Comparing continuous subcutaneous insulin infusion and multiple daily injections in children with Type 1 diabetes in Sweden from 2011 to 2016—A longitudinal study from the Swedish National Quality Register (SWEDIABKIDS)

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Abstract
Objective: This study aimed to compare metabolic control measured as hemoglobin A1c (HbA1c), the risk of severe hypoglycemia, and body composition measured as body mass index standard deviation scores (BMI-SDS) in a nationwide sample of children and adolescents with Type 1 diabetes with continuous subcutaneous insulin infusion (CSII) and multiple daily injections (MDI), respectively.

Research Design and Methods: Longitudinal data from 2011 to 2016 were extracted from the Swedish National Quality Register (SWEDIABKIDS) with both cross-sectional (6 years) and longitudinal (4 years) comparisons. Main end points were changes in HbA1c, BMI-SDS, and incidence of severe hypoglycemia.

Results: Data were available from 35,624 patient-years (54% boys). In general, HbA1c decreased approximately 0.5% (2–5 mmol/mol) from 2011 to 2016 (p_trend < 0.001) and the use of CSII increased in both sexes and all age groups. Mean HbA1c was 0.1% (0.7–1.5 mmol/mol) lower in the CSII treated group. Teenagers, especially girls, using CSII tended to have higher BMI-SDS. There was no difference in the number of hypoglycemias between CSII and MDI over the years 2011–2016.

Conclusions: There was a small decrease in HbA1c with CSII treatment but of little clinical relevance. Overall, mean HbA1c decreased in both sexes and all age groups without increasing the episodes of severe hypoglycemia, indicating that other factors than insulin method contributed to a better metabolic control.

Keywords
continuous subcutaneous insulin infusion, metabolic control, multiple daily injection, HbA1c, hypoglycemia
1 | INTRODUCTION

Every year around 900 children and adolescents between 0 and 17 years of age develop Type 1 diabetes in Sweden, corresponding to an annual incidence of 44/100,000.1 This disease presents challenges to everyday life with a need for daily insulin injections, glucose testing, regular meals, and regular physical activity to keep the blood glucose well balanced. In addition, poor metabolic control during adolescence increases the risk of severe complications later in life.2,3 Even people with well controlled Type 1 diabetes have a doubled risk of death from any cause as well as from cardiovascular causes compared to the general population, and the risks are several times higher among patients with poor glycemic control.4

Traditionally, Type 1 diabetes has been treated with subcutaneous insulin injections 5–6 times daily. More than 40 years ago continuous subcutaneous insulin infusion (CSII) was introduced as a way to achieve a better metabolic control.5,6 In randomized controlled trials7 CSII among adolescent and adults with Type 1 diabetes has been demonstrated to improve metabolic control by lowering hemoglobin A1c (HbA1c) and decrease complications.8 Also, in children CSII is considered the most physiological way to administer insulin today.9 In young children, CSII reduces the incidence of severe hypoglycemic events10 which is an important feature of its use in this age group.11,12

However, in terms of efficacy, studies show varying results regarding the ability of CSII to sustain lower HbA1c levels after the first 6–12 months of use.13–15 Smaller studies previously carried out in Sweden have given somewhat different results concerning the efficacy of CSII. In 2008, Skogberg et al. were not able to show a better metabolic control with CSII compared to multiple daily injections (MDI).16 In another follow-up of patients who started CSII treatment in the years 2005–2009 compared to matched controls, CSII treatment improved the metabolic control during the first year but not thereafter.17 The group with CSII treatment had fewer incidents of severe hypoglycemia during follow-up but the number of ketoacidosis events increased.

A better glucose metabolic control may contribute to a normal body mass index (BMI), but there is no evidence from previous studies that CSII treatment can accomplish this.13,18,19

The aim of this retrospective study using real life data was to compare CSII treatment with MDI treatment in terms of metabolic control, BMI, and prevalence of severe hypoglycemia in a large national cohort of children and adolescents with Type 1 diabetes.

