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ORIGINAL ARTICLE

Mortality in childhood-onset type 1 diabetes mellitus with onset between 1959 and 1996: A population-based study in Hokkaido, Japan

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Abstract

Aim To examine the mortality rate and causes of death in childhood-onset type 1 diabetes in Japan.

Methods For a median 36.7 years, we followed 391 patients under the age of 15 years who developed type 1 diabetes between 1959 and 1996. We calculated the mortality rate per 100,000 person-years and the standardised mortality ratio (SMR) according to risk factors.

Results The mortality rates and SMRs were 823 and 8.8 with onset during 1959—1979, 370 and 5.9 with onset during 1980—1989, and 133 and 3.2 with onset during 1990—1996, respectively. The mortality rates and SMRs were 359 and 8.4 in men, and 235 and 6.0 in women. Mortality rates and SMRs were 452 and 7.3 in patients with diabetes onset before puberty and 514 and 6.3 in patients with onset after puberty. The main causes of death with shorter disease duration were sudden death, accident/suicide, and acute diabetic complications. With a more than 30-year disease duration, the main causes of death were end-stage renal disease and cardiovascular disease.

Conclusions This cohort study revealed a decrease in the mortality rate between 1959—1979 and 1990—1996 in patients with childhood-onset type 1 diabetes in Japan. Patients with onset after puberty had a higher mortality rate than those with onset before puberty.

Keywords Type 1 diabetes · Mortality · Standardised mortality ratio · Cause of death · Dead-in-bed syndrome · Acute diabetic complications

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Introduction

The long-term mortality rate of childhood-onset type 1 diabetes has been reported in European and North American countries as well as in Australia [1–7]. In Japan, the mortality rate of a large number of patients who experienced onset between 1965 and 1979 was reported in the Diabetes Epidemiology Research International (DERI) study [8]. However, the follow-up in this Japanese study was not long enough to report the mortality rate after the year 1980. Although another hospital-based study at the Tokyo Women's Medical University (TWMU) Diabetes Centre had a long follow-up duration [9], the age of study participants was older than that in our previous study in Hokkaido [10].

Hokkaido Prefecture is located in the northernmost part of Japan and has approximately 5.3 million residents, a population similar to that of Finland, Denmark, and Norway. The Hokkaido registry of childhood-onset type 1 diabetes

was established in 1973 when a summer camp for paediatric patients was started; registration was repeated every year until 1996. Using this registry, in 1998 we reported the incidence of type 1 diabetes as 1.63 per 100,000 person-years [10], which is approximately 5%–10% of the incidence in European countries. In the present cohort study in Hokkaido, we followed up with the patients in this registry for a long period to assess mortality. We determined the long-term mortality rate in Japanese patients with disease onset from 1959 to 1996 and analysed the causes of death in relation to disease duration. Furthermore, we compared the mortality rate with that in Scandinavian countries, where the incidence of childhood type 1 diabetes is very high.

Material and methods

Patients

This cohort study enrolled all of the 521 patients in Hokkaido under the age of 15 years who developed type 1 diabetes and required insulin between 1959 and 1996. All patients reported in the previous paper [10] were included in this study. Information on patients' characteristics at baseline was gathered upon enrolment. Although islet cell antibodies were not measured in the baseline period, we used the term 'type 1 diabetes' instead of 'insulin-dependent diabetes mellitus' because most reports used the term at that time.

Follow-up survey

In this cohort, we contacted the attending physicians through postal mail or telephone calls if contact by postal mail was difficult. First, we sent a query via postal mail asking whether the patients were still being treated in the same institution or had moved to another institution. In this process, we identified the present attending physician. Then, we sent a questionnaire querying attending physicians about the current vital status of their patients. If a patient had died, we requested the date of death and enquired about the cause of death. We conducted this follow-up survey between February 2020 and March 2022.

