Long-term efficacy and safety of Control-IQ technology in younger children with type 1 diabetes in Italy (2020–2023): a longitudinal multicentre real-world study

Valentino Cherubini,[a] Roberto Franceschi,[b,*] Andrea Fargalli,[c] Marta Bassi,[d] Riccardo Bonfanti,[e] Giulia Bracciolini,[f] Barbara Felappi,[g] Riccardo Foglino,[e] Dario Iafusco,[h] Anna Lasagni,[i] Bruno Bombaci,[j] Claudio Maffeis,[k] Giulio Maltoni,[l] Chiara Mameli,[m] Enza Mozzillo,[n] Nicola Minuto,[d] Barbara Piccini,[o] Lara Devilli,[o] Giulia Pezzino,[p] Carmelo Pistone,[q] Elena Prandi,[g] Ivana Rabbone,[r] Andrea Scaramuzza,[s] Sara Santarelli,[a] Francesca Silvestri,[t] Riccardo Schiaffini,[t] Valentina Tiberi,[a] Davide Tinti,[u] Marco Marigliano,[k] and Rosaria Gesuita,[c] Italian Society for Pediatric Endocrinology and Diabetology (ISPED) Study Group[v]

[a]Department of Women's and Children's Health, Salesi Hospital, Ancona, Italy
[b]Centre for Medical Sciences, University of Trento, Trento, Italy
[c]Center of Epidemiology, Biostatistics and Medical Information Technology, Università Politecnica delle Marche, 60020, Ancona, Italy
[d]Department of Pediatrics, IRCCS Istituto Giannina Gaslini, 16147, Genoa, Italy
[e]Department of Pediatrics, Pediatric Diabetology Unit, Diabetes Research Institute, IRCCS San Raffaele Scientific Institute, Vita Salute San Raffaele University, 20132, Milan, Italy
[f]Pediatric Hospital, SS Antonio and Biagio and Cesare Arrigo, 15121, Alessandria, Italy
[g]Department of Pediatrics, ASST Spedali Civili, Brescia, Italy
[h]Department of Woman, Child and General and Specialistic Surgery, Regional Center of Pediatric Diabetes, University of Campania L. Vanvitelli, Naples, Italy
[i]Pediatric Unit, Department of Obstetrics, Gynaecology and Paediatrics, Azienda AUSL-IRCCS, Reggio Emilia, Italy
[j]Department of Human Pathology in Adult and Developmental Age "Gaetano Barresi," University of Messina, Messina, Italy
[k]Pediatric Diabetes and Metabolic Disorders Unit, Azienda Ospedaliera Universitaria Integrata Ospedale della Donna e del Bambino, 37126, Verona, Italy
[l]Pediatric Unit, IRCCS AOU Bologna, Bologna, Italy
[m]Department of Pediatrics, V Buzzi Children's Hospital, Università di Milano, Milan, Italy
[n]Department of Translational Medical Science, Section of Pediatrics, Regional Center of Pediatric Diabetes, Federico II University of Naples, 80138, Naples, Italy
[o]Diabetology Unit, AOU Meyer Children's Hospital IRCCS, 50139, Florence, Italy
[p]Maternal and Child Health Department, Pediatric Diabetology Unit, Garibaldi Hospital, Catania, Italy
[q]Department of Pediatrics, IRCCS Policlinico San Matteo, Pavia, Italy
[r]Department of Health Sciences, University of Piemonte Orientale, 28100, Novara, Italy
[s]Pediatric Diabetes, Endocrinology and Nutrition, Pediatric Unit, ASST Cremona, Ospedale Maggiore, 26100, Cremona, Italy
[t]Diabetology and Growth Disorders Unit, Bambino Gesù Children's Hospital, IRCCS, 00165, Rome, Italy
[u]Pediatric Diabetology Unit, Azienda Ospedaliero Universitaria Città della Salute e della Scienza di Torino, 10126, Turin, Italy

eClinicalMedicine
2026;93: 103829
Published Online 12 March 2026
https://doi.org/10.1016/j.eclinm.2026.103829

Summary

Background Automated insulin delivery (AID) systems have demonstrated significant improvements in glycemic control in children and adults with type 1 diabetes, but long-term real-world data in preschool-aged children remain limited, particularly in Europe, where Control-IQ is not approved for children under 6 years. This study aimed to evaluate the long-term effectiveness and safety of the t:slim X2 insulin pump with Control-IQ technology in children aged 0.5–5 years compared with those aged 6–10 years in a real-world multicenter Italian cohort.

Methods In this longitudinal, observational study conducted from 2020 to 2023, data were collected from 32 Italian centers on children <11 years diagnosed with type 1 diabetes for at least six months and using the t:slim X2 with Control-IQ technology (CIQ). Participants were grouped into 0.5–5 years or 6–10 years at CIQ initiation. Primary endpoints were the percentage of time spent in range (TIR, 70–180 mg/dL) and in tight range (TITR, 70–140 mg/dL) in the two age groups, evaluated according to children's demographic, socioeconomic, and clinical characteristics using mixed-effects models for repeated measures.

*Corresponding author. Centre for Medical Sciences, University of Trento, Vicolo S. M. Maddalena 1, 38121, Trento, Italy.
E-mail address: roberto.franceschi@unitn.it (R. Franceschi).
[v]The members of steering committee and collaborative group are listed in the Supplementary Material.

Findings We evaluated 253 children with 18-month follow-up, 131 into the 0.5–5-year group and 122 in the 6–10-year group. In the 0.5–5-year group, TIR and TITR increased significantly from baseline to 6 months and were then maintained through 18 months. In the 6–10-year group, similar improvements were observed, with no statistically significant differences between age groups in the TIR or TITR trajectories. In the adjusted mixed-effects models, TIR increased from baseline to 6 months by 5.45% (95% CI 3.78–7.11) and TITR increased by 5.56% (95% CI 3.60–7.51), with stabilization thereafter. Children of parents with a high level of education had a significantly greater mean TIR. A longer interval between T1D diagnosis and CIQ initiation was associated with a lower mean TITR (–1.21%, 95% CI –2.32 to –0.10). During observation, there were no episodes of severe hypoglycemia in younger children and only one episode in a 6–10-year-old. One episode of DKA occurred after the start of CIQ in a younger child.

Interpretation CIQ was associated with sustained improvements in glycemic outcomes, especially within the first six months. Adverse events were rare. These findings support potential supervised off-label use in young children.

Funding No specific funds were received for this study.