2 | METHOD

The study population consisted of all children and adolescents from 0 to 17 years of age with Type 1 diabetes, as reported in the Swedish National Diabetes Register for Pediatric Diabetes in Sweden, SWEDIABKIDS, hereinafter referred to as the Register. The period 2011–2016 was selected because of the general decrease in mean HbA1c that occurred during these years while the frequency of CSII usage increased. The study was approved by the Regional Ethics Committee at Umeå University, Umeå, 2017/12-31.

2.1 | SWEDIABKIDS

All 43 pediatric clinics in Sweden have used the Register since 2007, resulting in a coverage of nearly 98% for prevalent cases.1 The Register is continuously validated against the Swedish Prescribed Drug Register for incident cases.1 The Prescribed Drug Register is maintained by the National Board of Health and Welfare and covers all redeemed medical prescriptions since July 2005.20

Since 2008, the Register has been web-based and clinical data are recorded from every patient visit to the out-patient pediatric clinics, which is usually three to four times per year per patient. In 2016, data from 7310 unique patients up to 17 years of age were recorded in the Register from 27,186 visits21 and on average 6915 patients per year were recorded from 2011 to 2016. The target for HbA1c for children and adolescents with diabetes Type 1 was <7% (<53 mmol/mol) during 2011–2016 but was revised to <6.5% (<48 mmol/mol) in 2017. The indications for CSII treatment during this period was difficulties achieving a good metabolic control with MDI treatment, eating disorders, frequent episodes with severe hypoglycemia, dawn phenomenon in teenagers and young age with difficulties administering low doses of insulin with MDI. The start of CSII treatment was often done with the patient and family staying at the hospital for 2–3 days. Some diabetic teams invited a representative from the CSII-industry to help out with the education to the patients and families while other teams educated the families themselves. During this period CSII treatment to small children became more frequent and the method to count carbohydrates was nationally introduced around 2011.

2.2 | Data measurement

At the different hospitals using the Register, analyses of HbA1c are performed according to different laboratory methods but all are quality assured through Equalis [External Quality Assurance in Laboratory Medicine in Sweden].22 which makes it possible to compare HbA1c values across different clinics. HbA1c is presented as International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) units (mmol/mol) and National Glycohemoglobin Standardization Program (NGSP) units. In comparison to NGSP, an HbA1c value of 53 mmol/mol corresponds to 7.0% and 75 mmol/mol to 9.0%.22 The conversion of HbA1c from IFCC (mmol/mol) to NGSP (%) was done using the tool provided by the National Glycohemoglobin Standardization program.24 Severe hypoglycemia was defined as blood glucose of <70 mg/dl (3.9 mmol/L) together with an event involving seizure or unconsciousness. Anthropometrical data (weight and height) were collected during each clinical visit. BMI standard deviation scores (BMI-SDS) were calculated during each visit using the BMI reference values for Swedish children.25
Anonymized individual-level data was extracted from the Register from January 1, 2011 to December 31, 2016. For each year and for each patient, data on age, sex, HbA1c, diabetes duration, insulin delivery method, BMI-SDS, and severe hypoglycemic events were collected. The cumulative number of severe hypoglycemic events was collected from the last visit for that year for every patient, so that each number corresponds to one individual having at least one or more severe hypoglycemic events during that year. Patients that had changed insulin delivery method during a year were excluded for that year; this group consisted of approximately 10% of the patients. The recorded number of ketoacidosis events were very few and since it was not routine at all clinics to register them during these years, we deemed that it was not reliable to use this data.

