diabetes and any form of cancer. If diabetes contributed to death, these deaths were grouped as 'other diabetes-related deaths' when presenting data in relation to diabetes.

(7) Sudden unexplained death: including sudden unexpected deaths in which the committee was unable to state the cause of death. Sudden unexpected deaths for which the committee concluded on a cause of death were grouped into the relevant category. This category includes 'dead-in-bed'. The criteria for 'dead-in-bed' syndrome were considered fulfilled in individuals without a history of long-term complications, observed to be in good health the preceding day, found dead in an undisturbed bed and autopsy not informative [18].

The committee also classified the causes of death in relation to diabetes: 'diabetes-related deaths' (diabetes caused or was a major contributor to death); 'non-diabetes-related deaths' (diabetes did not contribute to death) or 'unknown relation to diabetes' (sudden unexplained deaths).

To ascertain the number of individuals with end-stage renal disease we linked the NCDR to the Norwegian Renal Registry, a nationwide registry with data on all patients in Norway receiving renal replacement therapy since 1980 [19].

The Norwegian Regional Committee for Research Ethics approved the study protocol: reference number 2012/1939.

Data analysis

We used Stata, version 13 (StataCorp LP, College Station, TX, USA) for data handling and analyses. The follow-up period for each participant was calculated from the date of the first insulin injection to the date of death, emigration or 30 September 2013, whichever occurred first. We calculated cause-specific mortality rates and 95% CIs by dividing the number of deaths by person-years of follow-up for individuals at risk in the total cohort and by sex. We used years since diagnosis as the timescale in Cox regression models to estimate unadjusted and adjusted hazard ratios, for the association between cause-specific mortality, sex and year of diagnosis. Year of diagnosis was modelled as a continuous (linear) covariate (no deviations from linearity were indicated in categorical analyses). We estimated the slopes separately in the two cohorts and found them to be similar. We also found the linearity assumption to hold across the range of diagnosis years. The proportional hazards assumption was found to hold after testing and assessing plots of scaled Schoenfeld residuals for each cause of death. We compared causes of death in the study cohort with causes of death in the general population in Norway by estimating cause-specific SMRs: Violent death [including all accidents, intoxications and suicide (V01-V99, W00-X59, X4n, X60-X84, F10.0-F19.0)], suicide (X60-X84), traffic accidents (V01-V99), cancer (C00-C97), CVD (I20-I25, I44-I49, I60-I69, I70-I79), ischaemic heart disease (I20-I25) and cerebrovascular disease (I60-I69). SMRs were calculated by attained age and sex as the ratio of the observed to the expected number of deaths using cause-specific mortality rates obtained from the Norwegian Cause of Death Registry in 5-year calendar periods (1973–2013) and age groups for each sex. Each person contributed the time they spent within each age band and calendar period to the total person-years. We used a significance level of 5%.

Results

Among the 7871 individuals with Type 1 diabetes, 241 (3.1%) died during a mean (range) follow-up of 16.8 (0–40.7) years, representing 132 143 person-years. Characteristics of the study population are shown in Table 1. Information was missing in the Norwegian Cause of Death Registry for seven individuals, probably because of death outside Norway. An autopsy was performed in 51.0% of the deceased. Diabetes was mentioned on the death certificate in 74.8% of the cases.

Causes of death

The causes of death classified by the review committee are shown in Fig. 1 and Table S1. The leading cause of death in the total cohort was acute diabetic complications, representing 26.1% (63/241) of all deaths. DKA contributed to 68.3% (43/63) and hypoglycaemia to 31.7% (20/63) of deaths caused by acute complications. Hypoglycaemia was certain in 8/20 cases and considered probable in 12/20 cases. Comorbidity with a psychiatric disorder or drug abuse was present in 25.6% (11/43) of those who died from DKA. Among the non-drug-associated DKA deaths, 56% (18/32) were diagnosed in 1973–1982 and 44% (14/32) in 1989–2012. The proportion of men was 75% (24/32) and the mean age at death was in the 20s for both diagnosis cohorts and sexes. Two individuals died from DKA with cerebral oedema at diagnosis, in 1975 and 1997. Death caused by CVD increased by attained age and was the major cause of death after the age of 30 years