Keywords: Control-IQ; Automatic insulin delivery; Younger children; Type 1 diabetes

Research in context

Evidence before this study

Automated insulin delivery (AID) systems consistently improve time in range (TIR) and HbA1c in children, adolescents, and adults with type 1 diabetes without increasing hypoglycemia. In very young children (<6 years), however, evidence on AID use is limited. We searched PubMed and Scopus from January 1, 2019, to January 1, 2026, for studies reporting real-world outcomes of automated insulin delivery (AID) systems in preschool-aged children with type 1 diabetes. Search terms included combinations of "automated insulin delivery", "AID", "closed-loop", and "type 1 diabetes". We included observational studies and clinical trials of any language; we excluded case reports and studies without specific pediatric data. The quality of evidence was assessed using standard criteria for observational research; overall risk of bias was moderate due to limited sample sizes and heterogeneity in study designs. No meta-analyses specifically focused on children under 6 years were identified; pooled estimates from broader pediatric data suggest improved glycemic metrics with AID versus conventional therapy, though evidence in the youngest age group remains sparse. A randomized controlled trial of the t:slim X2 with Control-IQ (CIQ) in children aged 2–5 years demonstrated a 12.4% increase in TIR over 13 weeks, and a recent meta-analysis confirmed CIQ efficacy across age groups. Other AID systems (CamAPS FX, Omnipod5, MiniMed 780G) have also shown efficacy and safety in preschoolers. However, these studies were short-term, highly controlled, and small. Long-term, real-world evidence of CIQ use in children younger than six years is lacking, and CIQ is not approved for this age group in Europe.

Added value of this study

This 18-month, multicenter, real-world study is the largest to evaluate CIQ in children under six years of age. The analysis demonstrates sustained improvements in TIR, time in tight range, and HbA1c after CIQ initiation, with benefits most pronounced during the first six months and maintained thereafter. Outcomes were comparable in younger and older children. Importantly, no severe hypoglycemia events occurred in children under 6 years, and only one diabetic ketoacidosis episode was reported. Socioeconomic factors influenced the outcomes, with higher parental education associated with better glycemic control.

Implications of all the available evidence

The findings support the safe and effective off-label use of CIQ in children younger than 6 years, with outcomes consistent with controlled trials and comparable to older age groups. Early initiation of CIQ may help optimize long-term glycemic control during a critical neurodevelopmental period. These results reinforce the case for extending regulatory approval of CIQ to preschool-aged children and for expanding access to closed-loop systems in routine pediatric diabetes care.

Introduction

Young children diagnosed with type 1 diabetes often experience significant glycemic excursions, which can adversely affect neurodevelopment in childhood and adolescence.[1–3] In addition, persistent hyperglycemia during early childhood is associated with long-term

microvascular and macrovascular complications.[4] Hypoglycemia has its own challenges, raising considerable concerns for parents and complicating integration into social environments like school.[5] Over half of young children diagnosed with type 1 diabetes present with diabetic ketoacidosis (DKA),[6] which is associated with persistently elevated HbA1c over the following years.[7] It is essential to maintain "normal" glycemic control from the onset of the disease and throughout life.

There is ample clinical trial evidence of automated insulin delivery systems (AID) efficacy, although trial data in younger children have only recently been published. In a recent randomized controlled trial (RCT) of children aged 2–5 years with diabetes, children using t:slim X2 with Control-IQ technology (CIQ) AID had a mean-adjusted improvement in time in range 70–180 mg/dL (TIR) of 12.4% after 13 weeks, equating to approximately 3 more hours of TIR per day.[8] Recent findings from the LENNY[9] trial indicated that the TIR for the MiniMed™ 780G system in auto mode was non-inferior to that in manual mode in children aged 2–6 years requiring a total daily insulin dose exceeding six units. The CamAPS-FX and Omnipod5 systems have significantly improved glycemic control in this population without increasing the duration spent in hypoglycemia.[6,10] In a meta-analysis of RCTs on CIQ in individuals aged 2–72 years,[11] the beneficial effects of the system were present across a broad spectrum of participants, regardless of age. While these data are promising, there are scarce real-world data on the efficacy of these systems in young children.

Only a limited number of AID systems have received regulatory approval for use in preschool children, and CIQ has not yet received clearance in Europe for young children. Despite CIQ being off-label for children under six years of age, many parents request an AID system for their younger children in Italy. Several pediatric centers have started using these systems in children under six, provided parents provide informed consent. Evidence to support their clinical use in this age group is urgently needed.

The objective of this study was to compare the effectiveness and safety of the Tandem t:slim ×2 with CIQ system in real-world conditions in children aged six months to five years and those aged six to ten years.

Methods

Study population

This was a prospective, multicenter study of retrospective data collected between 2020 and 2023 from children diagnosed with type 1 diabetes for at least six months who started using the CIQ system. Inclusion criteria were: 1) use of a glucose sensor (Dexcom G6 or G7) prior to initiating the CIQ system and 2) age under eleven years. Additionally, CGM-derived data downloaded via Glooko® and/or Clarity® software needed to be available at least every six months. Any other diabetes diagnosis and children aged >10 years at CIQ initiation were excluded from this study.

Current CIQ technology requires a minimum total daily insulin dose higher than 10 units/day and a body weight >25 kg for activation. To enable the use of CIQ in younger children who did not meet manufacturer-specified criteria for age, body weight, or total daily insulin dose, Italian pediatric diabetes centers adopted a standardized practice of system activation using default values (25 kg body weight and 10 units/day total daily insulin dose), irrespective of the child's actual anthropometric characteristics or insulin requirements. All children were followed in specialized pediatric diabetes centers with extensive experience in AID and following standardized clinical protocols for AID initiation and follow-up, promoted by the Italian Society for Pediatric Endocrinology and Diabetology (ISPED). Specifically, the study included participants from 33 tertiary pediatric diabetes units distributed across Northern (Bolzano, Trento, Verona, Brescia, Milan S. Raffaele, Milan Buzzi, Pavia, Novara, Cremona, Turin, Cuneo, Genova, Udine, Mantova, Cesena, Ravenna, Ferrara, Reggio Emilia, Bologna), Central (Pisa, Florence, Ancona, Rome Bambino Gesù, Roma Tor Vergata) and Southern Italy (L'Aquila, Bari, Brindisi, Napoli Vanvitelli, Napoli Federico II, Messina, Catania Garibaldi, Catania Policlinico, Palermo). After CIQ initiation, glucose control was monitored intensively through remote CGM data review, with frequent clinician-led assessment and timely adjustment of insulin delivery parameters, particularly during the first 1–2 weeks. Although default values were required for system activation, the CIQ algorithm modulates insulin delivery dynamically based on real-time CGM data and individualized basal rates, insulin-to-carbohydrate ratios, and correction factors; therefore, actual insulin delivery was tailored to the child's needs and could be substantially lower than the initialization values, including total daily doses below 10 units/day.