Strata

We divided our cohort into three groups, as patients with onset years 1959–1979, 1980–1989, and 1990–1996, which we named the 1970 group, the 1980 group, and the 1990 group, respectively. We further divided patients according to whether diabetes onset occurred before or after puberty. 'After-puberty' was defined as age 12 years or more for boys and 10 years or more for girls.

Statistical analyses

We describe the data as number (percentage), mean ± standard deviation, or rate or ratio (95% confidence interval [CI]). We calculated overall and stratified mortality rates as the number of deaths per 100,000 person-years [11]. We further calculated the standardised mortality ratio (SMR) using the Japanese Mortality Database operated by the National Institute of Population and Social Security Research [12]. Then, 95% CIs for the mortality rate and SMR were calculated based on a Poisson distribution. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). R version 4.2.2 (The R Project for Statistical Computing, Vienna, Austria) was used to generate the Poisson distribution and Kaplan–Meier curves. All reported p values were two-sided, with $p < 0.05$ considered to indicate statistical significance.

Ethical approval

The protocol for this study was approved by the ethics committee of Hokkaido University (approval number: 019–0256). Informed consent was verbally obtained from each participant by the attending physicians. The follow-up survey was started after approval of the ethics committee was received, beginning on 10 January 2020 and ending in March 2022.

Results

Mortality rate and SMR

We followed up with 391 of the 521 registered patients. The median follow-up duration was 36.7 years. Table 1 shows the characteristics of the Hokkaido cohort at baseline. The number of patients in the 1970, 1980, and 1990 onset-year groups was 129, 264, and 128, respectively; patients' mean age at diagnosis was 10.3, 9.8, and 11.0 years, respectively.

A total of 66 patients had died by March 2022. The mortality rate was 823 (95% CI 573–1,145) per 100,000 person-years in the 1970 group, 370 (95% CI 239–546; $p = 0.0017$ vs. 1970 group) per 100,000 person-years in the 1980 group, and 133 (95% CI 27–389; $p = 0.0005$ vs. 1970 group, $p = 0.081$ vs. 1980 group) per 100,000 person-years in the 1990 group. The SMR was 8.3 (95% CI 5.9–11.9) in the 1970 group, 5.9 (95% CI 4.0–8.6) in the 1980 group, and 3.2 (95% CI 0.9–8.7) in the 1990 group. The mortality rates and SMRs were 452 (95% CI 320–621) per 100,000 person-years and 7.3 (95% CI 5.2–10.1), respectively, in patients with diabetes onset before puberty and 514 (95% CI 333–759;

Table 1 Characteristics, mortality rate and standardised mortality ratio of childhood-onset type 1 diabetic patients with onset in 1959–1979, 1980–1989 and 1990–1996

Years of onset	1959–1979	1980–1989	1990–1996	Overall
Enrolled patients, no	129	264	128	521
Men	54	98	66	218
Women	75	166	62	303
Age at onset, years				
Men	9.2 ± 4.4	10.0 ± 3.9	9.2 ± 4.2	9.6 ± 4.1
Women	8.8 ± 3.2	9.9 ± 3.5	9.9 ± 3.7	9.6 ± 3.4
Patients followed, no. (%)	104 (80.6%)	199 (75.4%)	88 (68.8%)	391 (75%)
Mean duration of diabetes, years	51.5 ± 3.1	42.3 ± 2.8	29.9 ± 1.8	41.0 ± 8.0
Mean age in 2022, years	59.7 ± 4.8	52.3 ± 4.1	43.7 ± 4.4	51.7 ± 6.9
Mortality rate per 100,000 person-years (95% confidence interval)	823 (573–1,145)	370 (239–546)	133 (27–389)	474 (365–608)
Standardised mortality ratio (95% confidence interval)	8.8 (6.1–12.2)	5.9 (3.8–8.8)	3.2 (0.7–9.4)	7.0 (5.3–8.8)
Patients who died, no	36	26	4	66
Mean diabetic duration, years	33.3 ± 11.7	21.8 ± 10.2	16.5 ± 9.8	28.2 ± 12.1
Mean age at death, years	42.2 ± 12.9	28.6 ± 11.4	27.9 ± 9.3	36.3 ± 13.7
Patients without follow-up, no. (%)	26 (20.1%)	63 (23.9%)	41 (32.0%)	130 (25%)
Age at diabetes onset, years	10.4 ± 3.6	9.8 ± 4.0	11.1 ± 2.6	10.3 ± 3.6