Table 1 Characteristics of the study cohort with childhood-onset (age < 15 years) Type 1 diabetes in Norway, diagnosed in the period 1973–2012

	Total	Men	Women	Diagnosed 1973–1982	Diagnosed 1989–2012
n (%)	7871	4242 (53.9)	3629 (46.1)	1888	5983
Mean (range) age at diagnosis, years	8.8 (0.6–14.9)	8.9 (0.6–14.9)	8.7 (0.6–14.9)	9.1 (0.6–14.9)	8.7 (0.6–14.9)
Mean (range) diabetes duration, years	16.8 (0.0–40.7)	16.8 (0.0–40.7)	16.8 (0.03–40.7)	34.1 (0.00–40.7)	11.3 (0.03–24.7)
Mean (range) age at end of follow-up, years	25.6 (1.8–55.3)	25.7 (1.8–55.3)	25.5 (1.8–54.8)	43.2 (3.9–55.3)	20.1 (1.8–39.5)
Person-years of follow-up	132 143	71 105	61 038	64 417	67 726
Dead, *n* (%)	241 (3.1)	172 (4.1)	69 (1.9)	180 (9.5)	61 (1.0)
Emigrated, *n* (%)	85 (1.1)	38 (0.9)	47 (1.3)	24 (1.3)	61 (1.0)

*Data are presented stratified by sex and in the cohorts collected retrospectively (1973–1982) and prospectively (1989–2012).

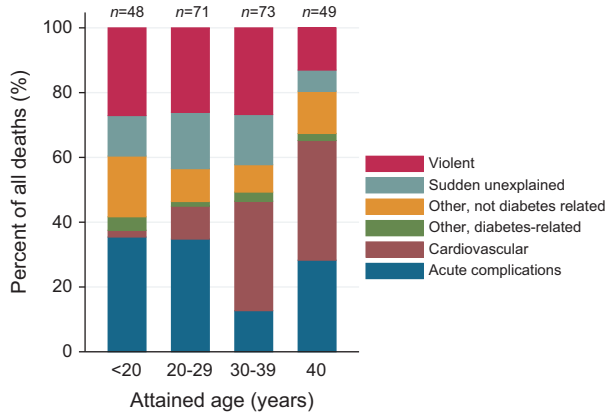

FIGURE 1 Causes of death. Data are sorted by age at death in 234 individuals with childhood-onset Type 1 diabetes in 1973–2012 in Norway, aged 2–55 years.

(41/122, 33.6%); however, acute complications still caused 18.1% (22/122) of the deaths after the age of 30 years, and 26.5% (13/49) of the deaths after the age of 40 years. Causes of death stratified by sex are shown in Fig. S1. In 54% (130/241) of the cases the review committee considered the cause of death to be diabetes-related, in 30% (72/241) the cause was unrelated to diabetes and in 13% (32/241) it was unknown if death was related to diabetes.

In total, 19.1% (46/241) of the deceased were registered, with the underlying cause of death 'diabetes mellitus without complications' (E10.9 or E14.9). The review committee grouped 41.3% (19/46) of these deaths as sudden unexplained deaths, 30.4% (14/46) as acute complications, 21.7% (10/46) as CVD, 4.3% (2/46) as diabetes-related infections and 2.2% (1/46) as suicide.

Causes of death in patients with end-stage renal disease

We identified 29 deceased individuals (12.4%) with end-stage renal disease by linkage to the Norwegian Renal Registry (19 men and 10 women). Transplantation had been performed in seven cases and 22 had ongoing dialysis until death. Of these individuals, 65.5% (19/29) died from CVD. Acute complications and diabetes-related infections contributed to 17.2% (5/29) of the deaths, while 10.3% of the cases (3/29) were violent deaths and 6.9% (2/29) of the deaths were from cancer. Renal failure contributed to death in 10.8% of the cases (26/241); however, none of the patients died from actual renal failure, although one patient died from septicaemia directly attributable to an infected dialysis catheter.

