Complications

Poor metabolic control in childhood strongly correlates to diabetes-related premature death in persons <30 years of age—A population-based cohort study

John Samuelsson¹,² | Ulf Samuelsson² | Lena Hanberger³ | Marie Bladh² | Karin Åkesson¹,²

¹Department of Pediatrics, Ryhov County Hospital, Jönköping, Sweden
²Department of Clinical and Experimental Medicine, Division of Children's and Women's Health, Linköping University, Linköping, Sweden
³Department of Medicine and Health Sciences, Division of Nursing, Linköping University, Linköping, Sweden

Correspondence
John Samuelsson, Department of Pediatrics, Ryhov County Hospital, 551 85 Jönköping, Sweden.
Email: john.samuelsson@rjl.se

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Abstract

Background/objective: The importance of metabolic control in childhood regarding excess risk of death in young persons has not been well studied. This registry-based study aimed to investigate mortality rates and cause of death related to metabolic control in young persons (≤29 years) in Sweden with type 1 diabetes.

Methods: All 12 652 subjects registered in the Swedish pediatric diabetes quality register, from 2006 to 2014, were included. Data were merged with the Swedish Cause of Death Register. Standardized mortality rates were calculated using the official Swedish population register.

Results: Of 68 deaths identified, 38.2% of the deaths were registered as being due to diabetes whereof the major cause of death was acute complications. Overall standardized mortality ratio was 2.7 (2.1-3.4, 95% CI). Subjects who died from diabetes had a mean HbA1c of 74 ± 19 mmol/mol (8.9 ± 1.7%) during childhood vs 62 ± 12 mmol/mol (7.8 ± 1.1%) in those still alive (P < .001).

Conclusions: In this nationwide cohort of young subjects with type 1 diabetes, there was a high mortality rate compared to the general population. Mean HbA1c in childhood was significantly higher in those who died from diabetes, compared to subjects who were still alive. To decrease mortality in young persons with type 1 diabetes it is essential not only to achieve but also to maintain a good metabolic control during childhood and adolescence.

Keywords
adolescent, children, glycated hemoglobin a, mortality, type 1 diabetes mellitus

1 | INTRODUCTION

Patients with type 1 diabetes mellitus diagnosed in childhood or adolescence are at increased risk of premature death compared to the general population.¹ A systematic review by Morgan et al calculated standardized mortality ratios (SMRs) in 23 studies worldwide, ranging from 0 to 8.54, covering time periods from 1970 to 2007.² Excess mortality was less marked in more recent studies²,³ and in countries with higher health expenditure.² A Swedish register study between the years 1977 and 2000 found an average SMR of 2.15 in young patients with type 1 diabetes.⁴ A more recent Norwegian study presented an average SMR of 3.6 from 1973 to 2012 (n = 7884),⁵ the same as a...
Finnish study of childhood-onset (<15 years) diabetes covering the period 1970 to 2007 (n = 17 306),6 and a study from northern Ireland, from 1989 to 2012 calculated an average SMR of 2.96.7 In Denmark, a cohort of 720 children was followed from 1987 to 2014, rendering an SMR of 4.8, where HbA1c in 1989 was found to be the only predictor for increased risk of death.8 An Australian study following subjects until the end of 2012 presented an average SMR of 3.3, 1.7 for men and 10.1 for women (n = 1309). Death during early adulthood was significantly associated with elevated mean HbA1c level, recurrent episodes of severe hypoglycemia, and low socio-economic status.9

Sweden, after Finland, is the country with the highest annual incidence of type 1 diabetes in the world,10,11 in 2014 44.7/100 000 and approximately 890 children were diagnosed.12 The Swedish pediatric diabetes care is well organized and nationwide population-based data are provided in a quality register with high ascertainment rate, enabling benchmarking of the outcome of care and follow-up of quality improvement. In spite of this, a high proportion of children and adolescents do not achieve the national goal of metabolic control.12

Intensive treatment is known to give better metabolic control, reduced morbidity, and lower mortality.13-15 An increasing number of studies illustrate the importance of good glycemic control early in the course of disease, in order to avoid future morbidity.16-19

Lind et al have shown an excess risk of death from any cause for adult Swedish patients with type 1 diabetes; a doubled risk even with good glycemic control, ≤ 52 mmol/mol (6.9%), and an almost 10 times higher mortality risk with a mean HbA1c above 83 mmol/mol (9.7%). Adults ≤34 years of age had an increased risk of premature death, and diabetic ketoacidosis and hypoglycemia contributed to 31.4% of this risk.20 It is not known how these subjects presented at onset, and what kind of metabolic control they experienced during childhood.

