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ORIGINAL ARTICLE

Continued improvement of metabolic control in Swedish pediatric diabetes care

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Background: To prospectively investigate if the grand mean HbA1c and the differences in mean HbA1c between centers in Sweden could be reduced, thereby improving care delivered by pediatric diabetes teams.

Methods: We used an 18-month quality improvement collaborative (QIC) together with the Swedish pediatric diabetes quality registry (SWEDIABKIDS). The first program (IQ-1), started in April 2011 and the second (IQ-2) in April 2012; together they encompassed 70% of Swedish children and adolescents with diabetes.

Results: The proportion of patients in IQ-1 with a mean HbA1c <7.4% (57 mmol/mol) increased from 26.4% before start to 35.9% at 36 months ($P < .001$), and from 30.2% to 37.2% ($P < .001$) for IQ-2. Mean HbA1c decreased in both participating and non-participating (NP) centers in Sweden, thereby indicating an improvement by a spatial spill over effect in NP centers. The grand mean HbA1c decreased by 0.45% (4.9 mmol/mol) during 36 months; at the end of 2014 it was 7.43% (57.7 mmol/mol) ($P < .001$). A linear regression model with the difference in HbA1c before start and second follow-up as dependent variable showed that QIC participation significantly decreased mean HbA1c both for IQ-1 and IQ-2. The proportion of patients with high HbA1c values (>8.7%, 72 mmol/mol) decreased significantly in both QICs, while it increased in the NP group.

Conclusions: The grand mean HbA1c has decreased significantly in Sweden from 2010 to 2014, and QICs have contributed significantly to this decrease. There seems to be a spatial spill-over effect in NP centers.

KEYWORDS

diabetes mellitus type 1, hemoglobin A1c protein, human, pediatrics, quality of health care

1 | INTRODUCTION

HbA1c is the standard index of glycemic control over the preceding period of 8 to 12 weeks. Several studies have shown good correlation between HbA1c and blood glucose levels over time.[1] Studies have shown that early improvement of glycemic control, measured as HbA1c, is very important in preventing, delaying or slowing down the progression of long-term complications.[2,3] A high proportion of adolescents do not reach treatment targets for HbA1c,[4] and there is a correlation between metabolic control during adolescence and early adulthood.[5] There is evidence showing that metabolic control deteriorates during adolescence[6] and does not begin to improve until early adulthood.[7] On the other hand, some studies show that stricter glycemic control is associated with increased risk of severe hypoglycemia,[8] while others do not,[9] and a balance between glucose control and risk of hypoglycemia is necessary.

The treatment of children with diabetes in Sweden follows national guidelines, which are based on the ISPAD guidelines[10] with the same HbA1c target value of <7.4% (57 mmol/mol) since 2008. ISPAD's (The International Society for Pediatric and

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Adolescent Diabetes) HbA1c target was <8% (64 mmol/mol) in the 2000 guidelines, and is <7.5% (58 mmol/mol) in the 2009 and 2014 guidelines. The Swedish population of children and adolescents with diabetes is relatively homogenous, and pediatric diabetes centers treat all patients in their catchment area. The families do not bear any of the costs for the insulin treatment, hospital care, or visits to the outpatient clinic. Despite this, the pediatric diabetes teams do not succeed in providing equal care to all children and adolescents with diabetes in Sweden, which is shown by the differences in mean HbA1c between centers within the country.[11,12]

Differences between centers have also been found in other countries.[4,13] The differences between centers were not explained by clinical or treatment variables.[13,14] In a study within the Swedish pediatric diabetes quality registry (SWEDIABKIDS), contributing factors were found to be team members' policies and approaches, and the professional experience of the team members.[11]

It has been shown that participation in a quality improvement collaborative (QIC), with the aim of improving and standardizing the quality of pediatric diabetes care, can facilitate improvements in the quality of care by pediatric diabetes teams. The centers' mean HbA1c decreased by 0.3% (3.7 mmol/mol) for all the teams that participated in the QIC.[15] The Swedish pediatric diabetes quality registry, SWEDIABKIDS,[12] was used as a tool and resource for feedback and outcome measures.