Figures indicate number (percentage), mean ± standard deviation, or rate or ratio (95% confidence interval)

p = 0.62 vs. before puberty) per 100,000 person-years and 6.3 (95% CI 4.1–9.4), respectively, in patients with onset after puberty.

Causes of death

Figure 1 shows the causes of death at 10-year intervals after diagnosis. Death due to acute diabetic complications (ADCs) and sudden death were common during the first 30 years after the onset of diabetes. However, end-stage renal disease (ESRD) and cardiovascular diseases (CVDs) were the most common causes of death 30 years or more after onset.

Sex differences in causes of death

Among the 66 patients who died, 30 were men and 36 were women. The mortality rates and SMRs were 559 (95% CI 372–808) per 100,000 person-years and 8.4 (95% CI 5.0–12.3), respectively, in male patients and 424 (95% CI 295–589) per 100,000 person-years and 6.0 (95% CI 4.2–8.3), respectively, in female patients. ADCs, sudden death, and ESRD accounted for 13.3%, 20.0%, and 20.0% of the causes of death, respectively, in male patients and 2.8%, 5.6%, and 58.3% of the causes of death, respectively, in female patients. ADCs, sudden death, and ESRD were common causes of death in male patients whereas ESRD

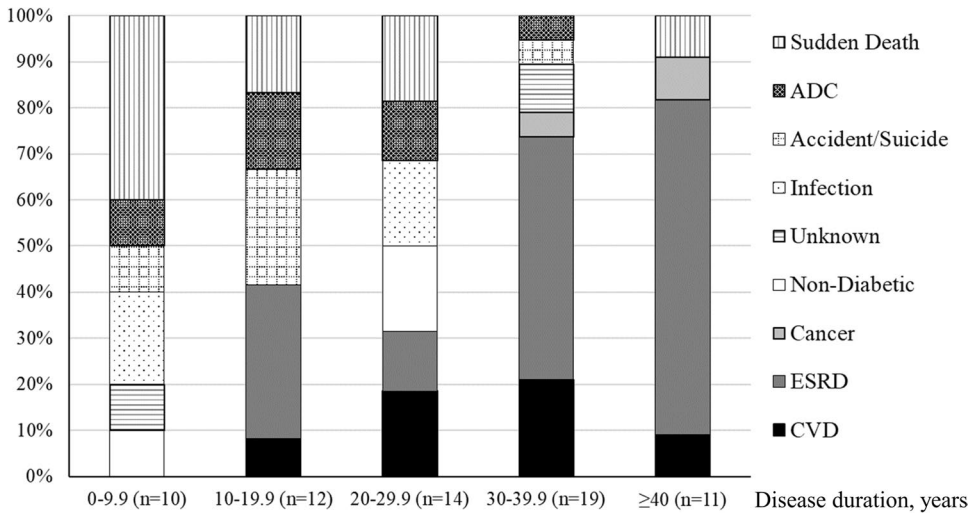

Fig. 1 Causes of death by 10-year intervals of type 1 diabetes duration. ADC, acute diabetic complication; ESRD, end-stage renal disease; CVD, cardiovascular disease

was the most common cause of death in female patients (Fig. 2).

Diabetes-related causes of death

Consistent with Patterson et al. [2], the causes of death in patients with diabetes were divided into the following four categories based on the World Health Organization International Classification of Diseases, 10th Revision: A) diabetes-related causes, B) causes with an uncertain relationship to diabetes, C) causes unrelated to diabetes, and D) unknown/insufficient information. Figure 3 shows causes of death in these categories in the 1970 and 1980 groups. Categories A and B were the main categories of death cause in the 1970 and 1980 groups. The percentage of death causes from categories C and D was higher in the 1980 group than that in the 1970 group among male patients.