As type 1 diabetes is a common pediatric disease, with high mortality rates, it is important to increase the knowledge regarding mortality, and its risk factors in type 1 diabetes. The impact of metabolic control in childhood and adolescence on future mortality has not been well studied, and never using a nationwide population-based pediatric quality register.

The aim of the present study was to calculate mortality rates in young persons (≤ 29 years) in Sweden, with type 1 diabetes diagnosed <18 years of age, and to study metabolic control in childhood related to cause of death.

2 | METHODS

2.1 | The Swedish pediatric diabetes quality register, SWEDIABKIDS

The SWEDIABKIDS database (SWE), established in 2000, contains outpatient data from all Swedish pediatric diabetes centers (n = 43). Since 2007 the register has included data on 99% of children, and adolescents with diabetes in Sweden. It includes data from onset as well as from every patient visit, until 18 years of age when patients are referred to adult care. According to the Swedish national guidelines, each child should visit the pediatric outpatient diabetes clinic about four times per year.21

The SWE is financially supported by the Swedish Association of Local Authorities and Regions, SALAR, which represents the governmental, professional, and employer-related interests of Sweden's municipalities, county councils, and regions.22 The register has the status of a national quality register, and the families/patients give informed consent to be included in the register.

All laboratory methods used in Sweden are standardized through EQUALIS (External Quality Assurance in Laboratory Medicine in Sweden). Data on HbA1c are derived from capillary blood samples taken in connection with visits to the diabetes center. The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) reference method is used in Sweden, and HbA1c values are presented both as IFCC (mmol/mol) and as NGSP/DCCT (%).23

2.2 | The Swedish Cause of Death Register (CDR)

The CDR is held by The National Board of Health and Welfare in Sweden. Data has been recorded since 1961 and the register is updated every year. Until 2011, the register included all deceased persons who at the time of death were nationally registered in Sweden, regardless of whether the actual death took place within Sweden or abroad. Since 2012, all deaths in Sweden have been included in the register, even those where the subject was not nationally registered in Sweden at the time of death. The diagnoses in the cause of death register are coded according to the international version of ICD.24,25

2.3 | Study population

Data on all subjects registered in the SWE were collected. To investigate if any of these subjects had died, and the causes of death, personal identification numbers were linked with the CDR. When linking the SWE with the CDR, 110 subjects were identified as deceased. Subjects were followed from January 1, 2006, until death or December 31, 2014. The coverage of the SWE was not complete until 2006, which is why this year was chosen as the start time for the study. All subjects born before 1987 were excluded, as they were above 18 years of age at the start of the study. After exclusion, in total 12 652 subjects (54% males) with type 1 diabetes between the years 2006 and 2014 ≤29 years of age were included in the SWE, whereof 68 were deceased. This rendered a study population that was nationwide, and population-based.

Mortality in the study population was compared with mortality in the general population in Sweden using the official Swedish population register, Statistics Sweden. Date and diagnosis of death were retrieved from the CDR. Subjects were divided into age groups: 10-14, 15-19, 20-24, and 25-29 years. Diagnoses were grouped into diabetes-related death (ie, where diabetes was registered as the immediate cause of death) (E10, E14), cardiovascular disease (I20-25, I30-52, I60-69, I70-79), poisoning (X58-59, X40-49, Y10-34), accidents (V01-99), neurological disease (G00-99), suicide (X60-84), malignancy (C00-97), infection (A00-B99), other (cystic fibrosis, lung embolus, immune deficiency, cystic kidney disease, strabismus, and aplasia), and unknown
causes of death. ICD codes do not differentiate hypoglycemic comas from hyperglycemic comas (E10.0: type 1 diabetes mellitus with coma and E14.0: unspecified diabetes mellitus with coma).

