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An equity-oriented analysis on using diabetes-related technology in children and adolescents with type 1 diabetes mellitus

DOCTORAL THESIS

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Tiago Jeronimo dos Santos

To my family

Para a minha família

In honor of Leonard Thompson, who at his 14 years old, was the first person to receive insulin therapy, one hundred years ago.

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List of Abbreviations

T1D: type 1 diabetes mellitus

MDI: multiple-daily injections

CSII: continuous subcutaneous insulin infusions

CGM: continuous glucose monitor

SRMA: systematic review and meta-analysis

PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols

PRISMA-E: Preferred Reporting Items for Systematic Reviews and Meta-Analysis – Equity Report

MOOSE: Meta-analyses of Observational Studies in Epidemiology

HTA: Health Technology Assessment

PROGRESS: place of residence, race/ethnicity/culture/language, occupation, gender/sex, religion, education, socioeconomic status, and social capital

HbA_{1c}: glycosylated hemoglobin

DKA: diabetic ketoacidosis

SH: severe hypoglycemia

HRQoL: health-related quality of life

TIR: time-in-range

TAR: time-above-range

TBR: time-below-range

PRO: patient-reported outcome

RCT: randomized controlled trials

NRS: non-randomized studies

SMD: standardized mean difference

MD: mean difference

CI: confidence interval

SD: standard deviation

GRADE: Grading of Recommendations Assessment, Development and Evaluation

CYP: children and young people

SES: socioeconomic status

HCP: healthcare professional

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General Summary

Optimal type 1 diabetes mellitus care requires lifelong appropriate intensive insulin treatment, which can be provided either by multiple-daily injections of insulin or by continuous subcutaneous insulin infusions (CSII). Although both therapies have shown to be effective to manage type 1 diabetes in children and adolescents, lately the CSII have gained ground over conventional treatment with syringes and pens. However, little is known on equity and fairness regarding access to the newest diabetes-related technologies, and whether the decision to start on these technologies is influenced by previous experience of healthcare professionals instead of recommendations from clinical guidelines. Moreover, uptake of these technologies may be affected by considerable differences in healthcare system coverage between countries, and individuals' and families' preferences. Therefore, this thesis aims to address issues on (i) the benefits of the newest diabetes devices on improving glycemic outcomes, (ii) the equity of starting the CSII among those who would benefit more, and (iii) the uptake of these technologies among providers by their decision-making on recommending to individuals with type 1 diabetes.

Resumen

El manejo óptimo de la diabetes mellitus tipo 1 requiere un tratamiento intensivo de insulina de por vida, que puede ser empleado mediante múltiples dosis de insulina o mediante infusiones subcutánea continuas de insulina (ISCI). Aunque ambas terapias han demostrado ser efectivas en el manejo de la diabetes tipo 1 en niños y adolescentes, últimamente la ISCI ha ganado terreno frente al tratamiento convencional con jeringas y bolígrafos. Sin embargo, se sabe poco sobre la equidad y la imparcialidad con respecto al acceso a las nuevas tecnologías relacionadas con la diabetes, y si la decisión de comenzar con estas tecnologías es influenciada por la experiencia previa de los profesionales de salud en lugar de las recomendaciones de las guías clínicas. Además, la adopción de estas tecnologías puede verse afectada por diferencias considerables en la cobertura del sistema de salud entre los países y las preferencias de los individuos y de las familias. Por lo tanto, esta tesis tiene como objetivo abordar cuestiones sobre (i) los beneficios de los nuevos dispositivos para la diabetes en la mejora de los resultados glucémicos, (ii) la equidad de iniciar la ISCI entre aquellos que se beneficiarían más y (iii) la adopción de estas tecnologías entre proveedores por su toma de decisiones en recomendarlas a las personas con diabetes tipo 1.

Summary of articles 1 and 2

Background: An increasing number of trials and previous systematic reviews and meta-analyses (SRMA) of the literature have compared the efficacy of CSII and MDI but have provided limited information on equity and fairness regarding access to, and the effect of, those insulin devices. In order to compare the effectiveness and equity of the CSII versus MDI on glycemic and patient-reported outcomes for pediatric type 1 diabetes, we conducted a systematic review and meta-analysis of randomized controlled trials (RCT) and non-randomized studies (NRS).

Methods: A study protocol was developed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P), the PRISMA-E (PRISMA-Equity 2012 Guidelines), and the Cochrane Collaboration Handbook. Searches were conducted for articles between 2000 and 2019 in four different electronic medical libraries - MEDLINE, CENTRAL, EMBASE and HTA – using specific Boolean operators. Included studies compared the CSII vs MDI in children and young people (CYP) ≤ 20 years with type 1 diabetes. Two independent reviewers screened the articles, extracted the data, assessed the risk of bias, evaluated the quality of evidence, and identified equity data. We selected studies that compared therapies according to glycemic outcomes - glycosylated hemoglobin (HbA1c) values, severe hypoglycemic episodes, diabetic ketoacidosis events, and/or time spent below, above or in glucose range of 70–180 mg/dl (3.9–10.0 mmol/L) -, and patient-reported outcomes by assessing health-related quality of life (HRQoL). Subgroup analyses were performed according to age group, length of follow-up, and the use of adjunctive technological therapies that might have

influenced glycemic outcomes. Sensitive analyses were performed according to the quality of evidence. Results were pooled with a random-effects model.

To assess health inequality, we used the PROGRESS framework, which is an acronym to guide data extraction according to dimensions across which health inequities may exist, as follows: place of residence, race/ethnicity, occupation, gender/sex, religion, education, socioeconomic status, and social capital.

Results: A total of 578 articles were screened and 147 were assessed for eligibility; of these, 99 studies (214162 CYP) were included in the qualitative review, and 86 (16 RCT and 70 NRS) in the meta-analysis. In RCTs, the participants' age ranged from 1 to 18 years, and the duration of intervention varied from 4 to 24 months. The model of insulin pump was reported in 15 studies, and the types of insulin were similar (analogues) in both CSII and MDI in 8 studies. Considering the NRS, 58 were diabetes registries/cohorts, 20 cross-sectional studies and 2 case-control studies. Participants' age ranged from 1 to 19.3 years. The model of insulin pump was mentioned in 15 studies, and the types of insulin were similar between therapies in 8 studies.