All-cause mortality and mortality related to diabetes

Figure 4A and 4B show Kaplan–Meier curves for all-cause mortality and deaths related to diabetes, respectively, by year of onset group. The long-term mortality rate was lower in the 1990 group than that in the 1970 group. Figure 4C shows Kaplan–Meier curves for mortality related to diabetes before and after puberty. The mortality in patients with diabetes onset after puberty was significantly higher than that in patients with onset before puberty.

Early mortality including overnight death

In total, 36 deaths occurred within 30 years of diabetes onset (defined as early mortality). Unexpected sudden death occurred in nine patients, death owing to ADC in eight

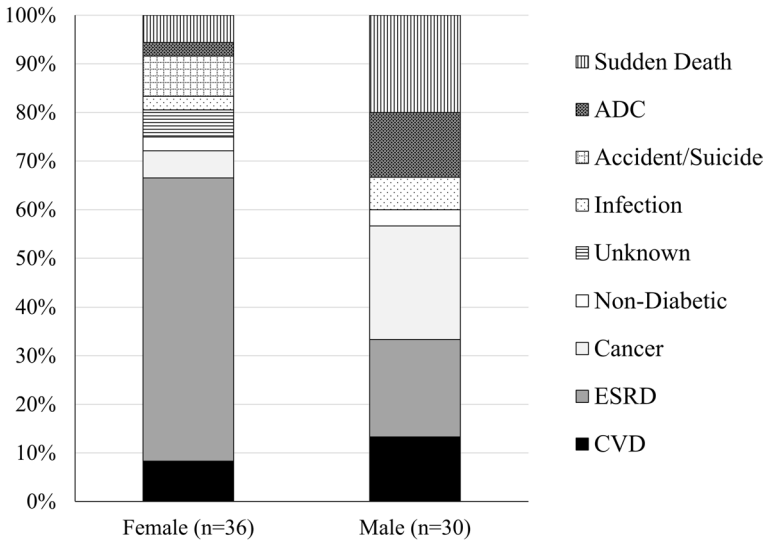

Fig. 2 Sex differences in the cause of death among patients with type 1 diabetes. ADC, acute diabetic complication; ESRD, end-stage renal disease; CVD, cardiovascular disease

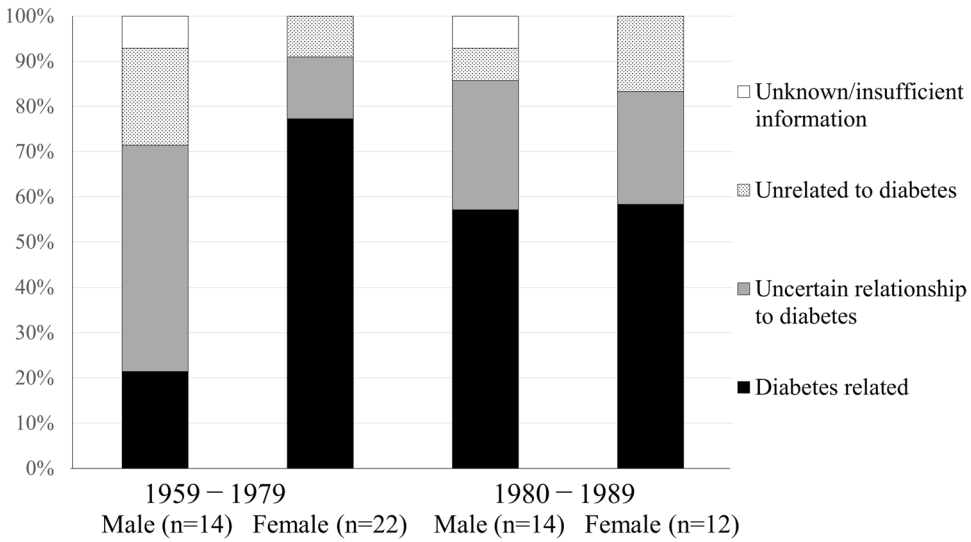

Fig. 3 Percentage of diabetes-related causes of death in patients with type 1 diabetes