2.4 Statistics

IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, NY) was used for the analyses. Student’s t test was used for comparison of means. When there were indications of skewed distribution, a Mann-Whitney U test or a Kruskal Wallis test was used. Groups were compared by crosstabs, and chi-square was used for proportions. The mean HbA1c was calculated for each individual; thereafter, mean HbA1c for the whole population and for males and females was derived. SMRs and the corresponding 95% confidence interval (Mid P exact test) were calculated using http://www.openepi.com/SMR/SMR.htm. A Cox proportional hazards model with years since diagnosis of type 1 diabetes as timescale was used to estimate hazard ratios for the association between cause of death, sex, age at onset, year of diagnosis and mean HbA1c. Subjects exited the analyses at time of death or when reaching the end of the follow-up. A two-sided P value < .05 was regarded as statistically significant. The HbA1c results are presented as mean ± SD.

The study was approved by the regional ethics committee in Linköping, Sweden.

3 RESULTS

Sixty-eight out of 12 652 subjects included in the study died between years 2006 and 2014, 36 males and 32 females. Twenty-six (38%) of these, 15 males and 11 females, had diabetes registered as the immediate cause of death, where acute complications, that is, hypoglycemia or ketoacidosis were the major contributors (22 cases, 15 males and seven females [32%]). Cardiovascular reasons were the cause of death in seven cases (10%) and the SMR was significantly elevated in females (8.7, 95% CI 2.8-21.0) but not in males (1.8, 95% CI 0.5-4.9). This sex difference was also seen for the six cases (9%) of neurological disease as cause of death, with significantly elevated female SMR (10.9, 95% CI 4.0-24.1) compared to male SMR (1.0, 95% CI 0.1-5.0). Poisoning was the cause of death in three (4%), accident in six (9%), suicide in six (9%), malignancy in two (3%), infection in two (3%), other cause of death in seven (10%), and unknown cause of death in three (4%) cases (Table 1). Sixteen subjects (24%) died before 18 years of age, of which six deaths were registered as due to diabetes.

The present study contributed to 95 334 person-years. Overall SMR was calculated to be 2.7 (2.1-3.4, 95% CI), male SMR 2.0 (1.4-2.7, 95% CI) and female SMR 4.4 (3.1-6.2, 95% CI). The SMR increased with increasing age. In the highest age group, 25-29 years, it was 6.3 (3.4-10.7, 95% CI) (Table 2). In the younger age groups, up to 24 years, the increased SMR among female subjects was partly a reflection of lower mortality rates in these age groups in the general population in females compared to males.

### TABLE 1 Causes of death and SMRs in 68 deceased, out of a total of 12 652 subjects with type 1 diabetes, followed from 2006 to 2014

| Causes of death                        | Observed deaths, Males/ females no. | Expected deaths | SMR total (95% CI) |
|---------------------------------------|-------------------------------------|-----------------|--------------------|
| Total                                 | 36/32                               | 25.4            | 2.7 (2.1-3.4)      |
| Diabetes mellitus                     | 15/11                               |                 |                   |
| Coma                                  | 15/7                                |                 |                   |
| Complications                          | 0/2                                 |                 |                   |
| Kidney failure                         | 0/1                                 |                 |                   |
| Non-specified                          | 0/1                                 |                 |                   |
| Cardiovascular causes                  | 3/4                                 | 2.0             | 3.4 (1.5-6.8)      |
| Poisoning                             | 3/0                                 | 0.3             | 0.06 (0-2.1-0.7)   |
| Traffic accident                       | 5/1                                 | 0.3             | 1.7 (0.7-3.6)      |
| Neurological disease                   | 1/5                                 | 1.4             | 4.2 (1.7-8.8)      |
| Suicide                                | 2/4                                 | 6.9             | 0.9 (0.4-1.8)      |
| Malignancy                             | 2/0                                 | 3.2             | 0.6 (0.1-2.1)      |
| Infection                              | 1/1                                 | 0.3             | 7.4 (1.2-24.5)     |
| Other                                  | 2/5                                 |                 |                   |
| Unknown                                | 2/1                                 |                 |                   |