Data collection and outcome measures

At T1D diagnosis, demographic data [sex, date of birth and parents' age, citizenship, and years of education (low ≤8 years, medium 9–13 years, high >13 years)], clinical characteristics, and the presence of thyroiditis or coeliac disease were recorded. As pH values were not collected by clinicians in a few cases, the presence of DKA was also recorded as either "yes" or "no."

Starting at CIQ initiation and every six months thereafter up to 18 months, we collected clinical data (weight, height, BMI, pubertal stage), HbA1c levels, and CGM-derived data, including the percentage of time spent in the following ranges: <54 mg/dL, 54–70 mg/dL, 70–140 mg/dL (TITR), 70–180 mg/dL (TIR), 180–<250 mg/dL, and >250 mg/dL, together with % coefficient of variation (CV) and glucose management indicator (GMI).

All patients provided informed consent to the collection of data from the electronic medical record system used in Italy. Data were extracted using a predefined standardized data collection template developed by the study coordinators. For the purposes of the study, data were anonymized at the local level before transmission to the coordinating center (Università Politecnica delle Marche), so that direct traceability to individual medical records was not possible.

Ethics committee approval was not required, as the Italian General Authorization for the processing of personal data for scientific research purposes (authorization no. 9/2014) states that retrospective studies on archival data using identification codes preventing the direct traceability of data to the data subject do not require ethical approval.

Statistical analysis

Demographic, parents' socio-economic status, and clinical characteristics at diabetes diagnosis and at each time point (at CIQ initiation and after 6, 12, and 18 months of CIQ initiation) were summarized using absolute and relative frequencies for qualitative variables. Given the large sample size in both age groups, approximate normality of continuous variables was evaluated using Q–Q plots, and means and standard deviations (SD) were used to summarize quantitative variables. Children were classified according to age at CIQ initiation into 0.5–5 years or 6–10 years. The two age groups were compared using the *t*-test for continuous variables and the chi-square test for categorical variables. Fisher's exact test was applied when expected frequencies were below 5.

Three mixed-effects models for repeated measures were estimated. In the first two models, the dependent variables were the percentage of time in glucose range 70–180 mg/dL (TIR) and the percentage of time in tight glucose range 70–140 mg/dL (TITR); in the third model, HbA1c was the dependent variable. The explanatory variables were time points of the CGM-derived assessment (from baseline to 18 months after CIQ initiation), age groups at CIQ initiation (0.5–5 vs. 6–10 years), sex, DKA at diabetes diagnosis, time from T1D diagnosis to CIQ, presence of at least one non-Italian parent, and family socioeconomic characteristics as assessed by considering the highest level of education among parents. A sequential difference contrast approach was applied to model time, allowing comparisons between consecutive follow-up time points of the CGM-derived assessment; the interaction term between time points of the CGM-derived assessment and age groups was evaluated to assess whether differences in glucose metrics varied between the two age groups across different time points. The final model was the most parsimonious one. To account for repeated measures, patient identifiers were included as a random effect. Mixed-effects models that included only patients with complete data on all baseline, time-invariant covariates were also fitted. The analysis was conducted in R v4.5.0.

Role of the funding source

No funds have been received for conducting the present study.

Results

A total of 253 patients from 32 Italian pediatric diabetes centers were recruited, 131 aged 0.5–5 years (74 males, 56.5%) and 122 aged 6–10 years (52 males, 42.6%). There was no significant difference in parents' socio-demographic status between the two groups (Table 1).

At diabetes onset, there were no statistically significant differences in HbA1c levels, BMI z-score, venous pH, or bicarbonate levels (HCO_3) at diabetes diagnosis between groups, nor were there differences in BMI z-score, time from T1D diagnosis, glycemia levels, and related SDs at CIQ initiation (Table 1). The older age group contained significantly more individuals with thyroiditis, but there was no difference in the percentage of coeliac disease between groups.

At CIQ initiation, younger children exhibited higher HbA1c levels ($p = 0.020$), lower time between T1D diagnosis and CIQ initiation ($p < 0.001$), and higher SD of glycemia ($p = 0.023$). There were no statistically significant differences in the other CGM-derived data such as GMI, CV, TIR, TITR, time below range (TBR), time above range (TAR), and time CGM active (Fig. 1A, Supplementary Table S1). No device malfunctions or technical issues clearly attributable to the workaround initialization method (25 kg, 10 U) were identified. System functioning following activation appeared comparable to standard initialization in children older than 6 years.

Effectiveness

All patients in both age groups continued using the CIQ system throughout the study period, with no discontinuations reported, reflecting good overall tolerability and adherence. After 18 months of CIQ use, the mean HbA1c was 6.9% in children younger than six years and 6.8% in those aged six to ten years. TIR values were 66.7% and 68.5% and TITR values were 43.9% and 45.1%, respectively. There were no statistically significant differences between the two age groups in most CGM-derived metrics, except for the percentage of time spent <54 mg/dL, which was significantly lower in older children, and for the percentage of time CGM was active, which was significantly lower in the youngest age group, although this 3% difference was probably of limited clinical relevance (Fig. 1B, Supplementary Table S1).