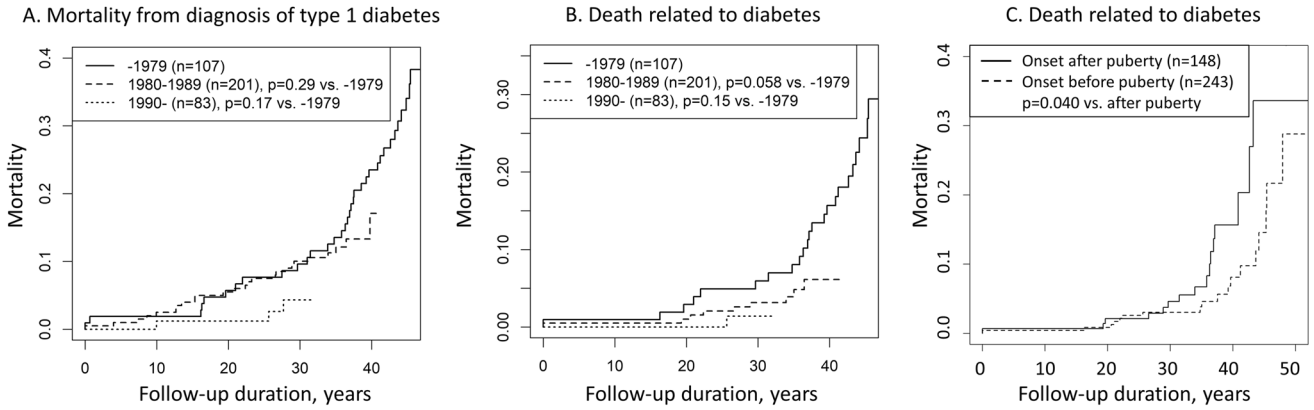

Fig. 4 A. Kaplan–Meier curves of all-cause mortality by onset period. B. Kaplan–Meier curves of diabetes-related causes of death (category A) by onset period. C. Kaplan–Meier curves of diabetes-related causes of death (category A) by onset before and after puberty

patients (including four deaths at onset), death caused by ESRD in six patients, death from accident/suicide in four patients, death owing to infection in four patients (all in children with disabilities), death owing to CVD in three patients, and death from other causes in two patients. Among all deaths, six overnight deaths (9.1% of total deaths), including dead-in-bed syndrome, were observed in the study; no patients had serious chronic complications of diabetes. Patients who died were in their early 20 s or 30 s. All patients lived alone in a large city, such as Sapporo or near metropolitan Tokyo. All six patients who died overnight underwent forensic autopsy and one received an internal examination; however, the causes of death remained unclear. The last-measured glycated haemoglobin (HbA1c) level before death in these six patients was 6.2% (44.6 mmol/mol), 6.9% (51.5 mmol/mol), 6.9% (52.1 mmol/mol), 7.0% (53.3 mmol/mol), 7.4% (57.0 mmol/mol), and 7.5% (58.3 mmol/mol). HbA1c levels in these patients were considered to be within levels of good or relatively good control.

Discussion

Herein, we report the long-term mortality in a population-based study in Hokkaido with a median follow-up duration of 37.6 years. The study results showed decreased mortality in the 1990 onset-year group compared with the 1970 onset-year group. The leading causes of death in early mortality were sudden unexpected death, ADC, ESRD, and accident/suicide whereas the causes in late mortality were ESRD and CVD.