aNone with ischemic heart disease (I20-25).
bPoisoning with insulin: 1.
cBrain disorder, sequelae of inflammatory disease of CNS, degenerative disease of nervous system, mitochondrial myopathy, cerebral palsy, anoxic brain damage.
dAcute lymphoblastic leukemia, malignant neoplasm of the tongue.
ePneumonia: 2.
fCystic fibrosis, lung embolus: 2; immune deficiency, cystic kidney disease, strabismus, aplasia.

3.1 HbA1c and premature death

Subjects who died from diabetes-related causes had, during childhood, a mean HbA1c of 74 ± 19 mmol/mol (8.9 ± 1.7%). This was significantly higher (P < .001) compared to those still alive (62 ± 12 mmol/mol [7.8 ± 1.1%]). There was no significant difference in mean HbA1c between those who died from other causes and those still alive. The same was true regarding last registered HbA1c in the SWE (before referral to adult care, or last registered HbA1c before time of death for those deceased before 18 years of age). There were no significant differences between death registered as being due to diabetes, death due to other causes, and those still alive regarding sex, age at onset, and duration of disease (Table 3).

When analyzed by a Cox proportional hazards model, the likelihood of death registered as due to diabetes was significantly increased with increasing mean HbA1c (hazard ratio 1.06, 95% CI 1.02-1.10), an effect not seen in those with death registered as due to other causes. There was a non-significant tendency towards increased risk of death registered as due to diabetes in males (hazard ratio 1.24, 95% CI 0.43-3.59). Diagnosis in later years in the study period contributed to an increased risk of death registered as due to diabetes (hazard ratio 1.29, 95% CI 1.04-1.61), but age at diagnosis had no predicting value in this group (Table 4).
4 | DISCUSSION

In this nationwide, population-based cohort of 12 652 young subjects with type 1 diabetes, there was a significantly higher mortality rate than in the general population. A high proportion of deaths were directly related to diabetes.

The subjects in this study were all younger than 30 years of age, and there was a remarkably increased risk of dying registered as being due to diabetes in those with poor metabolic control during childhood. Almost all diabetes-related deaths were caused by acute and not micro- or macrovascular complications. As the cohort was young this is not surprising, and similar results have been shown in Norway by Gagnum et al.26 In 22 persons (32%), the cause of death was acute diabetes coma (hypo and hyperglycemic). HbA1c was significantly higher in those for whom diabetes was the immediate cause of death, compared to death from other causes, or compared to subjects still alive. This was true both regarding last registered HbA1c before referral to adult care, or before death, and mean HbA1c during childhood. Children with earlier onset year did not have an increased risk of premature death. However the study period is short. Guidelines regarding the treatment of type 1 diabetes are constantly being updated and the treatment of the disease has improved. The introduction of insulin pumps and Continuous Glucose Monitoring (CGM) systems might further contribute to decreased mortality rates. Today, a high percentage of Swedish children with diabetes have a CGM system attached to their body, and future studies are needed to evaluate the effect of CGM on the risk of acute death.

Most deaths occur after referral to adult diabetes care, which is why this might be a problem that is overlooked by the pediatric diabetes team. The transition to adult diabetes care is a sensitive period. There is need for a well-structured transition care and it is important not to lose subjects from follow up.27 It must be emphasized that health professionals treating and supporting children and adolescents are aware of the importance of good metabolic control during childhood to reduce the risk of death in young patients with type 1 diabetes.