A cohort was also created consisting of all patients from 0 to 15 years of age and with a diabetes duration of >6 months in 2013, based on data extracted from the Register from January 1, 2013 to December 31, 2016. The patients needed to have had at least one registered HbA1c value for each of the 4 years from 2013 to 2016 and they had to have remained on the same insulin delivery method, that is, CSII or MDI, and not become >18 years of age throughout the follow-up period. An initial group of 6674 unique patients was identified but 1411 patients were excluded due to missing HbA1c values. Another 868 patients changed their insulin delivery method, and 467 patients were also excluded as data were missing on their insulin delivery method during this period. This left 3928 patients in the final cohort. For each year and for each patient, data on age, sex, A1c, diabetes duration, insulin delivery method, BMI-SDS, and severe hypoglycemic events were collected.

There were no differences in sex or BMI-SDS distribution in the group missing HbA1c values compared to the group with HbA1c values in the cohort. In the group, 74% received MDI treatment, they had a shorter diabetes duration and there were very few patients with severe hypoglycemia. No systematic skewness was found in the group with missing HbA1c values. However, younger patients were over-represented thus having a shorter diabetes duration.

The annual data was stratified according to insulin treatment (CSII vs. MDI), age groups (0–6, 7–12, and 13–17 years old), and HbA1c groups (<6.5 [<47.9 mmol/mol], 6.5–7.3 [48.0–55.9 mmol/mol], 7.3–8 [56.0–63.9 mmol/mol], 8–8.7 [64.0–71.9 mmol/mol], and > 8.7 [≥72 mmol/mol]). The age groups were based on major clinical differences in developmental psychology, ability to self-care, and bodily maturation and hormonal impact on the glucose metabolic control. As girls tend to have a higher HbA1c than boys, a sex stratified analysis was performed. The longitudinal data were stratified according to insulin treatment (CSII vs. MDI) and sex. All statistical analyses were performed using IBM SPSS version 24 with independent two-sample t-tests for normally distributed data and one-way ANOVA for calculating p-trends. The multivariate analyses included: (a) multiple logistic regression in which the dependent variable was set to insulin delivery method and the independent variables were HbA1c, BMI-SDS, duration of diabetes, and sex, and (b) multivariable linear regressions with two models, one where the dependent variable was set to HbA1c and...
the independent variables were sex, BMI-SDS, and duration of diabetes and the other model where the dependent variable was set to BMI-SDS and the independent variables were HbA1c, sex, and duration of diabetes. Statistical significance was defined as \( p < 0.05 \). A linear mixed model was used to study HbA1c, BMI-SDS, and severe hypoglycemic events of the cohort.

3 | RESULTS

Baseline data are presented in Table S1. In total, data from 35,624 patient-years (54% boys) of patients from 0 to 17 years of age were available.

3.1 | Cross-sectional data

3.1.1 | Choice of insulin delivery method

Between 2011 and 2016, the frequency of CSII treatment increased from 41% to 60% in girls and from 35% to 56% in boys (\( p_{\text{trend}} < 0.001 \)) (Figure 1, Table S1). Patients using CSII were generally younger (Figure 2(B), Table S2) but had a longer diabetes duration compared with those treated with MDI, except for the HbA1c group >8% (64 mmol/mol) where there was no difference in patient age between the different insulin delivery methods (Figure 2(B), Table S3).
3.1.2 | Metabolic control

An overall decrease in HbA1c of around 0.5% (2–5 mmol/mol) was seen in the different age and sex groups from 2011 to 2016 (Figure 1, Table S1). There was no difference in mean HbA1c between the patients using CSII or MDI except for the group with HbA1c >8.7% (72 mmol/mol) in which the group using CSII had a lower HbA1c compared to the MDI group; (CSII: 9.2% [77.4 mmol/mol] vs. MDI: 9.4% [79.8 mmol/mol], \( p < 0.01 \)) (Table S3) and in boys 13–17 years where the group using CSII had a higher HbA1c; (CSII: 7.7% [60.3 mmol/mol] vs. MDI: 7.5% [58.2 mmol/mol], \( p < 0.001 \)) (Figure 1, Table S2).