The aim of this study was to explore if the improved results in pediatric diabetes care from the first QIC (IQ-1) could be repeated in a second QIC (IQ-2) that was performed during the period of 2012-2014. Another aim was to investigate if the improved quality of care in the first QIC was sustainable in a longer follow-up, and if this would have an impact on the grand mean HbA1c in Sweden and the HbA1c difference between centers.

2 | METHODS

2.1 | The Swedish pediatric diabetes quality registry

The quality registry SWEDIABKIDS was established in 2000 and includes outpatient ambulatory data from all Swedish pediatric diabetes centers (N = 42). By 2007, data completeness had reached 100%. Since 2008, the registry has been available online to all pediatric diabetes centers in Sweden. All children and adolescents aged 0 to 18 years with diabetes are treated at specialized pediatric centers in Sweden, and the registry includes data on almost all (around 99%) of the children and adolescents with diabetes in Sweden. The results are presented online, openly naming the centers, and can be accessed by the public (www.swediabkids.se). SWEDIABKIDS allows each team to online continuously follow its quality indicators and results, and to benchmark its results with other teams as well as with the national results.

SWEDIABKIDS is financially supported by the Association of Local Authorities and Regions, SALAR, which represents the interests of Sweden's municipalities, county councils, and regions. SWEDIABKIDS has the status of a national quality registry.

2.2 | HbA1c analysis and clinical parameters

All methods used in Sweden have been standardized since 1997 through EQUALIS (External Quality Assurance in Laboratory Medicine in Sweden), ensuring alignment with IFCC (International Federation for Clinical Chemistry and Laboratory Medicine) standards since 2007. The data on HbA1c obtained from SWEDIABKIDS were derived from capillary blood samples measured locally with the Bayer/Siemens DCA-2000/Vantage analyser or using local HPLC (High Performance Liquid Chromatography) laboratory methods. The results were obtained in IFCC units (mmol/mol) and recalculated to DCCT/NGSP units (%) by a master equation.[16] According to the Swedish guidelines, children with diabetes visit a diabetes center at least 4 times per year, and HbA1c and other clinical parameters such as insulin dose, weight, height, physical activity, and blood pressure are recorded. The mean of all visits in 1 year per patient is used to calculate the mean HbA1c of a clinic.

2.3 | The QIC program

All 42 pediatric diabetes centers in Sweden were invited to participate in a QIC. Twelve teams accepted the invitation and the first program started in April 2011 (IQ-1), which has been described earlier.[15] In 2010, about 30% (2302/7660) of the patients in the 0 to 18 age range in Sweden were treated at these centers. A second program including 14 diabetes teams started in August 2012 (IQ-2). These 14 teams treated approximately 40% of the pediatric patients with diabetes in Sweden. In total 70% of the pediatric patients with diabetes were included in the 2 programs.

With inspiration from the "breakthrough" method,[17,18] the QIC included 6 seminars over 18 months (Figure 1). The first 4 seminars included learning sessions with lectures on improvement methods, teamwork and learning, and sharing experiences between the teams. Two meetings were performed to follow-up results and to support the teams to continue their improvement work. The teams identified problems and areas of possible improvement, created action plans, tested changes, and innovations, and followed up on the results by benchmarking through their own results in SWEDIABKIDS at the seminars. The systematic improvement methods that were used in the program included the value compass, microsystem analysis, flow charts, fishbone diagrams, and a plan-do-study-act wheel to test different improvement ideas.[17,19,20] Most of the work was done by the teams at the home centers in the intervals between the learning sessions as an integrated part of their daily team work. Examples of altered concepts in the QICs included improved local guidelines, improved teamwork with weekly or bi-weekly meetings, active use of the registry at every visit, introducing a lower HbA1c target of 7% (52 mmol/mol), carbohydrate counting from the onset in all patients, injection aids (i-Port) from the onset of diabetes for younger children, keeping track of weekly and bi-weekly mean glucose on patient meters, increased use of pumps in all age groups with pump start for preschool children within a few weeks of diagnosis, improved patient education regarding pump treatment and promotion of exercise and other health and educational activities.