There was moderate-level evidence that the CSII lowers HbA1c in RCT (pooled mean difference [MD]: -0.22%; 95% confidence interval [CI]: -0.33, -0.11%; 982 CYP, I^2:34%) and insufficient in NRS (pooled MD: -0.45%; 95%CI: -0.52, -0.38%; 125213 CYP, I^2:99%). The pooled incidence rate ratio of severe hypoglycemia on CSII vs MDI in RCT was 0.87 (95%CI: 0.55, 1.37; 993 CYP I^2:0%; low-level evidence), and 0.71 (95%CI: 0.63, 0.81; 70204 CYP, I^2:57%, insufficient evidence) in NRS. The frequency of DKA episodes did not differ between CSII and MDI in both RCT (8 studies; risk ratio: 1.29; 95% CI: 0.62 to 2.69; 790 CYP, I^2 0%, moderate-

level evidence) and NRS (28 studies; risk ratio: 0.98; 95% CI: 0.75 to 1.29; 45399 CYP, I^2 63%, insufficient-level evidence). There was insufficient-level evidence for the percentage of time-in-range (mean difference: 5.21; 95% CI: -2.04 to 12.46; 68 CYP, I^2 0%), percentage of time-below-range (mean difference: -1.81; 95% CI: -6.33 to 2.72; 68 CYP, I^2 0%), and percentage of time-above-range (mean difference: -3.88; 95% CI: -13.92 to 6.16; 68 CYP, I^2 0%). Overall HRQoL mean difference (±SD) scores at the end of the follow-up for RCT was 0.42 (95%CI: 0.07–0.76; 217 CYP; I^2:29%, insufficient evidence); corresponding values for NRS were 0.35 (95% CI: 0.15–0.55; 699 CYP; I^2:33%, insufficient evidence).

Equity data were scarcely reported as most socioeconomic data corresponded to baseline socio-demographic characteristics of CYP/families and very few studies included subgroup analyses aimed to establish if potential benefits of CSII vary according to the PROGRESS variables. There was a suggestion of improvement of the glycemic outcomes globally, which was also observed across the disadvantaged groups, defined by race/ethnicity, parental occupation and educational level, and SES.

Conclusions: CSII modestly lower HbA1c when compared with MDI. As hypothesized in the study protocol, current literature did not provide adequate data on other glycemic outcomes. Future assessment on diabetes technology should include individual and area-level socioeconomic data.

Summary of article 3

Aim: To study healthcare professionals (HCP)'s perceptions on decision-making to start insulin pumps and continuous glucose monitoring (CGM) systems in pediatric type 1 diabetes.

Methods: An electronic survey supported by the International Society for Pediatric and Adolescent Diabetes (ISPAD) was disseminated through a weblink structured as follows: (i) HCP's sociodemographic and work profile; (ii) perceptions about indications and contraindications for insulin pumps and (iii) for CGM systems; and (iv) decision-making on six case scenarios.

Results: 247 responses from 49 countries were analyzed. Seventy percent of respondents were members of ISPAD. Most of participants were women over forty years-old, who practice as pediatric endocrinologists for more than ten years at university/academic centers and follow more than 500 people with type 1 diabetes. Although insulin pumps and CGMs are widely available and highly recommended among respondents, their uptake is influenced by access to healthcare coverage/insurance. Personal preference and cost of therapy were identified as the main reasons for turning down diabetes technologies. Parental educational level, language comprehension and income were the most relevant socioeconomic factors that would influence HCPs to recommend diabetes technologies, while gender, religious affiliation and race/ethnicity or citizenship the least.

Conclusions: HCPs seem to be markedly supportive of starting people on diabetes technologies. However, coverage/insurance for devices holds the biggest impact on the extent of their recommendations.

Introduction

1. General Introduction

1.1 Type 1 diabetes mellitus

Type 1 diabetes mellitus (T1D) is a chronic auto-immune disease caused by destruction of pancreatic β-cells, leading to insulin deficiency (1). The etiology is multifactorial, and usually disease is overt with the presence of one or more serologic markers of β-cell autoimmunity, including GAD, IA2, IAA, and ZnT8 (2). T1D accounts for over 90% of cases of diabetes in children and adolescents with, and has shown a sharp increase of incidence in countries that underwent economic transition in recent decades (3,4). T1D requires lifelong intensive care (5), which demands appropriate insulin treatment, glucose monitoring and educational interventions (3,4,6). However, to accomplish intensive care, and meet glycemic targets for pediatric T1D from current guidelines, is challenging (7–9). The emergence of diabetes devices has the potential to contribute to the improvement of glycemic outcomes and quality of life (10). However, most of this technology has not yet reached to those who would benefit the most (11,12).

Treatment with insulin is mandatory in T1D. Methods of insulin delivery range from multiple-daily injections (MDI), with the use of syringe or pen, to the continuous subcutaneous insulin infusions (CSII), popularly known as insulin pump, which is a device that continuously delivers basal insulin supply and mealtime or correction boluses whenever needed (13).

Blood glucose monitoring is necessary to improve glycemic control in T1D. Blood glucose can be monitored either by self-monitoring, with a kit including a glucose

monitor, lancet device and test strip, or by intermittently scanned or real-time continuous glucose monitoring (CGM) systems (14).

Continuous diabetes education has a beneficial effect on glycemic and psychosocial outcomes in T1D (15). Delivery of diabetes education requires specialized training and should be integrated into routine clinical care either through face-to-face visits with structured educational programs, or by technology-based diabetes teaching to coach people with personalized diabetes education (15–17).

1.2 Glycemic outcomes

Glycemic outcomes in children and adolescents with T1D can be assessed with glycosylated hemoglobin (HbA1c), the number of severe hypoglycemic episodes and diabetic ketoacidosis (DKA) events, as well as the percentage of time that the glucose level is in the target (TIR), below (TBR) or above the range (TAR) of 70 to 180 mg/dL (3.9 to 10.0 mmol/L)(18,19). Patient-reported outcomes (PRO) can be assessed from health/diabetes-related quality of life (HRQoL) questionnaires, and parents/caregiver satisfaction tools (by proxy measures)(18,20).

HbA1c values reflect average glycemia over approximately 3 months. This measure is the primary tool for assessing glycemic control, has strong predictive value for diabetes complications, and is still the metric used in clinical trials to demonstrate the benefits of improved glycemic control (19). However, HbA1c does not provide a measure of glycemic variability and lower values may be falsely met when exist much hypoglycemic events.

Hypoglycemia is the most common acute complication of T1D. The aim should be to maintain blood glucose level >70 mg/dL (3.9 mmol/L) while targeting to achieve

the best possible glycemic control avoiding severe hypoglycemia (SH), whose values are considered <54 mg/dL (3.0 mmol/L) (21). Severe hypoglycemia is defined as an event with cognitive impairment, including coma and convulsions, requiring external assistance by another person to actively administer carbohydrates, glucagon, or take other corrective actions (21). Use of CGM is more useful for capturing hypoglycemia missed by self-monitoring blood glucose, and much of the evidence on hypoglycemia has been obtained through conventional monitoring; the increased use of CGM and other technologies may provide more insights on this issue (18).

DKA is a well-understood condition caused by hyperglycemia (blood glucose >11 mmol/L [≈200 mg/dL]), venous pH <7.3 or serum bicarbonate <15 mmol/L, and ketonemia (blood ß-hydroxybuyrate ≥3 mmol/L) or moderate or large ketonuria, with well-recognized signs and symptoms (18,22,23). Given that current evidence is sufficient to support the definition described, and as DKA events produce acute damage on the myocardium in adults and children (24), this seems to be an important glycemic endpoint.

The wider utilization of CGM is modifying diabetes management and paved the way to assess new glycemic metrics. The use of CGM is essential for providing data on TIR, and on percentage of time spent above and below range (18,25). Today, TIR is a useful metric of glycemic control, as it captures fluctuations in glucose levels continuously, and correlates well with HbA1c (18). In fact, TIR is more specific and sensitive than HbA1c, and more likely to be comparable across patients than HbA1c values, as well as easier to correlate with PROs(18).