Among similar studies, the present study had one of the longest follow-up durations, and we also investigated diabetes-specific causes of death. The registry of childhood-onset type 1 diabetes in Japan was first established in 1984 by Hibi et al. of the Ministry of Health and Welfare, Japan with 1,572 patients with type 1 diabetes under 18 years of age registered [13]. This registry was the main source of participants in the DERI cohort study. Several patients from the 1960s to early 1970s in our Hokkaido cohort were also included in the DERI cohort. In the DERI cohort, ESRD and CVD were the leading causes of death. The mortality rate and SMR of the DERI cohort in the 1965–1969 diagnosis group were 1,240 per 100,000 person-years and 19.3, respectively; these values declined to 339 per 100,000 person-years and 6.6 in the 1975–1979 diagnosis group [8]. In our study, the mortality rate and SMR in the 1970 group (1959–1979) were 823 per 100,000 person-years and 8.8, respectively, which were comparable to the values in the DERI cohort study.

The TWMU Diabetic Centre reported the results of a long-term follow-up among patients with childhood-onset and young adult-onset (less than 30 years of age) diabetes [9]. The average age of participants was considerably older than that in our study. Because the TWMU Diabetic Centre is located in the centre of metropolitan Tokyo, only a small number of children who presented at diagnosis were observed in that cohort. Most patients were introduced to the Centre when they arrived in Tokyo from regional cities throughout Japan for employment or to enter university or college. Therefore, the TWMU Diabetic Centre's follow-up includes population flows (in and out of metropolitan Tokyo). The mean follow-up duration of the TWMC study among patients diagnosed between 1952 and 1979 was 17.1 years whereas that of our study was much longer at 51.5 years in the 1970 group. Compared with our study, the SMR in the TWMC study was considerably lower because all patients at the TWMC Diabetic Centre were treated by diabetes specialists and the follow-up duration was shorter.

It is of interest to compare the mortality rates in Scandinavian countries, which have a high incidence of type 1 diabetes, with those in Japan, which has a low incidence.

The mortality rates in Japan and Finland during 1965–1979 were 606 and 372 per 100,000 person-years, respectively; the SMRs were 12.9 and 3.7, respectively [11]. The leading cause of mortality in Japan was renal disease, which increases markedly in people with type 1 diabetes [14]. In a Norwegian study, the mortality rates during 1973–1982 and 1989–2012 were 132 and 143 per 100,000 person-years, respectively, and the leading cause of death before age 30 years was ADCs [7]. Although the mortality rate in Japan was 823 per 100,000 person-years in the 1970 group, this decreased to 133 per 100,000 person-years in the 1990 group—a rate comparable to that of Norway. The SMR of childhood-onset type 1 diabetes in Sweden during 1977–2000 was 2.15 (95% CI 1.70–2.68) [1]. Although the SMR in Japan (5.9) in 1980–1989 was much higher than that in Sweden, it dropped to 3.2 in the later 1990–1996 period, suggesting considerable improvement over time.

The leading causes of death with more than a 30-year disease duration from diabetes onset are ESRD and CVD [5, 7–9]. In contrast, the leading cause of short-term mortality differed in each cohort and varied according to medical care, education, and culture. These causes were ADC, accident/suicide, infection, and overnight death. We observed six cases of overnight death in our study. Each of the six patients was living alone in a large city. Three patients were in their early 20 s and had moved to a large city around metropolitan Tokyo or Sapporo after graduating from high school, vocational school, or university; the remaining three patients worked in a private company. All six patients sometimes drank alcohol. In a previous study, the proportion of early, sudden unexplained death, including overnight death or dead-in-bed syndrome, ranged from 1.41% to 21.8% of all deaths [15]; in our study, this rate was 9.1%, with higher mortality in male versus female individuals. The proportion of early, sudden unexplained death was 13.3% of all deaths in Norway [7], which is similar to that of our study in Hokkaido [7]. Secrest et al. reported risk factors of sudden death and dead-in-bed syndrome in Pittsburgh [16]. The authors divided sudden death into sudden unexplained death and dead-in-bed syndrome. Male sex increased the risk of sudden death tenfold. Furthermore, dead-in-bed syndrome was associated with higher HbA1c, higher doses of insulin, and lower body mass index [16].