Each team received support from an improvement coach.[21] Furthermore, 1 member of each team was selected to be the team coach and received extra training and support before the program started.
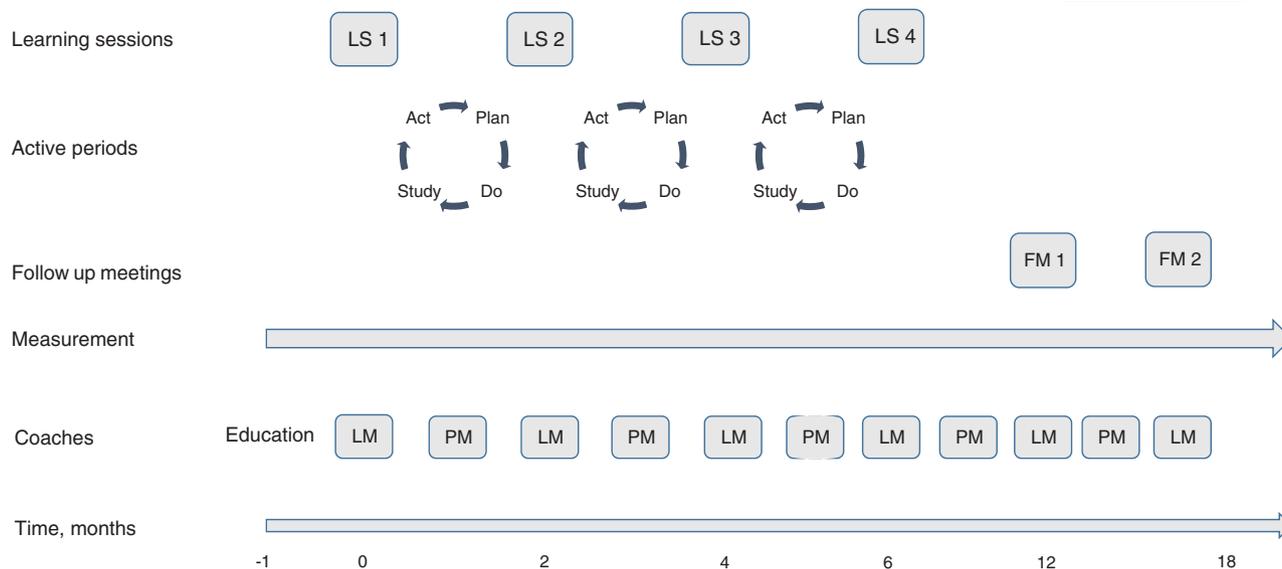
FIGURE 1 Flow chart presenting the time line and interventions of the quality improvement collaborative (QIC). The duration of the QIC was approximately 18-month with 4 learning sessions (LS) and 2 follow-up meetings (FM). The team coaches began with a 1-day education session followed thereafter by lunch-meetings (LM) at every LS and phone-meetings (PM) in between.

The outcome variables for the QIC were clinical, and included HbA1c, severe hypoglycemia (unconsciousness with or without seizures) and diabetesketoacidosis (DKA). The process measures were documentation of smoking habits and the degree of physical activity. The targets defined by a majority of centers were: (1) to increase the proportion of patients with HbA1c <7.4% (57 mmol/mol) and to reduce the number of patients with HbA1c >8.7% (72 mmol/mol), (2) to reduce the patients' mean HbA1c by lowering the target level for both HbA1c (below 7.0%, 52 mmol/mol) and blood glucose levels (average glucose <8 mmol/L, 145 mg/dL), and securing that patients and families encompassed the same targets, (3) compare it with the mean value of all centers in Sweden, (4) introducing carbohydrate counting at the onset of diabetes, and (5) not to increase the frequency of severe hypoglycemia.