Current definition of PRO is “any report of the status of a patient’s health condition that comes directly from the patient, without interpretation of the patient’s response by a clinician or anyone else.”(26) Diabetes-specific rather than general measures are preferred to assess more nuanced domains related to living with T1D, such as distress/burden and diabetes-related worries/fear(27). However, the use of validated PROs in T1D research is still not widespread, and to measure quality of life by surveys and questionnaires may be challenged.

1.3 Influence of social determinants of health in adopting diabetes technologies

The World Health Organization Commission on Social Determinants of Health (WHO-CSDH) strongly advocates reducing social disparities and preventing the inequitable distribution of health care (28). However, disparities of technology use and glycemic outcomes by socioeconomic status increased over the past decade (12). Moreover, despite an increasing worldwide adoption of diabetes technologies, especially in high-income countries, universal adoption has not occurred, even in those countries that rely upon universal healthcare coverage for diabetes devices (29). In countries where pump therapy is not covered or reimbursed by the health care/insurance system, low adoption rates of this technology is more likely (30,31).

The emergence of diabetes technology may increase health inequities in pediatric T1D (12). The use of CSII is lower in ethnic minorities, and in families with lower income and education (30,32,33). A positive impact on glycemic endpoints is likely to be found in disadvantage groups from high-income countries, who usually have worse baseline health status, if rates of access to diabetes technologies were higher, as lower area-level SES was associated with lower rates of use of CSII as

well as higher HbA_{1c} and higher rates of DKA (34). On the other hand, differences in use of CSII vs MDI are observed in children from more affluent families, whose parents faced lower unemployment rates and higher educational levels and, in consequence, they presented improved glycemic control when adopting CSII than those children treated with MDI (35).

1.4 Influence of healthcare professionals' preferences in adopting diabetes technologies

Recommendations to start on diabetes technologies vary widely worldwide. While in most of cases, economic status and access to healthcare insurance play the main role in adopting this technology, in some cases HCP's preference may mostly influence the use of insulin pumps or CGMs in a given center (30,31,36,37). In fact, universal coverage for diabetes technology may be as relevant as individuals' metabolic control when HCPs recommend diabetes technologies (38).

With the advent of diabetes technologies, diabetes care has become more patient-centered; however, the complexity and rapid change of this technology can also be a barrier to implementation, and HCP may have trouble to cope with newly released technology (37). On the other hand, being diabetes technologies innovative therapies, the more motivated are HCPs to improve outcomes and patient and families' satisfaction, the more willing they are to recommend this technology (39).

Objectives

2. Objectives

Objective 1: To develop a standardized and transparent methodology for a systematic review and meta-analysis of the literature (i) to assess the effectiveness of continuous subcutaneous insulin infusions (CSII) versus multiple-daily insulin injections (MDI) on glycemic endpoints and patient-reported outcomes among young people with type 1 diabetes (T1D) and (ii) to identify health inequalities among those on CSII therapy.

Objective 2: To conduct a systematic review and meta-analysis of randomized-controlled trials and non-randomized studies to (i) assess the effectiveness of CSII vs MDI on a) glycemic outcomes - HbA1c, severe hypoglycemic episodes, diabetic ketoacidosis events, and/or the percentage of time that the glucose level is in the target (TIR), below (TBR) or above the range (TAR) of 70 to 180 mg/dL (3.9 to 10.0 mmol/L) -, and b) on patient-reported outcomes, and (ii) identify health equalities among children and adolescents with T1D.

Objective 3: To assess the reasons why healthcare providers recommend CSII and continuous glucose monitoring (CGM) systems for children and adolescents with T1D, with a focus on four dimensions: (i) healthcare professionals' sociodemographic and work profile; (ii) perceptions about indications and contraindications for insulin pumps and (iii) for CGM systems; and (iv) decision-making on six case scenarios.

Section 3

3. New insulin delivery devices and glycemic outcomes in young patients with type 1 diabetes: a protocol for a systematic review and meta-analysis

Dos Santos TJ, Donado Campos JM, Fraga Medin CA, Argente J, Rodríguez-Artalejo F. New insulin delivery devices and glycemic outcomes in young patients with type 1 diabetes: a protocol for a systematic review and meta-analysis. Syst Rev. 2019 Nov 4;8(1):259.

3.1 Background

Optimal type 1 diabetes mellitus (T1D) care requires lifelong appropriate insulin treatment that can be provided by either multiple daily injections (MDI) of insulin or by a continuous subcutaneous insulin infusion (CSII) pump (13). Over the last years, the use of CSII has increased substantially among pediatric patients (13). However, the selection of CSII versus MDI might have not been based only on clinical indications (e.g., elevated glycosylated hemoglobin and higher hypoglycemia rate), but also could have been influenced by social factors, such as place of residence and socioeconomic status, which may have led to health inequalities (13,32,40).

Meeting glycemic targets is a challenging task in young patients with T1D; thus new insulin delivery systems represent an opportunity to improve glycemic control, to promote patient-centered decisions, and to reduce the burden of diabetes care (8,39). Although an increasing number of trials has assessed whether the CSII is more effective than the intensive insulin therapy with syringe and/or pen (41–48), previous systematic reviews and meta-analyses (SRMA) of trials have not reported adequate information concerning equity and fairness in treatment selection (49–52).

Given the greater difficulty for good glycemic control in patients/families with lower health literacy and poor access to some healthcare resources, it is possible that the

absolute benefit of CSII would be greater in those with lower socioeconomic status (53). However, we do not know if they have the chance to participate and benefit from this intervention. In addition, there might exist several barriers for patient access and/or maintenance using CSII, and only a few studies (e.g., diabetes registries) have investigated the role of unequal health care access and social disparities on glycemic outcomes (30,38,54). In consequence, SRMAs with an equity lens could assess whether unequal benefits across sociodemographic population groups could contribute to worsening health inequalities in T1D management (14,22,28).

Therefore, this paper aims to report a standardized and transparent methodology for conducting a SRMA of the literature (i) to assess the effectiveness of using CSII versus MDI on glycemic (glycosylated hemoglobin, severe hypoglycemia, diabetes ketoacidosis and glycemic variability) and patient-related outcomes among young patients with T1D and (ii) to identify health inequalities for those who use CSII.

3.2 Methods

3.2.1 Review design: This protocol was developed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P)(55) and was registered and published on PROSPERO international prospective register of systematic reviews (Registration Number CRD42018116474). The Cochrane Collaboration Handbook (56) will also be used to guide the review methods, and PRISMA-E (PRISMA-Equity 2012) Guidelines (57) to elaborate the final report. To perform the SRMA, we will include randomized clinical trials (RCT) and non-randomized studies (NRS) - which cover diabetes registries and longitudinal studies - that compared the clinical effectiveness of CSII versus MDI in youths with T1D.