3.1.3 | BMI-SDS

There were no changes in BMI-SDS over the period in any of the age groups. Patients using CSII tended to have a higher BMI-SDS and, for example, in teenage girls, the mean BMI-SDS with CSII treatment was 0.96 during the period 2011–2016 (Figure 2(A), Table S2).

3.1.4 | Prevalence of hypoglycemia

There was no difference in the recorded number of hypoglycemic events between the treatment groups from 2011 to 2016 despite the general decrease in HbA1c (Figure 3, Table S2).

3.2 | Longitudinal data

3.2.1 | Choice of insulin delivery method

Patients using CSII were younger than the patients using MDI, \( p < 0.001 \) (Table 1).

3.2.2 | Metabolic control

In general, there was an age-dependent increase in mean HbA1c similar for both insulin delivery methods (i.e., CSII or MDI). There was no difference in mean HbA1c between the insulin delivery methods (Table 1).

3.2.3 | BMI-SDS

There was no difference in the BMI-SDS between the insulin delivery methods in either of the sexes (Table 1).

3.2.4 | Prevalence of hypoglycemia

There was no difference in the number of severe hypoglycemic events between the patients using CSII or MDI (Table 1).

3.2.5 | Change in insulin delivery method

More girls (54%) than boys changed their insulin delivery method during the years 2013–2016 but the mean age (11 years) was the same. Most changes were from MDI to CSII treatment. The mean HbA1c for those who changed insulin delivery method increased for every year from 2013 to 2016, from 7.7% (60.3 mmol/mol) in 2013 to 7.9% (63.0 mmol/mol) in 2016, \( p < 0.001 \) and the increase was similar to the group not changing insulin delivery method. There was no difference in the BMI-SDS or in the number of severe hypoglycemic events between those changing and not changing insulin delivery method, (further data not shown).

Table 2 presents the multivariate logistic regression analysis with insulin delivery method as the outcome. Overall, the use of CSII was associated with female sex, higher BMI-SDS and long diabetes duration. In 2011, the likelihood of CSII was 30% higher in girls compared to boys (OR 1.30 [CI 1.16–1.45], \( p = 0.001 \)), which decreased to 22% by 2016 (OR 1.22 [CI 1.10–1.36], \( p = 0.001 \)).

Tables 3 and 4 presents the multivariable linear regression analysis with HbA1c and BMI-SDS as the outcomes, each outcome modeled separately and stratified by year. The multivariable regression of HbA1c indicated that a high HbA1c was associated with higher BMI-SDS, female sex, and long diabetes duration. In 2011, HbA1c was approximately 0.1% lower with CSII treatment compared to MDI.
### Table 1: The cohort group 2013–2016 stratified for sex and insulin method