The effect of the QIC was investigated by comparing the 6 months prior to the commencement of the collaborative (before start) with both the 12- to 18-month period after the start (first follow-up), and the 30- to 36-month period after the start (second follow-up). The non-participating (NP) centers were also included in the analysis, and their starting point in time was defined as the same as for IQ-1. At the starting point, the centers participating in IQ-1 and the NP centers had similar mean HbA1c values, 66 and 67 mmol/mol, respectively, while those in IQ-2 that started 16 months later had a lower value (62 mmol/mol).

2.4 | Statistics

Statistical methods included the Kolmogorov-Smirnov test, used to evaluate if data could be assumed to be normally distributed. As it was concluded that the data violated the assumptions of a normal distribution, Mann-Whitney's *U*-test and Wilcoxon's signed rank test were used to evaluate differences between the different measurements on mean HbA1c. In addition, a multivariate linear regression with mean HbA1c as the dependent variable and age, duration, and participation in QIC as independent variables was performed. Groups were compared by crosstabs, and chi-square was used for proportions. Univariate analysis of variance was used for trends over time. A *P*-value of <.05 (2-sided) was considered significant.

2.5 | Ethical consideration

This study treated only aggregated data for different health care organizations on a group level; no individual patients can be identified. The study is concerned with improvement efforts undertaken by the organizations, not the actions or performance of individuals. Therefore, the study did not require approval from a Swedish ethical review board.

3 | RESULTS

Clinical parameters of participating patients are shown in Table 1. The proportion of pump users increased during the time period in all 3 groups, to the highest for patients within IQ-1 and to the lowest for patients in NP clinics. The number of patients in each center, mean and range of HbA1c before start of the QICs is shown in Table S1, Supporting Information. As shown in this table, no obvious differences were found in mean HbA1c between small and big centers (number of patients) as both high and low values were seen in small as well as in big centers.

When including all patients, the baseline mean HbA1c value had decreased by 0.46% (5.1 mmol/mol) (*P* < .001) at the second follow-up for the centers participating in IQ-1. Because data are longitudinal, we have only included patients with values reported at the 3 time points; before start, the first, and second follow-up in further analyses. The mean decrease between the baseline and second follow-up was 0.26% (2.8 mmol/mol) (*P* < .001) in the centers participating in IQ-2. The corresponding figure for the NP centers was a decrease of

TABLE 1 Some clinical parameters before start and at first and second follow-up of the first (IQ-1), the second (IQ-2) QIC and centers not participating in the QICs (NP). Only patients with data at all 3 time points are shown

	IQ-1 (n = 1190)			IQ-2 (n = 1772)			NP (n = 1207)		
	Before start	First follow-up	Second follow-up	Before start	First follow-up	Second follow-up	Before start	First follow-up	Second follow-up
Age (mean and SD)	11 (3.4)	12.3 (3.4)	13.8 (3.5)	11.3 (3.2)	12.7 (3.5)	14.2 (3.2)	11 (4.1)	12.4 (3.5)	13.9 (3.5)
Duration of diabetes,ys (mean and SD)	4.3 (3.3)	5.6 (3.3)	6.9 (3.2)	5.2 (3)	6.7 (3)	8.4 (3)	4.4 (3.4)	5.7 (3.4)	7.1 (3.4)
Proportion of girls	46.6	46.6	46.6	47.7	47.7	47.7	48.1	48.1	48.1
Proportion of pump users	34.6	43.2	54.8	43.4	48.2	50.7	34.5	40.8	49.6

Abbreviations: NP, non-participating; QIC, quality improvement collaborative.

0.35% (3.8 mmol/mol) (P < .0001). When including only patients with values at all 3 time points (excluding those who had been too old for the registry at follow-up (≥18 years of age), and all new onset patients after the start of IQ), the difference between baseline and second follow-up for IQ-1 was −1.25 mmol/mol (median difference −2.5 mmol/mol) (P < .001), for IQ-2 the difference was −0.79 mmol/mol (median difference −1 mmol/mol)) (P < .001) and for NP the difference was +1.2 mmol/mol (median difference +0.5 mmol/mol) (P = .1). The difference in mean HbA1c between IQ-1 and NP clinics was significant between before start and second follow-up (P < .0001), but not between before start and first follow-up, P = .06. It was the same pattern between IQ-2 and NP-clinics.