3.2.2 Data sources and search strategy: The bibliographic search will be conducted from January 2000 to June 2019 in MEDLINE (via PubMed), EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Database of Systematic Reviews, and the Health Technology Assessment (HTA) Database. We will also carry out a handsearch of the previous reviews and the bibliography from the original articles for additional references, as well as of the grey literature focusing on abstracts from diabetes associations and conference proceedings, and from technical reports (research and governmental agencies). Search will use standardized subject terms and will be conducted by a librarian with the input from the principal investigator, using Boolean operators for MEDLINE, EMBASE, CENTRAL, and HTA database. The final search strategy will have no restrictions based on language or publication status (see Supplementary file).

3.2.3 Eligibility criteria: We will select studies that compared the use of CSII with MDI and evaluated any of the following glycemic outcomes: glycosylated hemoglobin ($HbA_{1c,\ \%}$), the incidence of hypoglycemia episodes [e.g., severe, serious and/or nocturnal], diabetic ketoacidosis (DKA) events, and/or time spent in range or in hyper-hypoglycemia. Studies that mentioned health-related quality of life (HRQoL) as a PRO will also be selected. Specifically, the studies must meet the following selection criteria: (i) to be conducted with children and adolescents (under 20 years of age); (ii) exclusively on patients with T1D; (iii) designed as RCT or NRS; and (iv) to have reported any of the outcomes of interest: HbA_{1c}, hypoglycemia, DKA, time in range or in hyper-hypoglycemia, and HRQoL. Bi-hormonal or dual-hormone closed-loop systems that deliver glucagon in addition to insulin will not be included.

3.2.4 Equity analysis: To explore equity in CSII, we will use indicators of social disadvantages defined by PROGRESS (58). The acronym PROGRESS is a framework to guide data extraction to relate the outcomes with equity of access to an intervention, according to *"Place of residence"* (residing in a high- or low-to-middle-income country, as per the World Bank database), *"Race, Ethnicity, Culture and Language"* (racial, ethnic and cultural background, when majority groups include belonging to a distinctive group who shares origin, culture, traditions and language through generations), *"Occupation"* (parental patterns of work that favor proper maintenance of a therapy or not), *"Gender/Sex"* (sex refers to identify sex distribution when recommended each therapy), *"Religion"* (religious affiliation, spiritual beliefs or values that promote better access to health services), *"Education"* (assumes that high parental educational level, or health literacy and numeracy, is an advantage), *"Socioeconomic status"* (access to resources and privilege with greater household wealth, as an advantage), and *"Social capital"* (benefits obtained by individuals due to their social relationships, as an advantage).

For each factor of inequality, we hypothesized different social gradients: (1) a positive gradient, when better glycemic outcomes are found in more socially advantaged groups; (2) a negative gradient, when better outcomes are found in less advantaged groups; and (3) a neutral gradient, when no significant differences exist between groups. The results will be summarized with the aid of a harvest plot, which is a graphical technique that helps to illustrate a narrative synthesis (59).

3.2.5 Study selection and data extraction: Two reviewers will work independently to check eligibility of studies (title and abstract and, if needed, full-text) and extract the appropriate information in full-text articles. Disagreements will be resolved by

consensus. Assessment of eligibility and its inclusion will be conducted according to the indications of the PRISMA statement. Data to be extracted from articles include year of publication, country, study design and period of data collection, baseline characteristics of participants, interventions and comparators, factors of inequalities at baseline, and outcomes (Tables 1 and 2).

The glycemic endpoints include (i) the mean value of HbA_{1c} (%), assessed preferably at the end of the study, (ii) the number of serious, severe and/or nocturnal hypoglycemia episodes [≤3.0 mmol/L (54 mg/dL) or an event associated with severe cognitive impairment (including coma and convulsions) requiring assistance], (iii) the number of patients with ≥ 1 DKA event, and (iv) the percentage of time spent in range [percentage of readings in the glycemic range of 3.9-10.0 mmol/L (70-180 mg/dl) per unit of time] or in hypo [<3.9 mmol/L (<70 mg/dL)] and hyperglycemia [>10 mmol/L (>180 mg/dL)] (4,14,27,60,61). PRO will be captured with the HRQoL questionnaires. When necessary, authors of eligible studies will be contacted to provide additional information.

3.2.6 Assessment of risk of bias: Two reviewers will independently assess risk of bias of each study using two different tools: the Cochrane Risk of Bias form RCT and the RTI Item Bank for NRS (62,63). A review of only RCT may provide insufficient information on vulnerable subpopulations. Still, the inclusion of NRS may increase the challenges in establishing causal inference because they are at greater risk of bias than RCT, resulting from confounding by indication and selection bias. In contrast, threats to validity from performance and detection bias, and to precision from inadequate sample size, should not differ markedly between RCT and NRS (although some features such as blinding of assessors that protect against detection

bias are more likely in experimental designs than in observational studies). By including NRS (mainly registries), we may capture valuable information on the intended population for whom CSII is preferred, because registries are larger, studied over a longer time, and may better reflect all subgroups of patients and routine clinical practice (40).

3.2.7 Statistical analysis: We will summarize the main characteristics of selected studies, including the study´s objectives and design, characteristics of study participants, intervention and comparator, inclusion of PROGRESS categories, and outcomes (Tables 1 and 2). Effects across the studies will be summarized with (i) the pooled mean difference for HbA_{1c}, (ii) the pooled rate ratio for hypoglycemia, (iii) the pooled risk ratio for DKA, (iv) the mean difference in percentage of time that blood glucose concentration remained in target range, in hypo or in hyperglycemia, and (v) the pooled standardized mean difference (SMD) for quality of life outcomes, with their 95% confidence interval (CI), calculated with inverse variance random-effects models to incorporate the level of heterogeneity found across studies (56,64)**.** The effect size of the SMD will be classified as small (0.1-0.3), medium (0.3-0.6) or large (≥0.6)(65). Heterogeneity among studies will be assessed with the I^2 statistic, whose values will be classified as follows: no relevant heterogeneity (0-25%), moderate heterogeneity (25-50%) and substantial heterogeneity (>50%) (66). Meta-analyses will be performed separately for RCTs and NRS when data are available for at least two studies with comparable results. For equity outcomes, results will be summarized as a narrative synthesis (59). Publication bias will be evaluated graphically using a funnel plot and also with the method of Egger et al.

(66). The strength of the body of evidence will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool (67).

3.2.8 Subgroup analysis: Subgroup analyses will be performed based on age group, length of follow-up, and the use of adjunctive technological therapies that might directly improve glycemic outcomes.

3.2.9 Sensitivity analysis: The analyses will be repeated after exclusion of studies with high risk of bias, and separately for RCT and NRS.

3.3 Discussion

Given the increase of worldwide incidence of T1D, the wider use of the CSII pump among some specific socioeconomic and demographic groups, and the lack of evidence of its superiority when compared with the conventional therapy using MDI, there is a need to critically assess the rise of inequalities in treatment selection (11). Furthermore, the inclusion of PRO captured by health-related quality of life questionnaires will contribute to a complete diabetes measures portfolio (68). Hence, the assessment of the effects of CSII versus MDI on glycemic outcomes, across social factors defined by PROGRESS, may contribute better to understand their impact on health equity (47,51,69,70).

A major issue will probably be the limited data reported in the reviewed studies on the PROGRESS factors. For this reason, supplementary information will also be gathered from authors of the included studies. We are aware that the lack of important published information on equity may be a limitation of our review.