The mixed-effects model for TIR 70–180 mg/dL showed a significant mean increase from baseline to six

Variable	0.5–5 years	6–10 years	p-value
Data at T1D diagnosis	n = 131	n = 122	
Sex, male [n (%)]	74 (56.5)	52 (42.6)	0.038
Age, years	n = 131	n = 122	
	3.01 (1.38)	4.68 (2.22)	<0.001
Father age, years	n = 109	n = 105	
	41 (7.5)	41 (12.8)	0.910
Father nationality, Italian [n (%)]	n = 129	n = 119	
	101 (78.3)	94 (79.0)	0.860
Father education [n (%)]	n = 113	n = 118	0.276
Low (≤8 years)	30 (26.6)	23 (19.5)	
Medium (9–13 years)	51 (45.1)	65 (55.1)	
High (>13 years)	32 (28.3)	30 (25.4)	
Mother age, years	n = 111	n = 107	
	36 (6.1)	37 (5.8)	0.174
Mother nationality, Italian [n (%)]	n = 130	n = 121	
	96 (77.1)	85 (75.2)	0.753
Mother education [n (%)]	n = 104	n = 118	0.174
Low (≤8 years)	22 (19.3)	19 (16.1)	
Medium (9–13 years)	46 (40.4)	62 (52.5)	
High (>13 years)	46 (40.4)	37 (31.6)	
Parental education level [n (%)]	n = 113	n = 118	0.183
Low (≤8 years)	17 (15.0)	11 (9.3)	
Medium (9–13 years)	45 (39.8)	60 (50.9)	
High (>13 years)	51 (45.1)	47 (39.8)	
BMI z-score	n = 92	n = 83	
	−0.61 (1.25)	−0.35 (1.46)	0.203
pH	n = 117	n = 102	
	7.26 (0.14)	7.24 (0.16)	0.515
HCO_3, mmol/L	n = 106	n = 90	
	16.17 (6.24)	14.77 (7.91)	0.175
DKA, yes [n (%)]	n = 117	n = 115	
	62 (52.3)	52 (45.2)	0.811
HbA1c, %	n = 116	n = 103	
	10.46 (1.84)	10.94 (1.96)	0.066
Coeliac disease [n (%)]	n = 128	n = 118	
	16 (12.5)	23 (19.5)	0.293
Thyroiditis [n (%)]	n = 119	n = 118	
	7 (5.9)	25 (21.2)	0.001
Data at CIQ initiation			
Age (years)	n = 117	n = 115	
	4.38 (1.28)	7.28 (0.90)	<0.001
BMI z-score	n = 117	n = 115	
	0.56 (1.52)	0.63 (1.11)	0.670
Time from T1D diagnosis, years	n = 131	n = 121	
	1.36 (1.34)	2.61 (2.20)	<0.001
Glycemia, mg/dL	n = 104	n = 113	
	163.16 (28.04)	161.07 (25.33)	0.564
Standard deviation of glycemia, mg/dL	n = 91	n = 106	
	63.3 (15.05)	58.34 (15.12)	0.023

Values are mean (standard deviation) unless otherwise specified. p-values refer to *t*-tests or chi-square tests, as appropriate.

Table 1: **Demographic and clinical characteristics of children with type 1 diabetes by age group.**

months (5.45%, 95% CI 3.78–7.11) followed by stabilization over time (Table 2, Fig. 2A). Children with high parental education had a significantly higher mean increase in TIR 70–180 mg/dL of 7.35% (95% CI 2.36–12.33) than those with low education.

For HbA1c, there was a significant mean reduction of −1.24% (95% CI −1.46 to −1.03) in the first six months following CIQ initiation, with no further significant changes at subsequent follow-ups, indicating stabilization over time (Fig. 2C, Table 2).

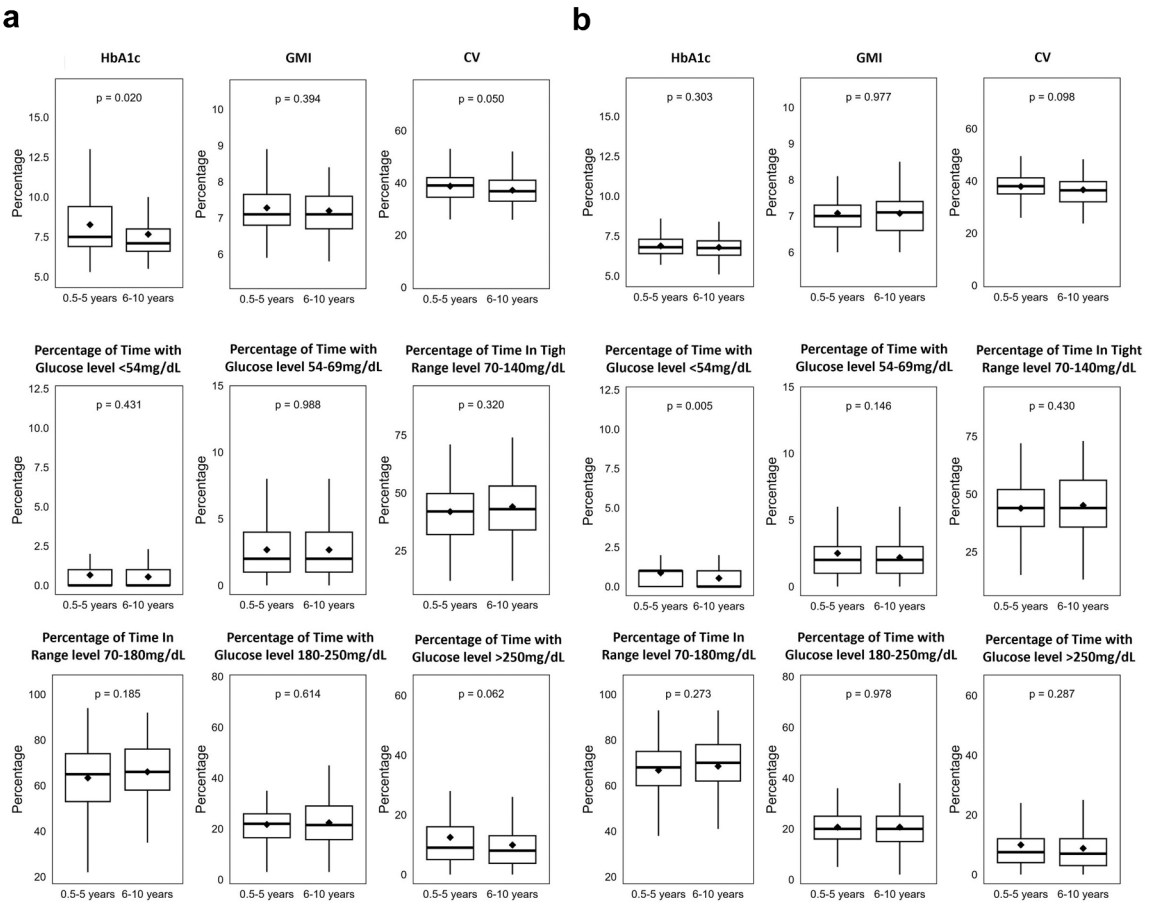

Fig. 1: Comparison of CGM data between age groups (0.5–5 years vs 6–10 years) at CIQ initiation (A) and after 18 months (B). The boxes represent the interquartile range (IQR), the horizontal line inside the box indicates the median, the whiskers represent the minimum and maximum values. ◆ indicates means.