A linear regression model with the difference in HbA1c before start and second follow-up for each individual patient as dependent variable showed that participation in the QIC significantly decreased the HbA1c value both for IQ-1 and IQ-2 (Table 2). Adding pump use to the multivariate linear regression model did not change the outcome.

The proportion of patients in IQ-1 with mean HbA1c <7.4% (57 mmol/mol) increased from 26.4% before start to 35.9% at the second follow-up (Figure 2), and the proportion of patients with high HbA1c (>8.7% (72 mmol/mol) decreased from 20.8% to 17.9% (P < .0001). Corresponding figures for IQ-2 from 30.2% to 37.2% and 19.4% to 17.1% (P < .001). The NP centers did not have the same

pattern; no change (34.1% to 34.0%) with mean HbA1c <7.4% (57 mmol/mol) and the proportion of patients with high HbA1c increased from 16.6% to 20.4% (P < .001).

The grand mean HbA1c in Sweden decreased each year between 2010 and 2014, and was 7.43 ± 0.26% (57.7 ± 2.8 mmol/mol) in 2014[12] compared to 7.88 ± 0.26% (62.6 ± 2.8 mmol/mol) in 2010 (Figure 3), P < .001. The differences between boys and girls decreased between year 2010 and 2014. Girls had 0.15% (1.6 mmol/mol) higher HbA1c compared to boys in 2010, which had decreased to 0.10% (1.1 mmol/mol) difference in 2014 (P < .05). As seen from the Figure 3, the decrease in HbA1c started first in IQ-1 and later in the NP centers. There was no correlation between center size and HbA1c at the start of the IQ project (data in Supporting Information), nor at the end.

The annual report from SWEDIABKIDS in 2011 (data from 2010) showed a difference of 1.2% (13.1 mmol/mol) between the centers with the lowest and highest mean HbA1c levels (7.1%-8.3%) (53.8-66.9 mmol/mol). In 2014, this span had changed to 51.9 to 69.0 mmol/mol (6.9%-8.5%), that is, an increase in difference to 1.6% (17.1 mmol/mol). However, there was 1 outlier in 2014 with 8.5% (69.0 mmol/mol), with the 2nd highest HbA1c being 7.9% (62.8 mmol/mol), and the SD and 95% confidence interval (CI) of the mean center HbA1c in 2014 (with the outlier included) are both lower than those in 2010 (SD 0.27%, CI 0.19-0.35 in 2014 vs SD 0.29%, CI 0.20-0.38 in 2010).

Before the study started, severe hypoglycemia was more common in the patients from centers within IQ-1: 3% compared to 1.9% of the patients in the NP centers (x^2 = 4.89, P < .03). The proportion was about the same at the first follow-up: 2.9% and 1.8%, respectively (x^2 = 5.19, P < .03). At the second follow-up, the difference almost disappeared: 2.1% and 1.9%, respectively. The proportion of patients with severe hypoglycemia in IQ-2 was 1.8% at the start, 2.1% in the first follow-up, and 1.0% at the second follow-up. During this time period, the proportion of hypoglycaemia was 1.0% for the children in IQ-1 and NP.

The quality of data entry in SWEDIABKIDS increased during IQ-1 and IQ-2. The registration of data regarding smoking habits in children above 12 years of age increased from 58% to 78% in IQ-2. Moreover, 10 out of 14 teams in IQ-2 improved their registration of data regarding physical activity in children above 10 years of age. Two teams reached the registration goal of 100% and 4 teams reached more than 90%. The same pattern was seen in IQ-1.

TABLE 2 Linear regression for some of the clinical data and participation or not in the first (IQ-1) and the second (IQ-2) QIC

The difference in HbA1c before start and second follow-up as dependent variable	B-coefficient	95% CI for B	P-value
Age	−0.436	−0.592 to −0.280	.000
Sex	0.094	−0.877 to 1.066	.849
Duration of diabetes	0.543	0.381 to 0.704	.000
Participation or not in IQ-1	−1,17	−1.656 to −0.685	.000
Age	0.05	−0.129 to 0.230	.581
Sex	−0.583	−1.60 to 0.434	.261
Duration of diabetes	0.235	0.047 to 0.423	.014
Participation or not in IQ-2	−1.749	−3.077 to −0.42	.01

Abbreviations: CI, confidence interval; QIC, quality improvement collaborative.