In a study of Swedish adults with type 1 diabetes Lind et al have shown an increased risk of premature death, clearly increasing with increasing HbA1c in adulthood.20 However, studies also including data regarding metabolic control during childhood are few. In an Australian cohort of 1309 subjects, Cooper et al have shown an association between increased HbA1c in childhood and death in early adulthood.9 Our results are in line with this. Furthermore, in some earlier studies, both the SWE, and the NDR (National Diabetes Register; the Swedish database for adults with diabetes) have shown that good metabolic control during childhood/adolescence reduced future morbidity.17,19 This linkage of the two registries could also show that poor metabolic control during childhood/adolescence could not be compensated for with good metabolic control during early adulthood.19

Moreover, teenage girls with poor metabolic control face more complications in early adulthood than teenage boys.28 However, we found no differences in the distribution between sex and cause of death. In absolute numbers, deaths were evenly distributed between males and females. When calculating SMRs, females with type 1 diabetes have an increased risk of death compared to the general population. In this material, this cannot be explained by worse metabolic control in females. Mostly, it is due to our finding that before 20 years of age the mortality rate in males with diabetes is almost equal to the
mortality rate in males in the general population. We found no significant sex difference regarding HbA1c in those deceased, but this might be because there were few deaths.

As has been shown by Rawshani et al, age at diagnosis is an important risk factor for premature death, most emphasized in cardiovascular cause of death, raising the question whether cardioprotective medication should be considered earlier than in current practice. Our results compliment the picture as data regarding metabolic control in childhood were not available neither in the study by Rawshani et al nor in the study by Lind et al. As well as considering cardiovascular medication in young adults, efforts aimed to keep a low HbA1c during childhood is essential to increase survival.

A strength of the present study is the use of a register with very good coverage and completeness, and the access to data regarding HbA1c in childhood. However, as with all registry studies, data is based on registry information and relies on correct information being entered into the registry.

A weakness of the present study is the classification of deaths based only on ICD codes from the CDR. ICD codes do not differentiate hypoglycemic coma from hyperglycemic coma (ketoacidosis). There is a need for future studies where medical records are reviewed in order to achieve a more accurate classification. Robust data regarding death from hypoglycemia and ketoacidosis would be clinically interesting. In six cases, the immediate cause of death was accident.

### TABLE 3
Baseline characteristics and metabolic control in 12 652 subjects with type 1 diabetes 2006–2014. Results are presented as mean ± SD. The sex difference in HbA1c is significant for those still alive regarding onset, mean and last registered value (P < .05, independent t test), but not significant for those deceased (independent samples, Mann-Whitney U test)

|                | Death registered as due to diabetes | Death registered as due to other cause | Still alive | Death registered as due to diabetes vs Still alive, P value | Death registered as due to other cause vs still alive, P value |
|----------------|------------------------------------|---------------------------------------|-------------|------------------------------------------------------------|------------------------------------------------------------|
| Males/females, no. (%) | 15/11 (58/42) | 21/21 (50/50) | 6830/5753 (54/46) | 0.73 | 0.58 |
| Age at onset, years | 9.5 ± 4.2 | 10.1 ± 4.4 | 9.0 ± 4.3 | 0.53 | 0.09 |
| Duration, years | 10.3 ± 5.4 | 9.4 ± 5.1 | 9.5 ± 5.7 | 0.46 | 0.38 |
| pH onset | 7.37 ± 0.07 | 7.29 ± 0.15 | 7.34 ± 0.10 | 0.29 | 0.06 |
| HbA1c, onset, mmol/mol (%) | 103 ± 30 (11.6 ± 2.7) n = 18 | 93 ± 32 (10.7 ± 2.9) n = 22 | 94 ± 26 (10.8 ± 2.4) n = 8776 | 0.17 | 0.89 |
| Males | 92 ± 22 (10.6 ± 2.0) n = 11 | 102 ± 27 (11.5 ± 2.5) n = 10 | 92 ± 25 (10.6 ± 2.3) n = 4818 | 0.97 | 0.21 |
| Females | 119 ± 34 (13.0 ± 3.1) n = 7 | 86 ± 35 (10.0 ± 3.2) n = 12 | 96 ± 27 (10.9 ± 2.5) n = 3958 | 0.027 | 0.18 |
| HbA1c, mean, mmol/mol (%) | 74 ± 19 (8.9 ± 1.7) n = 14 | 64 ± 14 (8.0 ± 1.3) n = 18 | 62 ± 12 (7.8 ± 1.1) n = 10 769 | <0.001 | 0.53 |
| Males | 77 ± 21 (9.2 ± 1.9) n = 8 | 62 ± 7 (7.8 ± 0.6) n = 9 | 61 ± 12 (7.7 ± 1.1) n = 5881 | <0.001 | 0.91 |
| Females | 69 ± 16 (8.5 ± 1.5) n = 6 | 66 ± 20 (8.2 ± 1.8) n = 9 | 63 ± 12 (7.9 ± 1.1) n = 4888 | 0.18 | 0.45 |
| HbA1c, last registered value, mmol/mol (%) | 83 ± 28 (9.7 ± 2.6) n = 24 | 64 ± 20 (8.0 ± 1.8) n = 39 | 64 ± 16 (8.0 ± 1.5) n = 11 841 | 0.004 | 0.88 |
| Males | 86 ± 28 (10.0 ± 2.6) n = 14 | 63 ± 15 (7.9 ± 1.4) n = 19 | 63 ± 15 (7.9 ± 1.4) n = 6436 | 0.009 | 0.92 |
| Females | 78 ± 30 (9.3 ± 2.7) n = 10 | 65 ± 25 (8.1 ± 2.3) n = 20 | 65 ± 16 (8.1 ± 1.5) n = 5404 | 0.19 | 0.97 |