Sudden unexplained death

In 13.3% of individuals (32/241; 26 men and six women) death was sudden and unexplained. The review committee could not conclude on the cause of death by assessing the available clinical information. Autopsy was performed in 59.4% (19/32) without revealing the cause of death, 78.1% (25/32) died at home. The mean (range) age at end of follow-up was 27.6 (11.0–46.3) years. Twelve individuals (12/32) met the criteria of 'dead-in-bed'; 11 men and one woman. The mean (range) age at death for these 12 was 22.0 (11.0–33.0) years.

Time trends and sex differences in cause-specific mortality

The Cox regression model showed that when compared with men, the risk of death for women was significantly lower for diabetes-related death in total (hazard ratio 0.52, 95% CI 0.36–0.76), acute complications (hazard ratio 0.43, 95% CI 0.25–0.76), violent death (hazard ratio 0.33, 95% CI 0.16–0.66) and sudden unexplained death (hazard ratio 0.27, 95% CI 0.11–0.65; Table 2).

The risk of all-cause mortality decreased during the period of follow-up, but we found no change in risk of death associated with more recent year of diagnosis from diabetes-related causes in total, from acute complications, or from causes with unknown relation to diabetes (Table 2), although death from CVD and causes unrelated to diabetes seemed to decline. These results must be interpreted with care because of the limited number of deaths for each group of causes.

Table 2 Cause-specific mortality rates (per 100 000 person-years) and hazard ratios in relation to diabetes in 7871 individuals with childhood-onset Type 1 diabetes in Norway

Causes of death	Total N = 7871	Men n = 4242		Women n = 3629		Female sex vs male		Year of diagnosis	
	n	n	Mortality rates (95% CI)	n	Mortality rates (95% CI)	HR† (95% CI)	P	HR† (95% CI)	P
Total deaths	241	172	241.9 (208.9–280.9)	69	113.0 (89.3–143.1)	0.47 (0.35–0.62)	< 0.001	0.98 (0.96–0.99)	0.02
Diabetes-related	130	90	126.6 (103.0–155.6)	40	65.5 (48.1–89.3)	0.52 (0.36–0.76)	0.001	0.99 (0.97–1.02)	0.68
Acute diabetic complications	63	46	64.7 (48.5–86.4)	17	27.9 (17.3–44.8)	0.43 (0.25–0.76)	0.003	1.02 (0.98–1.05)	0.35
Cardiovascular	49	32	45.0 (31.8–63.6)	17	27.9 (17.3-44.8)	0.63 (0.35–1.13)	0.12	0.92 (0.86–0.98)	0.02
Other diabetes-related*	18	12	16.9 (9.6–29.7)	6	9.8 (4.4–21.9)	‡		‡	
Not diabetes-related	72	50	70.3 (53.3–92.8)	22	36.0 (23.7–54.7)	0.51 (0.31–0.85)	< 0.009	0.96 (0.93–0.99)	0.01
Violent death	46	36	50.6 (36.5–70.2)	10	16.4 (8.8–30.4)	0.33 (0.16–0.66)	0.002	0.95 (0.91–0.99)	0.01
Cancer	9	5	7.0 (2.9–16.9)	4	6.6 (2.5–17.5)	‡		‡	
Other causes	17	9	12.7 (6.6–24.3)	8	13.1 (6.6–26.2)	‡		‡	
Unknown relation to diabetes	32	26	36.6 (24.9–53.7)	6	9.8 (4.4–21.9)	0.27 (0.11–0.65)	0.004	0.97 (0.92–1.02)	0.21
Sudden unexplained death	32	26	36.6 (24.9–53.7)	6	9.8 (4.4–21.9)	0.27 (0.11–0.65)	0.004	0.97 (0.92–1.02)	0.21
Missing§	7	6	8.4 (3.1–18.4)	1	1.6 (0.1–8.1)	‡		‡	

HR, hazard ratio.
*Includes violent deaths, infections and other deaths where diabetes caused or was a major contributor to death.
†Sex, age at diagnosis and year of diagnosis are included simultaneously in the regression model. Adjusted and unadjusted HRs were very similar (unadjusted HRs not shown).
‡Not analysed because of few deaths in the group.
§Missing information in the Norwegian Cause of Death Registry.