The results of an equity-oriented SRMA may yield an opportunity to discuss not only the effects of such interventions on glycemic endpoints, but also the existing

gap of information in the included studies regarding social inequities; it will pave the way to use those results to orient clinical practice, equity-based research, and health policy formulation.

Table 1: Table of evidence with main characteristics of the included studies

Reference	Design and registration details; Founding	Country	Year of baseline data collection	N and clinical characteristics	Setting	Type of diabetes-related technology	Type of conventional treatment comparator	Inequality assessed from baseline characteristics	Outcomes	Length of follow-up
Authors, year of publication, name of the study	Study design / registration number / Founding	Country or region	Year	Number of patients assigned and that received each treatment (CSII:MDI); Sex (M:F); Age; Baseline characteristics of participants (including duration of the disease, baseline HbA_{1c} [mean % (SD)] and HRQoL assessment tool); Other definition or comment	Community/ clinical based research	Continuous subcutaneous insulin infusion (CSII), including the use of adjunctive glucose monitors: model of devices and insulin	Multiple daily injections (MDI): injections and insulins	A. Place of residence B. Race, ethnicity, culture and language C. Occupation D. Sex E. Religion F. Education G. Socioeconomic status H. Social capital	1. HbA_{1c} at the end of the study: CSII vs. MDI [mean % (SD)], sig 2. Total number of hypoglycemic episodes: CSII vs. MDI, sig 3. Number of patients with a frequency of ≥ 1 Ketoacidosis episode: CSII vs. MDI, sig 4. Glycemic variability: % of time in range, hypo and/or hyperglycemia: CSII vs. MDI, sig 5. HRQoL score at the end of the study: CSII vs. MDI, sig	Duration of follow

CSII: Continuous subcutaneous insulin infusion; MDI: Multiple daily injection; M: male; F: Female; HbA_{1c}: glycosylated hemoglobin; SD: Standard deviation; sig: significance; HRQoL: health-related quality of life.

Table 2: PROGRESS framework to guide health equity data extraction on type 1 diabetes

PROGRESS framework	Social gradient		
	Positive	**Negative**	**Neutral**
 **Place of residence: Country where individuals reside (as per the World Bank database).**	To reside in a high-income country	To reside in a low-to-middle income country	No matter the place of residence, outcomes are non-significant
 **Race, ethnicity, culture and language: Self-identification racial or ethnic group, or different culture and language, including nationality status.**	To be a based-country language comprehension inhabitant or to be part of an ethnic majority	To be part of minority groups or to be a foreign with low language comprehension	No matter the race or ethnic group, outcomes are non-significant
 **Occupation: Patterns of work that provide proper maintenance of a treatment.**	Affordability to have access and maintain technological devices	No affordability to have access and maintain technological devices	No matter the parental occupancy status, outcomes are non-significant
 **Gender/Sex: Boys and girls were identified between groups.**	Characterization of sex distribution between therapies; girls are related to belonging to an advantaged group	No characterization of sex distribution between therapies; boys are related to belonging to a disadvantaged group	No matter the sex distribution, outcomes are non-significant
 **Religion: Religious affiliation of spiritual beliefs or values.**	Access to health services is favored for a subgroup because of its religious affiliation or beliefs	Access to health services is limited because of its religious affiliation or beliefs or due to the lack of religion	No matter the religion or beliefs, outcomes are non-significant
 **Education: Assessed by the informed educational level or approximated by health literacy and numeracy.**	High educational level or health literacy and numeracy are considered advantaged group	Low educational level or health literacy and numeracy are considered disadvantaged group	No matter the education, outcomes are non-significant

 **Socioeconomic status (SES): To obtain information considering access to resources and privilege.**	A higher household wealth is considered advantaged group	A lower familial income is considered disadvantaged group	No matter the SES, outcomes are non-significant
 **Social capital: Benefits obtained by individuals due to their social relationships, e.g.: to be member of a diabetes foundation, to participate in diabetes camp.**	To have network involvement	Not to have network involvement	No matter the network involvement, outcomes are non-significant

Supplemental File 1:

Search Strategies:

Medline (via PubMed)

Search	Query	Items found
#31	Search (#27 AND #28) Filters: Publication date from 2000/01/01 to 2019/06/30; Humans	391
#30	Search (#27 AND #28) Filters: Humans	446
#29	Search (#27 AND #28)	536
#28	Search ((((((((((infant OR infan* OR child OR children OR schoolchild* OR schoolchild OR school child OR school child* OR kid OR kids OR toddler* OR adolescent OR boy OR girl OR minors OR minors* OR underag* OR under ag* OR juvenil* OR youth* OR kindergar* OR puberty OR puber* OR pubescen* OR prepubescen* OR prepuberty* OR pediatrics OR pediatric* OR paediatric* OR peadiatric* OR schools OR nursery school* OR preschool* OR pre school* OR primary school* OR secondary school* OR elementary school* OR elementary school OR highschool* OR highschool* OR school age OR school age OR school age* OR schoolage* OR infancy OR schools, nursery))) NOT fetus) NOT newborn) NOT neonatal)))))	4687061
#27	Search (#19 AND #26)	1096
#26	Search (#20 OR #21 OR #22 OR #23 OR #24 OR #25)	18225
#25	Search ((“short acting insulin”[tiab] or "regular insulin" or "isophane insulin" or "human insulin" or "humulin")) OR “rapid acting insulin”[tiab] or "aspart" or "insulin aspart" or "Insulin-Aspart" or "NovoLog" or "Novorapid" or "lispro" or "insulin lispro" or "lyspro" or "Humalog Kwikpen" or "humalog" or "apidra" or "insulin apidra")))	10123
#24	Search ((basal*[tiab] AND bolus[tiab] AND (injection*[tiab] OR regime*[tiab] OR routine*[tiab] OR system*[tiab])))	1959
#23	Search MDI[tiab]	3457
#22	Search (((“multiple injection”[tiab] or “multiple injections”[tiab] or “multiple insulin”[tiab] or “multiple regime”[tiab] or “multiple regimes”[tiab] or “multiple routine”[tiab] or “multiple routines”[tiab]))))	2837
#21	Search (((“multiple dose injection”[tiab] or “multiple dose injections”[tiab] or “multiple dose insulin”[tiab] or “multiple dose regime”[tiab] or “multiple dose regimes”[tiab] or “multiple dose routine”[tiab] or “multiple dose routines”[tiab]))))	61
#20	Search ((((“multiple daily injection”[tiab] or “multiple daily injections”[tiab] or “multiple daily insulin”[tiab] or “multiple daily regime”[tiab] or “multiple	1010