FIGURE 2 The proportion of patients with mean HbA1c <7.4%/57 mmol/mol (NGSP/DCCT and IFCC numbers) is shown before the start of IQ (light-gray bars), at the first follow-up (medium-gray bars) and at the second follow-up (dark-gray bars). White bars = before start, hatched bars = first follow-up, black bars = second follow-up.
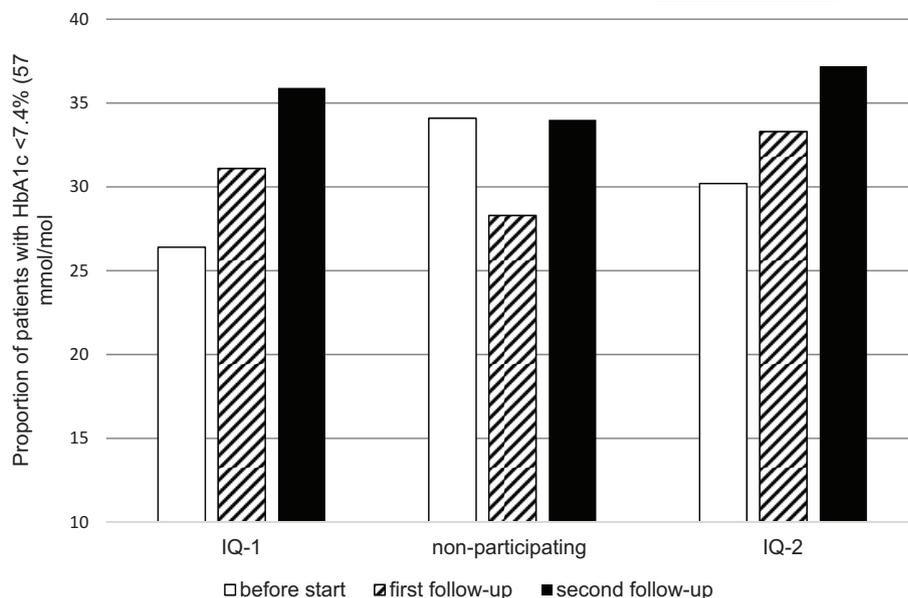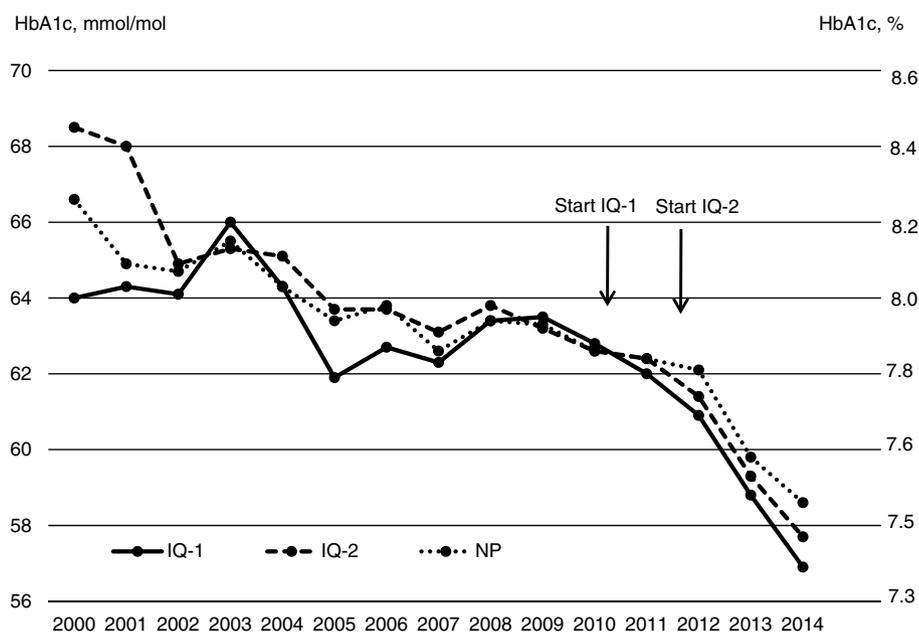
FIGURE 3 Mean HbA1c during the years 2000 to 2014 for IQ-1, IQ-2, and NP centers. Children and adolescents <18 years of age and a duration of diabetes >3 months are included. The left axis shows values in IFCC numbers and the right in DCCT/NGSP numbers. Solid line = IQ-1, dashed line = IQ-2, dotted line = NP.