Cause-specific mortality compared with the general population

The SMR for CVD was significantly elevated in women (13.6, 95% CI 7.5–24.6) and men (11.3, 95% CI 7.7–16.6). Similar results were found for ischaemic heart disease in both sexes (women: 26.4, 95% CI 12.6–55.4; men: 14.3, 95% CI 9.1–22.4) and for cerebrovascular disease in men, but not in women (women: 2.7, 95% CI 0.4–19.3; men: 11.9, 95% CI 5.7–24.9). The SMR for violent death was significantly elevated in women (2.0, 95% CI 1.1–3.3) and men (1.6, 95% CI 1.1–2.1), but we found no increased risk of dying in traffic accidents. We identified a significantly increased (twofold) mortality by suicide for women compared with the general population. Cause-specific SMRs stratified by sex are shown in Fig. 2 and in Table S2.

Discussion

A key finding of the present study was that acute complications were the leading cause of death in a cohort with both short and long duration of Type 1 diabetes, followed up to 2013. The risk of death from acute complications was twice as high in men compared with women and did not change significantly over the diagnosis period. CVD was the leading cause of death after 30 years of age.

A major strength of the present study is the fact that it was based on data from the nationwide NCDR and had one of the longest follow-up periods in a cohort with childhood-onset Type 1 diabetes (up to 40.7 years). The study population had known Type 1 diabetes and the NCDR has high ascertainment level [7,14]. Another strength is that a clinical review committee ascertained the causes of death by a thorough evaluation of all available sources of information, including medical records and autopsy reports, in addition to register data and death certificates. Studies that only rely on death certificates to determine diabetes status will underestimate the number of individuals with diabetes because of under-reporting [10]. Furthermore, reliance on death certificates and ICD-10 codes as the only sources of information on the cause of death is known to provide data of insufficient reliability [13].

One limitation of the present study is the small number of events. Assessment of whether cause-specific mortality changed over time might be influenced by the limited statistical power to detect minor to moderate changes over time; however, the present results are consistent with those of other, larger reports [2,8]. Another limitation is that we did

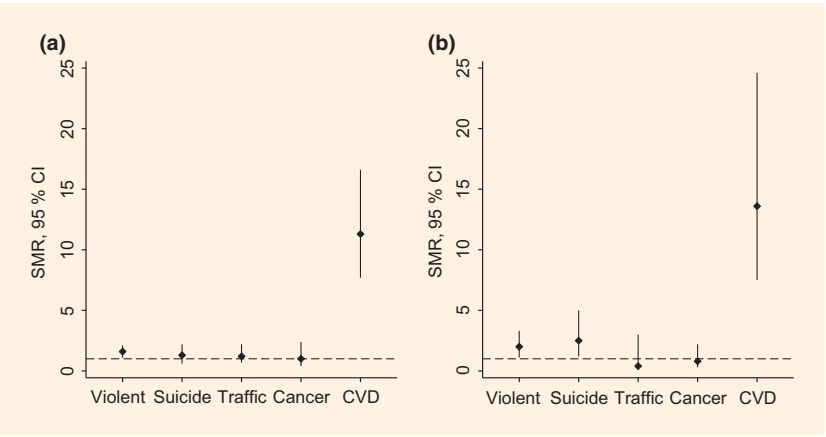

FIGURE 2 Standardized mortality ratio (SMR). Data are given for (a) men and (b) women in 7871 individuals with childhood-onset Type 1 diabetes in Norway, diagnosed in 1973–2012, followed until September 2013. CVD, cardiovascular disease.

not have complete information on HbA_{1c}, smoking status or medical treatment.