<table>
<thead>
<tr>
<th></th>
<th>Longitudinal data in the cohort group</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
</tr>
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<tr>
<td></td>
<td></td>
<td>MDI</td>
<td>CSII</td>
<td>MDI</td>
<td>CSII</td>
</tr>
<tr>
<td><strong>Boys</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%</td>
<td>1130 (54.9)</td>
<td>930</td>
<td>45.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age (years [range]</strong></td>
<td>11.3 (2.2;15.8)</td>
<td>10.6</td>
<td>1.5</td>
<td>15.8</td>
<td>12.5</td>
</tr>
<tr>
<td><strong>HbA1c (%[CI])</strong></td>
<td>7.3 (7.3;7.4)</td>
<td>7.5</td>
<td>7.4</td>
<td>7.6</td>
<td>7.4</td>
</tr>
<tr>
<td><strong>HbA1c (mmol/mol [CI])</strong></td>
<td>56.5 (56.8;57.2)</td>
<td>58.5</td>
<td>57.8</td>
<td>59.1</td>
<td>57.3</td>
</tr>
<tr>
<td><strong>BMI SDS (CI)</strong></td>
<td>0.54 (0.47;0.60)</td>
<td>0.61</td>
<td>0.54</td>
<td>0.68</td>
<td>0.56</td>
</tr>
<tr>
<td><strong>Hypoglycemic events n (%)</strong></td>
<td>38 (3.4)</td>
<td>36</td>
<td>3.9</td>
<td></td>
<td>25</td>
</tr>
<tr>
<td><strong>Girls</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%</td>
<td>1013 (54.2)</td>
<td>855</td>
<td>45.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age (years [range]</strong></td>
<td>11.0 (2.5;15.8)</td>
<td>10.6</td>
<td>0.8</td>
<td>15.7</td>
<td>12.2</td>
</tr>
<tr>
<td><strong>HbA1c (%[CI])</strong></td>
<td>7.4 (7.3;7.5)</td>
<td>7.5</td>
<td>7.4</td>
<td>7.6</td>
<td>7.5</td>
</tr>
<tr>
<td><strong>HbA1c (mmol/mol [CI])</strong></td>
<td>57.4 (56.6;58.1)</td>
<td>58.5</td>
<td>57.8</td>
<td>59.2</td>
<td>58.5</td>
</tr>
<tr>
<td><strong>BMI SDS (CI)</strong></td>
<td>0.58 (0.51;0.66)</td>
<td>0.69</td>
<td>0.63</td>
<td>0.75</td>
<td>0.69</td>
</tr>
<tr>
<td><strong>Hypoglycemic events n (%)</strong></td>
<td>27 (2.7)</td>
<td>32</td>
<td>3.7</td>
<td></td>
<td>30</td>
</tr>
</tbody>
</table>

*Note: Values presented are numbers, percentages, means with CI. Hypoglycemic events were defined as unconsciousness or seizures.*

*Abbreviations: BMI, body mass index (kg/m²); CI, confidence intervals; CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections; SDS, standard deviation score.

*p < 0.05. **p < 0.01. ***p < 0.001.
treatment. Furthermore, the multiple linear regression of BMI showed that a high BMI was associated with CSII treatment, higher HbA1c, and female sex. In 2011, BMI was 0.1 SDS higher in CSII treated patients compared to MDI treated patients. There was no interaction effect between sex and insulin method. The model was also made with calendar year with the same result. This finding was due to the association between diabetes duration and insulin delivery method. The diabetes duration among CSII treated subjects decreased with a year from 2011 to 2016 and during the same time reduced their HbA1c by 0.6% (4–7 mmol/mol) while diabetes duration and HbA1c have remained constant over the years among those using MDI.

4 | DISCUSSION

Our main findings were a minute decrease in HbA1c in CSII treated patients and a general, severalfold larger reduction in the mean HbA1c irrespective of treatment from 2011 to 2016, without any increase in severe hypoglycemia. The difference in HbA1c between CSII and MDI treatment was only 0.1% (0.7–1.5 mmol/mol) and of little clinical relevance. During the same period the use of CSII treatment increased by more than 50%. This indicates that the CSII regimen per se was no better in improving the metabolic glucose control than MDI at the group level. A meta-analysis of randomized controlled studies of pediatric cohorts using CSII have shown a modest HbA1c reduction but most of these studies had a duration less than 3 months. Our study is based on real-life data which might explain the different results compared to RCTs. Our finding corroborates some previous studies, which demonstrated no difference in glucose metabolic control between CSII and MDI. An Israeli study following children and young adults for 6 years after CSII initiation found a decrease in HbA1c similar to ours and also with no increase in the rate of hypoglycemia. Recently, episodes of severe hypoglycemia have been demonstrated to be associated with a progressive increase in HbA1c in children and adolescents with Type 1 diabetes. It is thus important to avoid these events in order to avoid long-term diabetes complications.