Search	Query	Items found
	daily regimes”[tiab] or “multiple daily routine”[tiab] or “multiple daily routines”[tiab])))))	
#19	Search ((#9 AND #18))	4238
#18	Search ((((#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17)))	11793
#17	Search (((((“animas" or vibe) AND (pump* or infus* or system*)))))))	151
#16	Search (((“veo pump” or “veo pumps”)))	26
#15	Search ((((paradigm* AND (veo or pump*))))))	512
#14	Search (((“minimed" or "paradigmaveo")))	312
#13	Search ((((accu-chek[tiab] or cellnovo[tiab] or “dana diabecare”[tiab] or omnipod[tiab]))))))	245
#12	Search (((“subcutaneous insulin”[tiab] or CSII[tiab])))))	3261
#11	Search (((“pump therapy”[tiab] or “pump therapies”[tiab] or “pump treatment”[tiab] or “pump treatments”[tiab])))))	1451
#10	Search ((“insulin pump”[tiab] or “insulin pumps”[tiab] or “insulin infusion”[tiab] or “insulin infuse”[tiab] or “insulin infused”[tiab] or “insulin deliver”[tiab] or “insulin delivery”[tiab]))	9724
#9	Search ((#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8))	80050
#8	Search ((dm1[tiab] or “dm 1”[tiab] or t1dm[tiab] or “t1 dm”[tiab] or t1d[tiab] or iddm[tiab]))	19663
#7	Search ((“insulin dependent”[tiab] or insulindepend*[tiab]))	28768
#6	Search ((“brittle diabetic”[tiab] or “diabetic juvenile”[tiab] or “diabetic pediatric”[tiab] or “diabetic paediatric”[tiab] or “diabetic early”[tiab] or “diabetic labile”[tiab] or “diabetic acidosis”[tiab] or “diabetic sudden onset”[tiab]))	359
#5	Search ((“diabetic brittle”[tiab] or “juvenile diabetic”[tiab] or “pediatric diabetic”[tiab] or “paediatric diabetic”[tiab] or “early diabetic”[tiab] or “labile diabetic”[tiab] or “acidosis diabetic”[tiab] or “sudden onset diabetic”[tiab]))	1401
#4	Search ((“brittle diabetes”[tiab] or “diabetes juvenile”[tiab] or “diabetes pediatric”[tiab] or “diabetes paediatric”[tiab] or “diabetes early”[tiab] or “diabetes ketosis”[tiab] or “diabetes labile”[tiab] or “diabetes acidosis”[tiab] or “diabetes sudden onset”[tiab]))	323

Search	Query	Items found
#3	Search ((“diabetes brittle”[tiab] or “juvenile diabetes”[tiab] or “pediatric diabetes”[tiab] or “paediatric diabetes”[tiab] or “early diabetes”[tiab] or “ketosis diabetes”[tiab] or “labile diabetes”[tiab] or “acidosis diabetes”[tiab] or “sudden onset diabetes”[tiab]))	2691
#2	Search ((“diabetic type 1”[tiab] OR “type 1 diabetic”[tiab] OR “diabetic type i”[tiab] OR “type i diabetic”[tiab] OR “diabetic type1”[tiab] OR “type1 diabetic”[tiab] OR “diabetic typei”[tiab] OR “typei diabetic”[tiab]))	7149
#1	Search ((((“diabetes type 1”[tiab] OR “type 1 diabetes”[tiab] OR “diabetes type i”[tiab] OR “type i diabetes”[tiab] OR “diabetes type1”[tiab] OR “type1 diabetes”[tiab] OR “diabetes typei”[tiab] OR “typei diabetes”[tiab]))))	42483

Embase (via Elsevier)

'insulin dependent diabetes mellitus'/exp AND (**'insulin pump'**/mj OR **'accu chek spirit'** OR **'d-tron'** OR **'d-tronplus'** OR **'dana diabecare'** OR **'deltec cozmo'** OR **'h-tron plus'** OR **'h-tronplus'** OR **'minimed 508'** OR **'minimed 530g pump'** OR **'minimed paradigm 508'** OR **'minimed paradigm revel'** OR **'minimed paradigm veo'** OR **'minimed paradigm 512'** OR **'minimed paradigm 712'** OR **'omnipod'** OR **'onetouch ping'** OR **'v-go (device)'** OR **'vibe (device)'** OR **'zone (device)'** OR **'insulin infusion system'** OR **'insulin pump'** OR **'insulin pump, device (physical object)'** OR **'pump, infusion, insulin'** OR **'pump, insulin'** OR **'t:slim x2'**) AND (**'insulin injection pen'**/exp OR **'autopen (insulin injection pen)'** OR **'flexpen'** OR **'flextouch'** OR **'humapen'** OR **'humapen ergo'** OR **'humapen luxura hd'** OR **'humapen memoir'** OR **'humapen savvio'** OR **'innolet'** OR **'innovo (device)'** OR **'kwikpen'** OR **'novofine'** OR **'novopen 4'** OR **'novopen 5'** OR **'novopen echo'** OR **'opticlik'** OR **'solostar'** OR **'insulin injection pen'** OR **'insulin pen'**) AND **([adolescent]/lim** OR **[child]/lim** OR **[infant]/lim** OR **[preschool]/lim** OR **[school]/lim** OR **[young adult]/lim)**

#4 **[adolescent]/lim** OR **[child]/lim** OR **[infant]/lim** OR **[preschool]/lim** OR **[school]/lim** OR **[young adult]/lim -- 17**

#3 **'insulin injection pen'**/exp OR **'autopen (insulin injection pen)'** OR **'flexpen'** OR **'flextouch'** OR **'humapen'** OR **'humapen ergo'** OR **'humapen luxura hd'** OR **'humapen memoir'** OR **'humapen savvio'** OR **'innolet'** OR **'innovo (device)'** OR **'kwikpen'** OR **'novofine'** OR **'novopen 4'** OR **'novopen 5'** OR **'novopen echo'** OR **'opticlik'** OR **'solostar'** OR **'insulin injection pen'** OR **'insulin pen' -- 53**

#2 **'insulin pump'**/mj OR **'accu chek spirit'** OR **'d-tron'** OR **'d-tronplus'** OR **'dana diabecare'** OR **'deltec cozmo'** OR **'h-tron plus'** OR **'h-tronplus'** OR **'minimed 508'** OR **'minimed 530g pump'** OR **'minimed paradigm 508'** OR **'minimed paradigm revel'** OR **'minimed paradigm veo'** OR **'minimed paradigm 512'** OR **'minimed paradigm 712'** OR **'omnipod'** OR **'onetouch ping'** OR **'v-go (device)'** OR **'vibe (device)'** OR **'zone (device)'** OR **'insulin infusion system'** OR **'insulin pump'** OR **'insulin pump, device (physical object)'** OR **'pump, infusion, insulin'** OR **'pump, insulin'** OR **'t:slim x2' – 4,848**

#1 **'insulin dependent diabetes mellitus'**/exp – 111,599

CENTRAL (via Cochrane Library)

#1 MeSH descriptor: [Insulins] explode all trees and with qualifier(s): [administration & dosage - AD, therapeutic use - TU] -- 4223

#2 MeSH descriptor: [Insulin Infusion Systems] explode all trees -- 605

#3 MeSH descriptor: [Injections, Subcutaneous] explode all trees—4257

#4 {OR #2-#3} – 4756

#5 MeSH descriptor: [Diabetes Mellitus, Type 1] explode all trees – 4906

#6 (MULTIPLE DAILY INJECTION):ti,ab,kw – 875

#7 #5 AND #4 OR #6 AND #1 – 719

#8 (child or child* or young or young* or minors or underag* or juvenil or youth or pediatric* or peadiatric*):ti,ab NOT fetus NOT neonatal NOT newborn -- 147900