Variables	TIR 70–180 mg/dL (n = 211)		TITR 70–140 mg/dL (n = 189)		HbA1c (%) (n = 207)	
	b	95 CI%	b	95% CI	b	95% CI
Time						
6 months vs baseline	5.45	(3.78; 7.11)	5.56	(3.60; 7.51)	−1.24	(−1.46; −1.03)
12 months vs 6 months	−1.37	(−3.04; 0.29)	−1.49	(−3.44; 0.46)	0.09	(−0.12; 0.30)
18 months vs 12 months	−0.57	(−2.24; 1.1)	−0.99	(−2.95; 0.96)	−0.01	(−0.21; 0.22)
Age groups, 0.5–5 years vs 6–10 years	−2.65	(−5.73; 0.43)	−2.18	(−5.77; 1.41)	0.11	(−0.11; 0.32)
Gender (Male vs Female)	1.4	(−1.59; 4.39)	2.03	(−1.46; 5.52)	−0.07	(−0.28; 0.14)
Time to CIQ from T1D diagnosis, years	−0.87	(−1.77; 0.03)	−1.21	(−2.32; −0.10)	−0.08	(−0.14; −0.02)
DKA at diagnosis	−0.99	(−4.03; 2.05)	−1.81	(−5.30; 1.67)	0.08	(−0.13; 0.29)
At least one non-Italian parent	−3	(−6.99; 0.99)	0.44	(−4.33; 5.20)	0.18	(0.09; 0.46)
Parental education level						
Medium vs Low	3.08	(−1.75; 7.92)	2.45	(−2.83; 7.72)	−0.19	(−0.50; 0.13)
High vs Low	7.35	(2.36; 12.33)	5.37	(−0.13; 10.88)	−0.4	(−0.73; −0.07)

b Indicates either (i) the expected change in the percentage of TIR and TITR and in HbA1c levels associated with a one-unit increase in quantitative variables, or (ii) belonging to a given category compared with the reference category for categorical variables.

Table 2: **Factors associated with TIR 70–180 mg/dL, TITR 70–140 mg/dL, and HbA1c over time. Results of mixed-effect models.**

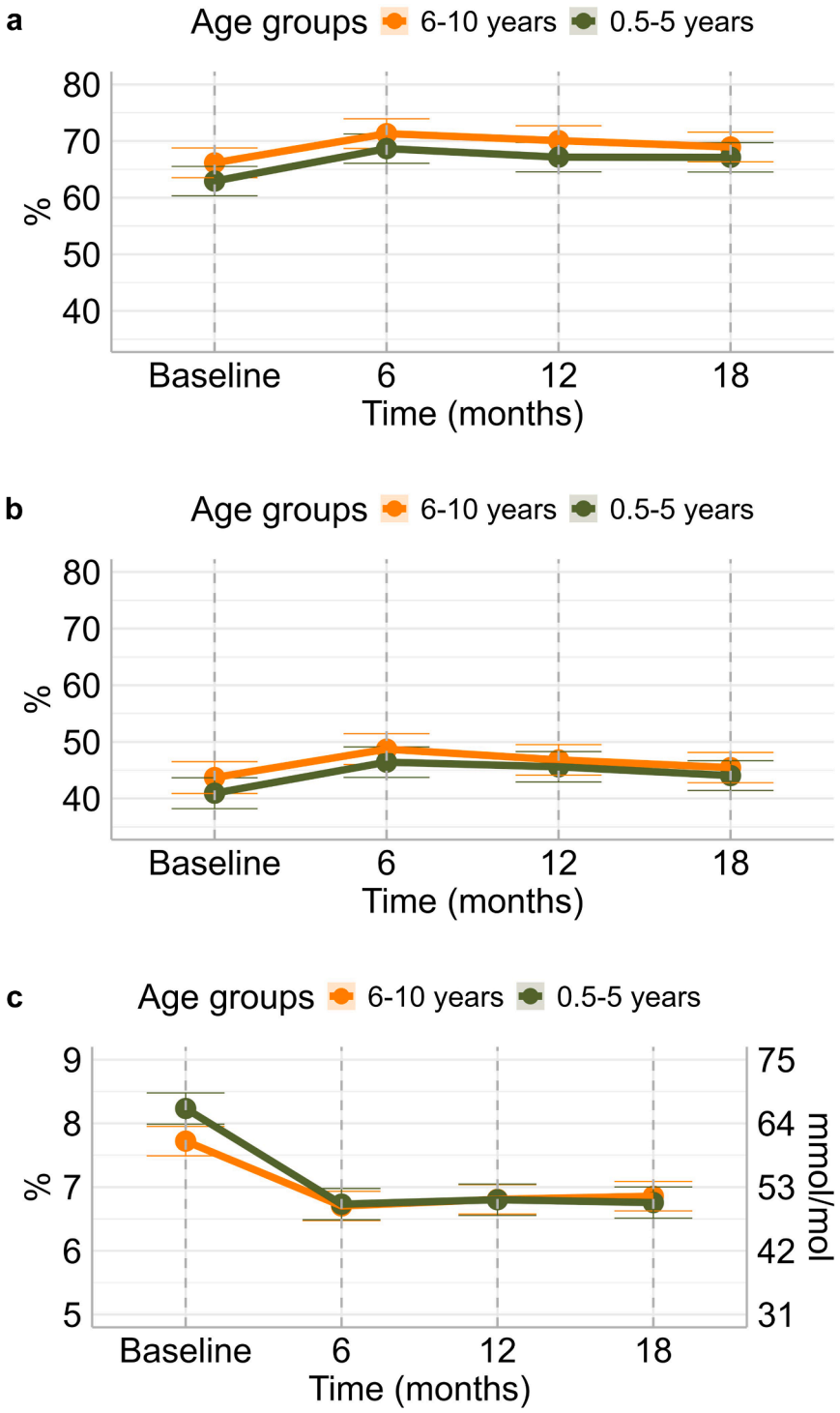

Fig. 2: Effect of time on glycemic metrics between age groups. (A) TIR 70–180 mg/dL, (B) TITR 70–140 mg/dL, (C) HbA1c.

A significant reduction in mean HbA1c of –0.08% per year (95% CI –0.14 to –0.02) was also observed in relation to the time from T1D diagnosis to CIQ initiation. This association was attributed to lower mean HbA1c levels at CIQ initiation and a longer duration between T1D diagnosis and CIQ initiation in older children.