4 | DISCUSSION

There has been a steady decrease in mean HbA1c in Sweden over the recent years (from 7.88%, 62.6 mmol/mol, in 2014 to 7.43%, 57.7 mmol/mol, in 2014, a drop of 0.11%, 1.2 mmol/mol, per year), and this level of continuous national improvement of pediatric diabetes care has not been, to our knowledge, reported previously. In this prospective study report, we describe how repeated QICs contributed significantly to the decrease in HbA1c.

There is always a risk, quite often found in clinical experience that HbA1c increases again after a period of lower values. Therefore, it is most promising that the patients participating in both QICs continued to reduce their HbA1c values 36 months after the start (18 months after the centers finished the QIC project). Patients in IQ-2 decreased the mean HbA1c by 0.16% (1.8 mmol/mol) during their first 18 months compared to the decrease of 0.3% (3.7 mmol/mol) achieved by IQ-1 during their first 18 months, regardless the center

size (number of patients treated at the center). One possible explanation is that the 14 centers in IQ-2 started at a lower mean HbA1c value. One important success factor is to have the patients/families strive for the same blood glucose levels and HbA1c as the team recommends. Boman et al[22] have shown that this is often not the case, in that one of the core categories in their study was "the tension between general recommendations and personal experience," where there was an experienced tension between managing the unique everyday life with the child and balancing this to meet the expectations of their diabetes team ("We try to do as the diabetes team wishes, but we can't satisfy them completely. They want him to be at 5 to 6 [mmol/L blood glucose level, 90-110 mg/dL] but we're happy with 11 [mmol/L, 200 mg/dL]").

As mentioned in the previous QIC report,[15] NP centers also reduced their patients' HbA1c values substantially and such a spill-over effect on non-enrolled clinics is known from other studies.[23] This type of spatial spill-over, that is, an indirect improvement effect,

has been described to take place in other areas of public health.[24-26] The spill-over effect continued and the NP centers, treating 30% of the pediatric patients with diabetes in Sweden, decreased their HbA1c values in total by 0.35% (3.8 mmol/mol) over the 36 months. A possible explanation for this is that the 2 QICs have been discussed at several forums in Sweden, presented at several professional meetings and also reported to officials in SALAR. This is an organization that represents the interests of Sweden's municipalities, county councils, and regions. Centers that participated in IQ-1 and IQ-2 have been invited to NP centers to share their methods and results. As the decrease in HbA1c started first among the teams that participated in IQ-1 and later in the NP centers, it indicates that the spill-over effect is delayed and that the NP clinics needed time to learn from participating centers (Figure 3).

The proportion of patients with high HbA1c values (>8.7%, 72 mmol/mol) decreased significantly in both QICs, while it increased in the NP group. It is important to find better ways to treat and support patients with such high values, as several studies have shown that high HbA1c values during adolescence continue up to adulthood.[27,28] This group of patients are at high risk not only of severe complications but also of premature death.[29,30]

Fear of hypoglycemia may have a negative impact on diabetes management, metabolic control, and subsequent health outcomes.[31] Hypoglycemia can lead to disruptions and practical problems in daily life and has also been found to correlate with a lower quality of life.[32] Moreover, it can also lead to premature death.[29] It is therefore understandable that clinicians may fear that decreasing HbA1c levels increase the risk of severe hypoglycemia. As in our first study,[15] we again found the opposite pattern, that is, a decrease in HbA1c and a concomitant decrease in severe hypoglycemia.