### TABLE 4
Hazard ratios based on a Cox proportional hazards model with years since diagnosis as timescale, adjusted for cause of death, sex, age at onset, year of diagnosis and mean HbA1c

|                | Hazard ratio (95% CI) | P value |
|----------------|-----------------------|---------|
| **Death registered as due to diabetes** | | |
| Sex | Female Reference | Male 1.24 (0.43–3.59) | 0.689 |
| Age at diagnosis, years | 0–9 Reference | 10–19 0.90 (0.16–5.26) | 0.911 |
| Year of diagnosis | 1.29 (1.04–1.61) | 0.023 |
| Mean HbA1c | 1.06 (1.02–1.10) | 0.002 |
| **Death registered as due to other causes** | | |
| Sex | Female Reference | Male 0.84 (0.34–2.13) | 0.721 |
| Age at diagnosis, years | 0–9 Reference | 10–19 12.95 (3.10–54.04) <0.001 |
| Year of diagnosis | 1.07 (0.86–1.32) | 0.542 |
| Mean HbA1c | 0.98 (0.94–1.03) | 0.437 |
One can speculate on whether some of these were in fact suicides or hypoglycemic events. However, we found no increase of SMR regarding accidents, and the same was true for suicides and poisoning. Socioeconomic factors and their association to poor metabolic control in childhood and subsequent mortality need further research. The present study does not include data on adult glycemic control. Future similar studies should include adult HbA1c data in order to control for the impact of glycemic control in adulthood and assess the time-dependent HbA1c related risk for mortality.

In conclusion, we have found an increased mortality in young subjects with type 1 diabetes, compared to the general population in Sweden. Female SMRs were higher than males. The SMRs increase with age. Mean HbA1c in childhood was significantly increased in those who died from diabetes-related causes, mainly due to acute complications. To achieve and maintain good metabolic control in childhood and adolescence are one of the most essential and important factors to reduce the risk of acute death in young persons with type 1 diabetes.

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AUTHOR CONTRIBUTIONS
J.N., U.S., L.H., and K.Å. contributed to the study concept and design. M.B., J.N., and U.S. did the statistical analyses. J.N. had the primary responsibility for writing the paper. All authors reviewed and revised subsequent versions of the manuscript.

CONFLICT OF INTEREST
The authors declare no potential conflict of interest.

ORCID
John Samuelsenso https://orcid.org/0000-0001-6010-3501
Lena Hanberger https://orcid.org/0000-0001-9504-2649

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