HbA1c values were significantly higher in children with at least one non-Italian parent (0.18%, 95% CI

0.09–0.46) and significantly lower in those whose parents had a high educational level (–0.40%, 95% CI –0.73 to –0.07). There were no statistically significant differences between the two age groups or between sexes in the three models, and DKA at diagnosis did not have a significant effect on any glycemic outcome.

No significant interaction was observed between the time points of the CGM-derived data and HbA1c with age groups in all models, showing comparable trends in outcomes between younger and older children.

Although the number of subjects in each of the three regression models was lower than the number of subjects recruited in the study due to missing values in baseline demographic and clinical characteristics, there were no significant differences between groups of subjects included and excluded from the analysis (Supplementary Table S3).

Safety

DKA at diagnosis was frequent (42%) and comparable between age groups. Seven children developed DKA during the first six months before CIQ initiation, four (3.1%) and three (2.4%) in the 0.5–5 and 6–10-year age groups, respectively (p = 0.999), whereas only one child in the 0.5–5-year group reported one DKA episode between 12 and 18 months after CIQ initiation. Severe hypoglycemia episodes were reported in children aged 6–10 years, two in the six months before CIQ initiation and one between 12 and 18 months after CIQ initiation.

At CIQ initiation, the mean percentage of time with glucose level <54 mg/dL and 54–69 mg/dL was less than 1% and 3%, respectively, in both age groups (Fig. 1, Supplementary Table S1). After 18 months, the mean percentage of time with glucose level <54 mg/dL was still less than 1% in both groups and significantly lower in older children.

Discussion

In this prospective, real-world, multicenter study, CIQ used for 18 months was highly effective and safe in children aged 0.5–5 years and those aged 6–10 years. An overall mean increase of 5.45% in TIR and 5.56% in TITR was estimated within the first six months, corresponding to an average of 78 and 80 min per day, respectively, and this gain was maintained for up to 18 months. At CIQ initiation, HbA1c was significantly higher in younger children and showed high variability compared with those aged 6–10 years. Overall, HbA1c dropped by an average of 1.24% after introduction of CIQ and was maintained over time, reaching 6.9% and 6.8% at 18 months in children under 6 and between 6 and 10 years, respectively. The reduction in HbA1c was particularly notable in the first six months, with trends over time up to 18 months completely overlapping.

Children aged 0.5–5 years are typically considered to be at higher risk of hypoglycemia because they are often unable to recognize and/or manage such episodes[12] and, consequently, are expected to have worse metabolic control. However, we found that TIR and TITR values in younger children were comparable to those of children aged 6–10 years throughout the study period. Furthermore, there were no episodes of severe hypoglycemia in younger children and only one in children aged 6–10 years. This is important evidence that AID may help protect younger children from hypoglycemia while helping them achieve more time in euglycemia.

There is RCT evidence of efficacy of CIQ in improving TIR in adolescents[13] and in children between 6 and 13 years old,[14] but data on children aged 0.5–5 years are scarce. Wadwa et al.[8] conducted an RCT of 68 children aged 2–6 years treated with CIQ. In this group, the TIR increased from a baseline of 56.7%–69.3% after 13 weeks, and the time >250 mg/dL decreased from 14.8% at baseline to 8.4 after 13 weeks. No change was observed in the time <70 or <54 mg/dL. In a pilot study, Ekhlaspour et al.[15] showed that a modified CIQ system was safe in 2–5-year-old children with T1D and improved glycemic control, with TIR increasing from 63.7% at baseline to 71.3% after 48 h. These were small studies conducted in well-controlled settings. Our study is the first real-world study to provide evidence on the safety and effectiveness of the CIQ system in a large number of children. Of note, the TIR after 6 months from CIQ initiation (69%) was similar to that reported by Wadwa et al.,[8] indicating similar real-world efficacy to controlled trials in this population.

Studies on other AID systems in young children report similar results. In a cross-over RCT, Ware et al.[10] reported that the CamAPS FX closed-loop system using a Dexcom sensor achieved a TIR of 71.6% after 16 weeks in 74 children aged 1–7 years. The system remained effective in maintaining TIR at 68.8% over 18 months, with an acceptable safety profile.[16] Similarly, real-world clinical evidence on the effects of the Minimed 780G in 35 younger children showed an increase in TIR and TITR and a reduction in HbA1c and TAR persisting for 18 months of follow-up.[4] Another small study of 11 participants between 2 and 7 years reported an improvement in TIR with a reduction in time spent in hypo- and hyperglycemia after adopting AHCL from manual mode for 6 weeks.[17] A retrospective real-life analysis of 12 children under seven years using the same system reported similar results over 12 months.[18] Finally, a single arm study[6] of 80 children aged 2–5 years using the Omnipod 5 for 13 weeks reported a reduction in HbA1c of 0.55% and an increase in TIR of 10.9% with no episodes of severe hypoglycemia or DKA. The extension phase of the study[19] confirmed the safety and effectiveness of Omnipod 5 up to two years of use.

In this specific young pediatric population, certain technical characteristics of Control-IQ may be particularly relevant from a safety perspective. Control-IQ is

currently the only commercially available AID system that allows the basal insulin rate to be set to 0 U/hour while keeping the algorithm active. Starting from a zero-basal setting, the algorithm can predictively modulate insulin delivery based on CGM values and trends. Importantly, the basal rate, as well as several other therapy settings, can be manually adjusted by the clinician when deemed clinically appropriate, allowing individualized optimization of therapy according to the child's needs. In addition, the system's micro-delivery technology enables the administration of very small insulin doses every 5 min. These features may be especially advantageous in very young children, who have low insulin requirements and a higher vulnerability to hypoglycemia, supporting the clinical rationale for its use in this age group.

DKA at diagnosis of type 1 diabetes in children is known to predict poor long-term glycemic control, independent of demographic and socioeconomic factors.[20] However, our results showed that the presence of DKA at diagnosis did not significantly affect metabolic control in children treated with CIQ over the study period. Additionally, for each year from diagnosis to the start of CIQ, TITR decreased by an average of 1.21%, corresponding to 17 min per day, suggesting benefit for the early initiation of closed-loop systems.