#9 #7 AND #8 – 118

with Cochrane Library publication date from Jan 2000 to Jun 2019

HTA Database (via CRD Database)

#1 MeSH DESCRIPTOR Diabetes Mellitus, Type 1 EXPLODE ALL TREES -- 312

#2 MeSH DESCRIPTOR Insulin Infusion Systems EXPLODE ALL TREES – 71

#3 MeSH DESCRIPTOR Injections, Subcutaneous EXPLODE ALL TREES – 127

#4 (MeSH DESCRIPTOR Diabetes Mellitus, Type 1 EXPLODE ALL TREES) OR (MeSH DESCRIPTOR Insulin Infusion Systems EXPLODE ALL TREES) OR (MeSH DESCRIPTOR Injections, Subcutaneous EXPLODE ALL TREES) IN HTA FROM 2000 TO 2019 -- 33

Section 4

4. Effectiveness and equity of continuous subcutaneous insulin infusions in pediatric type 1 diabetes: a systematic review and meta-analysis of the literature

Dos Santos TJ, Donado Campos JM, Argente J, Rodríguez-Artalejo F. Effectiveness and equity of continuous subcutaneous insulin infusions in pediatric type 1 diabetes: A systematic review and meta-analysis of the literature. Diabetes Res Clin Pract. 2021 Feb;172:108643.

4.1 Introduction

Continuous subcutaneous insulin infusions (CSII) are gaining ground over multiple-daily injections (MDI) as a standard therapy for pediatric type 1 diabetes (13). A number of clinical trials have highlighted that the CSII improve glycemic outcomes, promote patient-centered decisions, and reduce the burden of diabetes care in children and adolescents with type 1 diabetes (39,41–43,45–48). However, most of the trials in this field lacked data on clinical effectiveness, the extent to which clinical efficacy of CSII translates into better glycemic outcomes in a real-world setting (8,40). This information is usually provided by large clinical practice registries (30,71–75) and, to our knowledge, no previous systematic review of the literature on the CSII has included pediatric diabetes registry databases.

Moreover, the prescription of the CSII *vs* MDI may not have been based only on clinical indications (e.g., elevated glycated hemoglobin and frequent hypoglycemic events), but also on favorable social factors, which may have led to health inequalities in this field (32,53,58). In addition, because meeting glycemic targets is more difficult in young people and families with low health literacy and poor access to healthcare resources, it is possible that the absolute

benefit of the CSII varies according to socioeconomic status (SES) (8,53,58). Nevertheless, while there might still exist barriers to access and maintain this therapy, previous systematic reviews of clinical trials have not assessed equity and fairness in treatment selection (49–52,76,77), and only a few studies have investigated the role of unequal healthcare access and social disparities on glycemic outcomes (30,32,54). A systematic review of the literature using an equity lens could assist in bridging the gap between the clinical indications of CSII and the unmet needs of the socially disadvantaged young individuals and their families (14,22,28,70).

Therefore, we conducted a systematic review and meta-analysis of RCTs and non-randomized studies (NRS) to (i) assess the effectiveness of CSII *vs* MDI on glycemic outcomes, and (ii) identify health equity data among children and adolescents with type 1 diabetes.

4.2 Methods

This review was developed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (78), the PRISMA-Equity extension (57), the Meta-analyses of Observational Studies in Epidemiology (MOOSE) checklist (79), and the Cochrane Collaboration Handbook (56). A protocol for this review was registered in PROSPERO (Registration Number: CRD42018116474) and published elsewhere (80).

4.2.1 Data sources and search strategy

The bibliographic search was conducted from January 2000 to September 2019 in MEDLINE (via PubMed), EMBASE (via Elsevier), Cochrane Central Register of Controlled Trials (CENTRAL), and the Health Technology Assessment (HTA)

Database. We also hand-searched for additional references in previous reviews, and in abstracts from conference proceedings. Our search strategy used standardized subject terms and no language restrictions were set (supplementary content).

4.2.2 Eligibility criteria

We selected studies that compared CSII against MDI, and evaluated, as glycemic endpoints, any of the following: glycated hemoglobin (HbA_{1c}), severe hypoglycemia (SH) episodes, diabetic ketoacidosis (DKA) events, and the percentage of time that the glucose level was in the target (TIR), below (TBR) and above the range (TAR) of 70 to 180 mg/dL (3.9 to 10.0 mmol/L), assessed with continuous glucose monitoring (CGM) systems (27). As a secondary endpoint, we also selected studies that measured health/diabetes-related quality of life (HRQoL). We included all the studies that met the following criteria: (i) were conducted with children and adolescents ≤ 20 years; (ii) exclusively with type 1 diabetes; (iii) designed as RCT or NRS - such as diabetes registries, cohort and other types of observational studies; and (iv) reported any of the outcomes of interest: HbA_{1c}, SH, DKA, percentage in TIR, TBR and TAR, or HRQoL. We did not include studies that compared the use of single-hormonal or dual-hormonal closed-loop systems.

4.2.3 Study selection and data extraction

Two reviewers (TJ, JD) worked independently to check eligibility of studies (title and abstract and, if needed, full-text) and extracted the appropriate information in full-text articles (56). Differences in opinion were resolved through consensus between the two reviewers. Data extracted from articles included year of

publication, study design and period of data collection, country, baseline characteristics of participants (number of subjects by treatment including dropouts, sex, age, duration of type 1 diabetes, mean baseline HbA_{1c}, and HRQoL assessment tool), research setting, type of intervention (CSII device, including the use of adjunctive glucose sensor, and type of insulin), comparator (number of injections per day and type of insulin), factors of inequality, glycemic outcomes, and duration of follow-up (Supplemental Table S1).

We analyzed the following glycemic outcomes: (i) HbA_{1c} (%/mmol/mol), preferably at the end of the study, (ii) the number of severe hypoglycemia episodes [≤54 mg/dL (3.0 mmol/L) or an event associated with severe cognitive impairment (including coma and convulsions) requiring external assistance], (iii) the number of CYP with ≥ 1 DKA event, and (iv) the mean (±SD) percentage of TIR [percentage of readings in the glycemic range of 70-180 mg/dl (3.9-10.0 mmol/L) per unit of time], TAR and TBR assessed with any continuous glucose monitor systems (4,14,21,27,61). We collected information on questionnaires that assessed the overall mean (±SD) HRQoL score for each group at the end of the study.

4.2.4 Equity analysis

To explore health inequalities, we focused on indicators of social disadvantages defined by PROGRESS (58,81). Most of social factors were identified in the baseline patient characteristics. We still examined whether the existing studies reported each of the social determinants of health according to the given therapy and the benefits with such therapy, and if CYP and caregivers belonged to advantaged or disadvantaged groups. Advantaged groups were considered

those who reside in high-income countries, belong to major racial/ethnic/religious aspects, attain higher socioeconomic status and educational level, whose caregivers have better occupation and are recipients of governmental assistance, and that families are included in greater social network involvement; the disadvantaged groups comprised the rest of CYP/families. For gender/sex, we considered that a disadvantaged existed when there was an unequal prescription of CSII between boys and girls.