However, our findings contradict a Danish study where they followed patients for more than 5 years to show that children and adolescents in all age groups achieved an improved metabolic control on CSII treatment. There was a parallel rise in HbA1c in both MDI and CSII treated patients during follow-up, similar to other studies which showed a significant improvement in HbA1c only in the first year after starting CSII treatment but not thereafter. Possible explanations to our findings compared to other studies could be different indications for CSII treatment and different approaches to education in the multidisciplinary teams which can lead to different education of patients and families. As we show, the use of CSII has increased during recent years and at a later follow-up in 2018, 65% of children and adolescents <18 years of age were treated with CSII. The usage of CSII varies considerably between different counties and also between pediatric clinics with frequencies ranging from 19% to 91%. These differences remain largely unexplained and there is no correlation between mean HbA1c and frequency of usage of CSII in the pediatric clinics. The costs for insulin pumps in Sweden are covered by the National Healthcare system and the patient and their families do not have any costs for neither insulin nor the technology.

There is no standardized curriculum in Sweden for how to start CSII treatment in a patient, so this procedure varies between different pediatric clinics. National guidelines based upon ISPAD guidelines 2014 has been developed with indications for CSII treatment. A comparable reduction in mean HbA1c between the two insulin delivery methods indicates that other factors must be of importance for the improvement of glucose metabolic control.

A second result was the higher BMI-SDS in teenage girls using the CSII regimen. This is consistent with the findings of Ibfelt et al. and Birkebaek et al. One explanation could be that girls with a high BMI-SDS might have an insulin resistance, which can lead to a higher HbA1c prompting healthcare practitioners to provide them with CSII treatment in an attempt to improve their metabolic control. If this is the case, those involved in health care delivery to children with Type 1 diabetes should explore ways to prevent avoidable increases in BMI through support to patients and families, for example healthy food recommendations and encouragement to do physical activity. Since Samuelsson et al. showed that teenage girls with Type 1 diabetes have an increased risk of complications in adulthood this emphasizes the importance of helping this group achieve a better glucose metabolic control without negatively affecting other aspects of their health, such as increasing the risk of obesity. A somewhat lower HbA1c in the group with the highest HbA1c in patients using CSII may indicate treatment benefits, but these results need to be interpreted with caution. We also found that HbA1c was higher in teenage boys using CSII regimen. One explanation could be that boys with difficulties achieving a satisfying glycemic control resulting in high HbA1c values are provided with CSII treatment in an assessment to improve their metabolic control. If so, this indicates that the multidisciplinary teams need to find other ways to help

<table>
<thead>
<tr>
<th>Year</th>
<th>OR</th>
<th>95% CI</th>
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<th>95% CI</th>
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<td>2011</td>
<td>0.99</td>
<td>0.99–0.99</td>
<td>0.99</td>
<td>0.99–1.00</td>
<td>0.99</td>
<td>0.99–1.00</td>
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<td>0.99–1.00</td>
<td>0.99</td>
<td>0.98–0.99</td>
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<td>2012</td>
<td>1.13</td>
<td>1.07–1.19</td>
<td>1.11</td>
<td>1.05–1.16</td>
<td>1.09</td>
<td>1.04–1.15</td>
<td>1.07</td>
<td>1.02–1.12</td>
<td>1.05</td>
<td>1.00–1.10</td>
<td>1.06</td>
<td>1.01–1.11</td>
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<td>1.14–1.18</td>
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<td>1.10–1.13</td>
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<td>2014</td>
<td>1.15</td>
<td>1.14–1.16</td>
<td>1.12</td>
<td>1.09–1.35</td>
<td>1.15</td>
<td>1.04–1.28</td>
<td>1.16</td>
<td>1.05–1.29</td>
<td>1.17</td>
<td>1.06–1.30</td>
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<td>1.10–1.36</td>
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<td>2015</td>
<td>1.28</td>
<td>1.22–1.36</td>
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<td>1.22–1.36</td>
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<td>1.22–1.36</td>
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<td>1.22–1.36</td>
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<td>1.22–1.36</td>
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<td>1.22–1.36</td>
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<tr>
<td>2016</td>
<td>1.29</td>
<td>1.22–1.36</td>
<td>1.29</td>
<td>1.22–1.36</td>
<td>1.29</td>
<td>1.22–1.36</td>
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<td>1.22–1.36</td>
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<td>1.22–1.36</td>
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Abbreviations: BMI, body mass index (kg/m²); CI, confidence intervals; CSII, continuous subcutaneous insulin infusion; SDS, standard deviation score.
**TABLE 3** Coefficients from linear regression of HbA1c stratified by year, 2011–2016