On average, HbA1c was higher in children with at least one non-Italian parent and in those with a lower parental level of education; conversely, TIR and HbA1c were higher in children with a high parental level of education. These findings differ from the results of a meta-analysis,[11] which reported no differences in glycemic metrics based on socioeconomic status or ethnic group. The distribution of parental education levels and percentage of families with at least one non-Italian parent in our study were similar to those of the general Italian population.[21] Families with a lower level of education may face barriers when using CIQ technology, including reduced health literacy, greater difficulty in understanding device interfaces and alarms, challenges in interpreting glucose trends, and increased burden in managing technical issues. These findings suggest that successful adoption of the CIQ system may require tailored educational strategies, simplified and linguistically-appropriate training materials, reinforced follow-up, and proactive technical support to mitigate these disparities. Moreover, the lack of statistical significance in ethnic differences in TIR and TITR observed here may be attributable to the limited number of ethnic subgroups and may therefore conceal relevant disparities, an important area for future research in larger, more diverse populations.

In this cohort, thyroiditis was more frequent in older children with T1D, whereas the frequency of celiac disease was similar between younger and older children. Both conditions were more common in children with T1D than in the general population, consistent with the well-established association between T1D and other autoimmune disorders. Although the onset of these autoimmune diseases varies widely in T1D, and is influenced by genetic susceptibility, environmental factors, and duration of diabetes, the higher frequency of thyroiditis in older children is expected, as thyroid autoimmunity generally manifests later than gastrointestinal autoimmunity.[22]

Cost-effectiveness is relevant to the real-world implementation of CIQ, particularly in very young children. Economic evaluations of AID systems in pediatric populations have generally shown favorable cost-effectiveness profiles compared with standard pump therapy or multiple daily injections, with gains in quality-adjusted life years driven by improved glycemic control and reduced risk of long-term complications.[23,24] However, these analyses have largely been conducted in older children and adolescents, and specific cost-effectiveness data for CIQ use in children under 6 years are lacking. Given the potentially higher upfront costs and additional resource requirements related to training and follow-up in this age group, dedicated health economic studies are needed to assess the sustainability of CIQ implementation in very young children.

The main strength of this study is the long follow-up in a multicenter national setting, including the largest number of children under 6 years of age with T1D observed under real-world conditions treated with a closed-loop system. Despite real-world studies rarely reporting safety data, the long follow-up allowed us to monitor serious adverse events and the percentage of time spent in hyper- and hypoglycemia.

The study has some limitations. First, CIQ was used off-label in a subset of children who did not meet manufacturer-specified criteria for age, body weight, or total daily insulin dose. System activation in these cases required the entry of standardized default values, which may raise safety concerns, particularly in very young children. Importantly, insulin delivery was dynamically determined by the CIQ algorithm in response to real-time CGM data and individualized insulin settings, rather than being fixed by the initial input parameters. Although all participants were managed in specialized pediatric diabetes centers with intensive CGM-based monitoring and early individualization of insulin delivery parameters, these findings should be interpreted cautiously within this clinical context. In addition, the Control-IQ algorithm has previously been shown to be safe and efficacious in an RCT including children aged 2–5 years, supporting its use in this age group.[8] Nevertheless, prospective studies specifically designed to evaluate safety and efficacy in younger children and broader clinical settings would be valuable to further consolidate our findings. Additionally, missing values in socio-economic and clinical characteristics in both groups may have affected the precision of the estimates

and limited the assessment of the role of covariates. The potential difference in the frequency of insulin pump setting adjustments between younger and older children was not assessed, as this aspect was not captured in the study protocol, and subtle age-related differences in adjustments could not be reliably evaluated. Finally, quality-of-life (QoL) data were not collected as, in routine clinical practice, only some centers routinely administer QoL measures to caregivers, and it was difficult to assess the role of ethnic group membership given the small number of non-Italian children in the cohort.

In conclusion, this is the largest longitudinal real-world analysis of young and older children with T1D using the CIQ technology. We demonstrate consistent and sustained improvements in glycemic outcomes over 18 months with minimal adverse events. Significant improvements in TIR, TITR, and HbA1c were observed in both age groups, particularly in the first six months after CIQ initiation, benefits that were maintained over the long term regardless of initial glycemic status or DKA at diagnosis. The system was safe in younger children, supporting its potential use in off-label settings with appropriate clinical supervision. Our results reinforce the value of early adoption of closed-loop technology for optimizing long-term metabolic outcomes in pediatric T1D.

Contributors

VC and R.G. designed, drafted, and gave the final approval for this version to be published. MB, RB, GB, BF, RF, DI, AL, BB, CM, GM, CM, EM, NM, BP, LD, GP, CP, EP, IR, AS, SS, FS, RS, VT, DT, MM were local investigators. VC, MM, RF, collected data. AF and RG performed the statistical analysis and drafting the manuscript. All authors had access to the study data, were involved in data interpretation and the preparation and critical review of the first and all subsequent drafts of the manuscript. RG and RF were responsible for the integrity of the data and accuracy of the data analysis, and both have access to raw data and also verified it. VC and RG are guarantor of this work and have final responsibility for the decision to submit for publication.

Data sharing statement

Data sharing requests by researchers who provide a methodologically sound proposal will be considered and should be addressed to the corresponding author.

Declaration of interests

RF received travel grants from Movi, Medtronic, Theras. VC has received consultant/speaker fees from Novo Nordisk, Erbozeta, Sanofi, and Theras, and advisory board fees of Novo Nordisk, Sanofi, Abbott, and research grant from AstraZeneca, Eli Lilly, Medtronic, Novo Nordisk, Sanofi. AF, MB have nothing to declare. RB received grants from Medtronic, consultant/speaker fees from Medtronic, Abbott, Movi, travel grants from Abbott, Sanofi, Movi. GB, BF, RFO, DI have nothing to declare. AL received travel grants from Movi. BB received travel grants from Movi and Abbott. CM received grants from Medtronic, Movi, Sanofi, consultant/speaker fees from Abbott, Sanofi, Eli Lilly, travel grants from Sanofi, advisory board fees of Abbott and Sanofi. GM, CM have nothing to declare. EM received consultant/speaker fees from Medtronic, travel grants from MOVI, Theras and Abbott, participated on an Advisory Board of Sanofi. NM, BP, LD have nothing to declare. GP received travel grants from Movi, Theras, Roche, Abbott. CP has nothing to declare. EP received travel grants from Movi. IR has nothing to declare. AS participated on an Advisory Board of Medtronic, Movi, Theras, Sanofi, Ypsomed, has been coordinator of Diabetes Technology Group AMD, SID, SIEDP (non-paid), coordinator Diabetes Study Group of the Italian Society for Pediatric Endocrinology and Diabetes (non-paid). SS, FS have nothing to declare. RS has received consultant/speaker fees from Novo Nordisk, Theras, travel grants from Movi, Theras, participated on an Advisory Board of Sanofi. VT, DT have nothing to declare. MM received consultant/speaker fees from Theras, Novo Nordisk, Ypsomed and Medtronic, travel grants from Movi, Abbott, participated on an Advisory Board of Sanofi. RG has nothing to declare.