In our study, male sex was a risk factor for mortality with short-term disease duration. Female sex was a risk factor for early mortality in studies in Sweden [1], by EURODIAB [2], and in Australia [6]. ADCs, such as ketoacidosis or diabetic coma, are understood to be prevalent in infants or young children [17, 18]. However, we observed four cases of death at onset, including among three young male adolescents. A high risk of death at onset in early adolescence was also reported in Sweden [1], Chicago [3], Wales [4], and Australia [6]. Poor metabolic control in childhood is strongly correlated to diabetes-related premature death in those younger than age 30 years [19].

Early death owing to ischemic heart disease in childhood type 1 diabetes has been reported in England and Wales. In this study, the highest SMR was observed in the age group 10–19 years (SMR = 115.1), followed by the age groups 20–29 and 30–39 years [20]. Determining the criteria for death from ischemic heart disease is important because no deaths from this cause have been reported from other institutes. The risk of mortality in children with type 1 diabetes must be reconsidered.

We observed a higher mortality rate from diabetes-related causes in patients with onset after puberty than in those with onset before puberty (Fig. 4C). Nishimura et al. also reported a poorer prognosis of post-pubertal-onset type 1 diabetes than that of pre-pubertal onset diabetes [21]. The role of prepubertal diabetes duration in the development of angiopathy is controversial. Some reports describe no or slight effects [22] whereas others have reported this as a new independent risk factor for proliferative diabetic retinopathy [23]. From another perspective, patients who develop diabetes after puberty may have a shorter disease duration (by 5 years) than those who develop the disease before puberty, and the life span from birth may be similar for patients with pre-pubertal and post-pubertal onset. Indeed, we determined life expectancy within our data and found it to be similar between both groups (data not shown; $p = 0.46$, log-rank test).

Figure 2 reveals a higher proportion of mortality owing to ERSD in female than in male patients. This is because female patients had a longer average lifespan, and therefore a longer disease duration, which contributed to the progression of diabetic nephropathy. Additionally, in male patients, the proportions of CSV, ADCs, and sudden death were higher than those in female patients. Few male patients may have died owing to ESRD because they experienced early death from other causes.

This study has several limitations. First, because the investigation was limited to Hokkaido Prefecture, the results may not be representative of the entire Japanese population. Second, although the survey was population-based, the follow-up rate (75%) may be insufficient. Patients who were not included in the analysis may have had worse prognoses than those included in the analysis. Despite these limitations, this study also has several strengths. First, the follow-up duration was very long; therefore, the mortality rate reflects mortality from diabetes onset to recent years. Second, we interviewed patients' attending physicians who reviewed the patients' medical records in their hospital or clinic; therefore, the data on vital status are accurate.

In conclusion, we reported the mortality rate and SMR of childhood-onset type 1 diabetes with a long follow-up duration of over 35 years. We observed a decrease in the patient

mortality rate over time. To reduce premature mortality in childhood-onset type 1 diabetes, emphasis should be placed on the prevention of acute complications such as ADCs, overnight death, and deaths owing to accident/suicide by providing appropriate patient education and developing appropriate patient handover processes between paediatrics and internal medicine.

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Author contributions NM created the study concept and design, wrote the first draft, and obtained funding. YI, SS, and MM followed up with the patients and acquired the study data. HY analysed the data, performed the statistical analysis, wrote the first draft, and obtained funding.

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Data availability The data that support the findings of this study are not publicly available because they contain sensitive information; however, these are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest Matsuura N., Yokomichi H., Ito Y., Suzuki S., and Mochizuki M. declare that they have no conflicts of interest.

Ethical approval The protocol for this study was approved by the ethics committee of Hokkaido University (approval number: 019–0256). The follow-up survey was started after the approval of the ethics committee on 10 January 2020 and ended in March 2022.

Human or animal rights All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and/or with the Helsinki Declaration of 1964 and later versions. Informed consent or substitute for it was obtained from all patients for being included in the study.

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