<table>
<thead>
<tr>
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<tr>
<td>Method</td>
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<td>95% CI</td>
<td>B</td>
<td>95% CI</td>
<td>B</td>
<td>95% CI</td>
<td>B</td>
<td>95% CI</td>
<td>B</td>
<td>95% CI</td>
<td>B</td>
<td>95% CI</td>
</tr>
<tr>
<td>BMI-SDS</td>
<td>0.033</td>
<td>0.008;0.058</td>
<td>0.027</td>
<td>0.002;0.053</td>
<td>0.048</td>
<td>0.023;0.073</td>
<td>0.033</td>
<td>0.009;0.058</td>
<td>0.050</td>
<td>0.027;0.072</td>
<td>0.064</td>
<td>0.043;0.085</td>
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<tr>
<td>Duration (years)</td>
<td>0.110</td>
<td>0.103;0.118</td>
<td>0.114</td>
<td>0.107;0.122</td>
<td>0.121</td>
<td>0.114;0.128</td>
<td>0.109</td>
<td>0.102;0.116</td>
<td>0.089</td>
<td>0.082;0.095</td>
<td>0.082</td>
<td>0.076;0.088</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.106</td>
<td>0.051;0.161</td>
<td>0.091</td>
<td>0.037;0.145</td>
<td>0.060</td>
<td>0.005;0.114</td>
<td>0.088</td>
<td>0.035;0.142</td>
<td>0.101</td>
<td>0.052;0.150</td>
<td>0.076</td>
<td>0.029;0.122</td>
</tr>
</tbody>
</table>

Note: B, coefficient; Method, continuous subcutaneous insulin infusion (CSII). Abbreviations: BMI-SDS, body mass index (kg/m²) standard deviation score; CI, confidence interval.

**TABLE 4** Coefficients from linear regression of BMI stratified by year, 2011–2016

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Method</td>
<td>B</td>
<td>95% CI</td>
<td>B</td>
<td>95% CI</td>
<td>B</td>
<td>95% CI</td>
<td>B</td>
<td>95% CI</td>
<td>B</td>
<td>95% CI</td>
<td>B</td>
<td>95% CI</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>0.034</td>
<td>0.008;0.060</td>
<td>0.029</td>
<td>0.003;0.055</td>
<td>0.049</td>
<td>0.023;0.075</td>
<td>0.036</td>
<td>0.020;0.062</td>
<td>0.062</td>
<td>0.034;0.090</td>
<td>0.086</td>
<td>0.057;0.114</td>
</tr>
<tr>
<td>Duration (years)</td>
<td>0.008</td>
<td>0.000;0.016</td>
<td>0.006</td>
<td>−0.002;0.014</td>
<td>0.006</td>
<td>−0.001;0.014</td>
<td>0.010</td>
<td>0.003;0.018</td>
<td>0.014</td>
<td>0.007;0.022</td>
<td>0.014</td>
<td>0.006;0.021</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.190</td>
<td>0.135;0.246</td>
<td>0.194</td>
<td>0.138;0.249</td>
<td>0.181</td>
<td>0.126;0.236</td>
<td>0.158</td>
<td>0.103;0.213</td>
<td>0.165</td>
<td>0.110;0.220</td>
<td>0.181</td>
<td>0.127;0.235</td>
</tr>
</tbody>
</table>

Note: B, coefficient; Method, continuous subcutaneous insulin infusion (CSII). Abbreviations: BMI-SDS, body mass index (kg/m²) standard deviation score; CI, confidence interval.
these patients and families. This could, for example, include contact with a psychologist or screening for neuropsychiatric disorders such as attention deficit hyperactivity disorder (ADHD) which if present complicates everyday life for children and adolescents with diabetes Type 1.\textsuperscript{35}