All participating centers improved the data entry in the registry. The registration of both smoking habits and physical activity increased substantially. So, along with the improved metabolic control, the team members also gained more knowledge about other important factors regarding the treatment, and in that way had the possibility to aid in preventing severe hypoglycemia. Most of the participating centers also reached their goal to introduce carbohydrate counting and improved the patient education regarding pump treatment.

Available data show that even when improving metabolic control considerably to <7.4% (57 mmol/mol) as young adults, adolescents with HbA1c >9.3% (78 mmol/mol) are at high risk of developing retinopathy.[33] It is thus of utmost importance to instigate a lower HbA1c already in the pediatric years. In achieving this, our results compare favorably with previously published figures. The Hvidore study[13] did not achieve an improvement during a 3-year follow-up from 1995 to 1998 (HbA1c 8.7% vs 8.9%, 72 mmol/mol vs 74 mmol/mol). The German-Austrian DPV registry study[4] showed a decrease from 8.7% to 8.1% (72 mmol/mol to 65 mmol/mol) between 1995 and 2009 (0-20 years of age), while the US Type 1 Exchange Registry[34] reported a follow-up HbA1c increase of 8.7% (72 mmol/mol) to 9.0% (75 mmol/mol) in the 13- to 17-year-old and 8.3% (67 mmol/mol) to 8.5% (69 mmol/mol) in the 6- to 12-year-old, while there was no change in the 2- to 5-year-old (8.2%, 66 mmol/mol) . Tansey et al reported on persistently high glucose levels in young children with diabetes aged

4 to 10 years with no change in HbA1c over 18 months, HbA1c being 7.9% (63 mmol/mol), both at the beginning and at the end of the study.[35] An Australian cohort study[36] (age 12-20 years) showed mean HbA1c levels with no HbA1c improvement between 2000 and 2009 (8.5% vs 8.5%, 69 mmol/mol). A recently published report from the Danish national registry, which has a similar high coverage as the Swedish, found no improvement in HbA1c between 2005 (8.2%, 65 mmol/mol) and 2012 (8.1%, 65 mmol/mol).[37] In spite of a lower HbA1c levels, we found a frequency of severe hypoglycemia per 100 patient years similar to Germany (2.3% in 2009)[4] but lower compared to Australia (7%),[36] and the United States (2%-6% of participants in the prior 3 months).[34]

A limitation to this study is that there may have been unknown confounding factors that contributed to a lower HbA1c in both the QIC and NP centers. However, in the light of the published difficulties in reaching such a low mean HbA1c, especially on a national level, this seems unlikely. Another limitation is that we did not use central HbA1c analysis. However, almost all clinics participate in the national HbA1c quality control program (EQUALIS), where outliers in HbA1c methodology are identified. Strengths of the study are the very high enrolment (99%), and that the data are national. Furthermore, we have in the linear regression included only patients with values at all 3 time points to avoid temporal trends. Another strength is the long follow-up period of 36 months.

To conclude, we have clearly shown that it is possible to achieve a continuous lowering of mean HbA1c on a national level in children and adolescents with diabetes, and that the use of registry data through a structured approach with QIC has contributed significantly. A continued development of treatment routines and unified target setting by the team members and families is extremely important. Access to a quality registry to report data online, receiving continuous benchmarking feedback, and being able to compare results over time transparently with other openly named centers are important factors for successful improvement. In this report, we have demonstrated that a successful method for sustainable improvement of pediatric diabetes care also may contribute to a positive spatial spill-over effect on other centers.

Conflicts of interest

The authors declare that there is no duality of interest associated with this manuscript.

Author contribution

All authors took part in the QIC. U.S. took the initiative in producing the manuscript and designed and performed the statistical analysis.

U.S. together with L.H. and A.P. wrote the first draft of the manuscript. All authors edited and reviewed the manuscript, contributed with ideas for further data analysis and approved the final version. The guarantor of this manuscript is U.S.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.