We found an increase in the proportion of deaths caused by acute complications between ages 40 and 55 years. This is in contrast to studies showing that death from acute complications decreases after the age of 30 years [8,9]; however, we report a high proportion of deaths caused by acute complications before the age of 30 years, in line with other studies [6,7,9,20]. Consistent with earlier reports, death attributable to DKA was twice as frequent as death from hypoglycaemia [7,9,20]. In addition, we found that the risk of acute complications and diabetes-related death in total was twice as high in men compared with women. In a large US study, mortality from diabetes-related causes was observed to be higher in women [8], while similar mortality rates in men and women have also been reported [9,21,22]. Results are difficult to compare among studies because of differences between countries and study methods. In the present cohort we observed that contributing factors, such as drug misuse or psychiatric disorders, were present in 26% of those who died from DKA. This might, to some extent, explain the deaths from DKA, but many young adults died at home with all necessary diabetes treatment available. In spite of improved diabetes management during the study period we were not able to demonstrate a decreased risk of mortality from acute complications, although this result might be influenced by the limited statistical power, as discussed above. This result is, however, in accordance with a large Finnish study in people diagnosed between 1970 and 1999, which reported a non-significant trend towards an increase in acute complication-related deaths in early-onset Type 1 diabetes [2]. The study from the USA found no change in mortality from acute complications for those diagnosed between 1965 and 1979 [8]. In a country with good access to public healthcare, DKA should be an almost entirely preventable condition.

Mortality caused by CVD was 11–14 times higher than in the general population. This is consistent with a recent review article [23], although few studies report an excess mortality rate from CVD as high as that in the present study [1,3]. One reason for this discrepancy might be that studies that base their data on the underlying cause of death may underestimate the true burden of CVD in Type 1 diabetes. A proportion as high as 94% of the individuals who died from CVD was diagnosed with diabetes in 1973–1982. Since then diabetes management has improved markedly [24,25]. The estimates we present may therefore not be representative of individuals diagnosed today.

Survival in patients with renal failure has improved because of advances in renal replacement therapy. CVD causes the majority of deaths in these patients [26]. Consistent with this finding, the main cause of death among those with end-stage renal disease in the present cohort was CVD. It is notable that no one died directly from end-stage renal disease, but end-stage renal disease contributed to death in most cases when present. In other studies renal death rates have been substantial [8,9,27,28]. Renal death might be overestimated in studies that base their data only on health registries without additional clinical information. Diverging methods could lead to differences in interpretation and categorization of the causes of death. We believe that high-quality renal replacement therapy and an inexpensive and easily available healthcare system for the patient is the main explanation for the low mortality from renal disease in the present cohort.

The SMR was elevated for violent death. This was similar to the results presented in a recent systematic review [23]. In accordance with the results of a population-based Swedish study, mortality from traffic accidents was similar to that in the general population [11]. In the present study, mortality from suicides was significantly elevated only in women (SMR 2.5). Concerning the risk of suicide our results are not in accordance with a recent review article

reporting no evident sex difference in risk of suicides in people with Type 1 diabetes [23]. One might suspect that some suicides could be hidden among deaths from hypoglycaemia. The present results imply that the psychological burden of living many years with Type 1 diabetes is especially present in women. Improved psychosocial care in diabetes management seems essential to reduce the number of suicides.

The 5% of deaths attributed to 'dead-in-bed' syndrome in the present study was consistent with other studies [29], but lower than reported in a Swedish study [11]. We suspect that our estimate of 'dead-in-bed' might be too low because autopsy was performed in only 59.4% of the individuals who died suddenly and unexpectedly. Hence, forensic autopsies should be performed frequently to gain more knowledge of unexpected deaths in young people with Type 1 diabetes.

In conclusion, we report a high proportion of deaths from acute complications, especially before the age of 30 years. The risk of mortality attributable to acute complications did not change significantly with more recent year of diagnosis; however, it was twice as high in men than in women. We believe that improved diabetes education and increased psychosocial support could prevent acute complications in young adults with Type 1 diabetes. Special attention should be paid to men. The high proportion of deaths caused by CVD emphasizes the importance of continued work to reduce long-term complications.

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Competing interests

None declared.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Causes of death for each sex. Data are given by age at death in men (a) and women (b) in 234 individuals with childhood-onset Type 1 diabetes in 1973–2012 in Norway, age 2–55 years.
Table S1. Causes of death, stratified by age at death, assessed by a clinical review committee in 241 individuals with childhood-onset Type 1 diabetes diagnosed in 1973–2012 in Norway, aged 2–55 years.
Table S2. Standardized mortality ratios, stratified by cause of death and sex, in 7871 individuals with childhood-onset Type 1 diabetes in Norway, diagnosed in 1973–2012, followed up until September 2013.