One of the factors that could be of importance for the improvement of the glucose metabolic control could be the use of carbohydrate counting,\textsuperscript{36} which became an established method at all pediatric clinics in Sweden during the study. Also, the use of real-time continuous glucose monitoring (rtCGM) and intermittent continuous glucose monitoring (iscGM) became more prevalent and may have improved the chances of the patients achieving a more stable glucose balance with more “time in range” (70–180 mg/dl [3.9–10 mmol/L]) and a lower risk of hypoglycemia. Data on the use of CGM was not registered in SWEDIABKIDS until 2016. Since then, there has been an increase in CGM usage and in 2018 a majority (93%) of all children and adolescents with diabetes Type 1 in Sweden used CGM.\textsuperscript{1} Previous studies have demonstrated an increased treatment satisfaction and quality of life with CSII treatment\textsuperscript{16,28} but at present we have no such data in SWEDIABKIDS. Further studies are required to determine the contribution of these or other factors contributed most on the lowering of HbA1c in Swedish children with Type 1 diabetes from 2011 to 2016.

One major strength of this study is the large number of patients with real life data. Since the National Diabetes Register SWEDIABKIDS has a coverage of nearly 98% of prevalent cases, the study gives a good representation of the pediatric population with Type 1 diabetes in Sweden. A weakness of this study is that we do not know the indication for patients starting CSII treatment. It could be due to poor glucose metabolic control, young age, patient preference, or a combination of all these factors. Another weakness is the number of patients that changed insulin delivery method each year as this group is quite large (10%) and again, we do not know the reason behind the change. In the longitudinal cohort, the group missing HbA1c values is also quite large (21%) which may be explained by a short diabetes duration and young patients having extra visits to the clinic without HbA1c testing being done. The frequency of severe hypoglycemic events increased in the cohort group toward the end of the period, which can be explained by increasing age.

Even though we have been able to show only a minute benefit of CSII treatment in improving the glucose metabolic control compared to MDI, we find that the investment may nevertheless be worthwhile based on treatment benefits which we have not studied, for example, improved treatment satisfaction,\textsuperscript{16,17} improved quality of life,\textsuperscript{28} facilitating carbohydrate counting,\textsuperscript{36} and the coming combination with CGM to create closed-loop systems.\textsuperscript{37}

To conclude, we found, based on real-life data a minute decrease in HbA1c with CSII treatment compared to MDI treatment with little clinical relevance. There was a general reduction in HbA1c irrespective of insulin delivery method over the years 2011–2016 and this without increasing the incidences of severe hypoglycemia.

ACKNOWLEDGMENTS
None of the authors have any conflict of interest and the contributions are described in the following text.

AUTHOR CONTRIBUTION AND CONFLICT OF INTEREST
Financial support was provided by the Department of Research and Development Region Jämtland-Härjedalen, Stiftelsen Samariten, and Thuringstiftelsen. We have no potential conflicts of interest to report. A.F. contributed to the design of the study, collected and analyzed the data, wrote the first draft of the manuscript, and reviewed and edited the manuscript. M.L. contributed to the design of the study, collected and analyzed the data, contributed to the discussion, and reviewed and edited the manuscript. U.S. contributed to the design of the study, collected, and analyzed the data, contributed to the discussion, and reviewed and edited the manuscript. M.B. assisted with the statistical analysis and reviewed and edited the manuscript. U.S. is the guarantor of this work and as such, had all the access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Parts of this study were presented in abstract form at the annual meeting of the International Society for Pediatric and Adolescent Diabetes, Boston, USA, on October 30, to November 2, 2019.

PEER REVIEW
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DATA AVAILABILITY STATEMENT
Data can be provided upon request to the authors.

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REFERENCES