Aknowledgements

The authors received no specific funding for this study.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2026.103829.

References

1 Kariyawasam D, Morin C, Casteels K, et al. Hybrid closed-loop insulin delivery versus sensor-augmented pump therapy in children aged 6-12 years: a randomised, controlled, cross-over, non-inferiority trial. *Lancet Digit Health*. 2022;4(3):e158–e168.
2 Šuput Omladič J, Slana Ozimič A, Vovk A, et al. Acute hyperglycemia and spatial working memory in adolescents with type 1 diabetes. *Diabetes Care*. 2020;43(8):1941–1944.
3 Mauras N, Buckingham B, White NH, et al. Impact of type 1 diabetes in the developing brain in children: a longitudinal Study. *Diabetes Care*. 2021;44(4):983–992.
4 Pulkkinen MA, Varimo TJ, Hakonen ET, Hero MT, Miettinen PJ, Tuomaala AK. During an 18-month course of automated insulin delivery treatment, children aged 2 to 6 years achieve and maintain a higher time in tight range. *Diabetes Obes Metab*. 2024;26(6):2431–2438.
5 Von dem Berge T, Remus K, Biester S, et al. In-home use of a hybrid closed loop achieves time-in-range targets in preschoolers and school children: results from a randomized, controlled, crossover trial. *Diabetes Obes Metab*. 2022;24(7):1319–1327.
6 Sherr JL, Bode BW, Forlenza GP, et al. Safety and glycemic outcomes with a tubeless automated insulin delivery System in very young children with type 1 diabetes: a single-arm multicenter clinical trial. *Diabetes Care*. 2022;45(8):1907–1910.
7 Duca LM, Reboussin BA, Pihoker C, et al. Diabetic ketoacidosis at diagnosis of type 1 diabetes and glycemic control over time: the SEARCH for diabetes in youth study. *Pediatr Diabetes*. 2019;20(2):172–179.
8 Wadwa RP, Reed ZW, Buckingham BA, et al. Trial of hybrid closed-loop control in young children with type 1 diabetes. *N Engl J Med*. 2023;388(11):991–1001.
9 Battelino T, Kuusela S, Shetty A, et al. Efficacy and safety of automated insulin delivery in children aged 2–6 years (LENNY): an open-label, multicentre, randomised, crossover trial. *Lancet Diabetes Endocrinol*. 2025;13(8):662–673.
10 Ware J, Allen JM, Boughton CK, et al. Randomized trial of closed-loop control in very young children with type 1 diabetes. *N Engl J Med*. 2022;386(3):209–219.
11 Beck RW, Kanapka LG, Breton MD, et al. A meta-analysis of randomized trial outcomes for the t:slim X2 insulin pump with Control-IQ technology in youth and adults from age 2 to 72. *Diabetes Technol Ther*. 2023;25(5):329–342.
12 Maahs DM, Hermann JM, DuBose SN, et al. Contrasting the clinical care and outcomes of 2,622 children with type 1 diabetes less than 6 years of age in the United States T1D Exchange and German/Austrian DPV registries. *Diabetologia*. 2014;57(8):1578–1585.
13 Brown SA, Kovatchev BP, Raghinaru D, et al. Six-month randomized, multicenter trial of closed-loop control in type 1 diabetes. *N Engl J Med*. 2019;381(18):1707–1717.
14 Breton MD, Kanapka LG, Beck RW, et al. A randomized trial of closed-loop control in children with type 1 diabetes. *N Engl J Med*. 2020;383(9):836–845.
15 Ekhlaspour L, Schoelwer MJ, Forlenza GP, et al. Safety and performance of the Tandem t:slim X2 with Control-IQ

automated insulin delivery system in toddlers and preschoolers. *Diabetes Technol Ther*. 2021;23(5):384–391.
16 Ware J, Allen JM, Boughton CK, et al. Eighteen-Month hybrid closed-loop use in very young children with type 1 diabetes: a single-arm multicenter trial. *Diabetes Care*. 2024;47(12):2189–2195.
17 Abraham MB, Smith GJ, Dart J, Davis EA, Jones TW. Clinical outcomes with MiniMed(TM) 780G advanced hybrid closed-loop therapy in 2- to 6-Year-Old children with type 1 diabetes. *Diabetes Technol Ther*. 2024;26(5):341–345.
18 Tornese G, Carletti C, Lanzetta MA, Tamaro G, Barbi E, Faleschini E. Safety of real-life usage of advanced hybrid closed-loop system MiniMed 780G in children with type 1 diabetes younger than 7 years old. *Diabetes Care*. 2023;46(6):e123–e125.
19 DeSalvo DJ, Bode BW, Forlenza GP, et al. Glycemic outcomes persist for up to 2 years in very young children with the Omnipod((R)) 5 automated insulin delivery system. *Diabetes Technol Ther*. 2024;26(6):383–393.
20 Duca LM, Wang B, Rewers M, Rewers A. Diabetic ketoacidosis at diagnosis of type 1 diabetes predicts poor long-term glycemic control. *Diabetes Care*. 2017;40(9):1249–1255.
21 ISTAT. Resta fondamentale il livello di istruzione dei genitori per i percorsi di studio dei figli. https://www.istat.it/wp-content/uploads/2024/07/REPORT-livelli-istruzione.pdf; 2024. Accessed February 15, 2026.
22 Ziegler AG. The countdown to type 1 diabetes: when, how and why does the clock start? *Diabetologia*. 2023;66(7):1169–1178.
23 Fox DS, Ware J, Boughton CK, et al. Cost-effectiveness of closed-loop automated insulin delivery using the Cambridge Hybrid Algorithm in children and adolescents with type 1 diabetes: results from a multicenter 6-Month randomized trial. *J Diabetes Sci Technol*. 2025;19(4):982–991.
24 Vallivaara HL, Leppänen HA, Mustonen J, Saari A, Martikainen J, Rintamäki RM. Long-term health economic evaluation of automated insulin delivery system compared with continuous subcutaneous insulin infusion pumps and CGM in a real-world setting in Finnish paediatric and adult individuals with type 1 diabetes. *Diabetes Obes Metab*. 2025;27(9):4793–4801.