4.2.5 Assessment of risk of bias

Two reviewers (TJ, JD) independently assessed the risk of bias of each study using two instruments: the Cochrane Risk of Bias tool for RCT (63), and the RTI Item Bank for NRS (62). We assigned an "overall assessment" with three categories: a) Low risk of bias (low risk in each of the six domains of the Cochrane tool; or unclear risk in one domain); b) Intermediate risk of bias (high risk in one domain; or unclear risk in two domains, and the judgment that this was unlikely to bias the results); and c) High risk of bias (high risk in one or more domains; or unclear risk in two domains, and the judgment that this was likely to bias the results).

For RCT, lack of "Allocation concealment" was judged as the domain that is most likely to bias the study results, because an inadequate technique of concealment might lead to greater benefit in those with better clinical baseline parameters (63). Also, in line with well-established epidemiological knowledge, we considered that, for NRS, "Confounding" was most likely to bias the results (63). We also registered the sponsorship of studies by the pharmaceutical industry, though we did not equate such sponsorship with higher risk of bias (82).

4.2.6 Statistical analyses

We retrieved the standardized mean (±SD) HbA_{1c} (%/mmol/mol) among therapies. Results on hypoglycemia were extracted as incidence rates (event/100 patients-year), and those on DKA as the number of subjects with ≥ 1 DKA event. For TIR, TAR and TBR, we retrieved the mean (±SD) %. Finally, HRQoL data corresponded to the overall final score in each scale, presented as the standardized mean difference (±SMD). The effect size of the SMD was classified as small (0.1-0.3), medium (0.3-0.6) or large (≥0.6) (65).

The effect of CSII *vs* MDI was summarized with the pooled (i) mean difference for HbA_{1c}, (ii) rate ratio for hypoglycemia, (iii) risk ratio for DKA, (iv) mean difference in the percentage of time that blood glucose remained in target, above and below the range, and (v) standardized mean difference for HRQoL. Pooling was performed with inverse variance random-effects models, to incorporate the level of heterogeneity found across studies (64). Heterogeneity was assessed with the I^2 statistic, classified as follows: no relevant heterogeneity (0-25%), moderate heterogeneity (25-50%) and substantial heterogeneity (>50%) (66). Meta-analyses were performed separately for RCT and NRS. We conducted subgroup analyses for HbA_{1c} according to the length of follow-up (≤ or more than one year) and to different groups of age (under 6, 6 to 11, and over 11 years), when appropriate. Lastly, the main analyses were repeated for each type of NRS, and after exclusion of studies with high risk of bias. The STATA (v14.0; StataCorp, USA) and Review Manager Software (v5.3; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011) were used for all analyses.

For equity data, we elaborated a narrative synthesis aiming to identify the number and frequency of studies reporting the PROGRESS social determinants (83), to classify study participants as belonging to more or less advantaged groups, and to examine the potential benefit of each therapy according to PROGRESS variables.

4.2.7 Quality of the evidence

The quality of the body of evidence was assessed by the two independent reviewers (TJ, JD) using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool (67)**;** the rating of quality reflects the extent of our confidence that the estimates of the effect of CSII *vs* MDI on the outcomes are correct. Four levels of quality of evidence were used: high, moderate, low, and insufficient. For RCT, we downgraded the evidence from high-level by one level for five domains: *high risk of bias* (serious study limitations); serious *inconsistency* of results across studies (effect size are not in the same direction); *indirectness* of evidence (results may not directly apply to young people with type 1 diabetes); *imprecision* of effect estimates (wide confidence intervals); or *publication bias* - by means of funnel plots, which represents the effect estimates against their precision (standard error), and the Egger's test for funnel plot asymmetry (84). For NRS, level of evidence started at moderate quality, and was downgraded as for RCT.

The reviewers (TJ, JD) achieved a degree of agreement that, before consensus, ranged from 80-95% for screening and selection of studies, data extraction, and assessment of risk of bias.

4.3 Results

A total of 636 records were identified, and their abstracts were screened for eligibility. After removing duplicates and those articles that did not meet the inclusion criteria, we assessed the full text of 147 studies; of them, 48 were excluded with detailed reasons (Figure 1). A total of 99 studies (214162 CYP) were included in the qualitative review, and 86 (16 RCT) in the meta-analysis.

The characteristics of the articles reviewed are summarized in Supplemental Table S1. In total, there were 19 RCT, involving 765 CYP on CSII and 793 on MDI; of them, three RCT did not report outcome data as needed, and we could not obtain the information after contacting the authors, so they were excluded from the meta-analysis. Three RCT were cross-over trials. The participants' age ranged from 1 to 18 years, and the duration of intervention varied from 4 to 24 months. The model of insulin pump was reported in 15 studies, and the types of insulin were similar (analogues) in both CSII and MDI in 8 studies.

We screened 80 NRS, involving 93416 CYP on CSII and 120131 on MDI; of them, 58 were diabetes registries/cohorts, 20 were cross-sectional studies and 2 were case-control studies. We excluded 10 of them from the meta-analysis because they did not report the outcome data as needed. Participants' age ranged from 1 to 19.3 years. The model of insulin pump was mentioned in 15 studies and the types of insulin were similar between therapies in 8 studies.

4.3.1 Risk of Bias Summary Assessment

Supplemental Tables S2 and S3 show the risk of bias assessment in RCT and NRS, respectively. In RCT, 8 (42%) of them had an overall low risk of bias, 5 (26%) an intermediate risk, and 6 (32%) a high risk of bias based on the separate assessment of the glycemic outcomes; about half of the studies presented

HRQoL data, whose assessment entailed a high risk of bias. Most of the domains were judged to have a low risk of bias, although we observed selection bias especially in the cross-over trials that, eventually, affected the overall assessment. Blinding of participants and personnel was impractical to intervention group, so we judged this domain as being unclear without affecting the overall risk of bias assessment.

In NRS, 8 (10%) of them were judged to have an overall low risk of bias, 30 (37.5%) intermediate risk, and 42 (52.5%) high risk for all the outcomes (both glycemic variables and HRQoL). Potential residual confounding was the domain that most contributed to bias risk, because approximately half of the studies did not attempt to balance the baseline characteristics of participants by using statistical adjustments.

4.3.2 Glycated hemoglobin

The use of CSII was associated with lower values of HbA_{1c} when compared with MDI in both RCT (16 studies; mean difference: -0.22%; 95% CI: -0.33 to -0.11%; 982 CYP, I^2 34%) and NRS (64 studies; mean difference: -0.45%; 95% CI: -0.52 to -0.38%; 125213 CYP, I^2 99%). Results did not substantially differ according to the length of follow-up and type of NRS (Figure 2) or age group (Supplemental Figure S1) and were not materially modified after removing studies with high and intermediate risk of bias (Supplemental Figure S2).

In RCT, the quality of evidence was moderate because many RCT presented intermediate risk of bias; however, heterogeneity of results was moderate (I^2 34%), the results directly applied to young people with type 1 diabetes, and the pooled effect estimate had a relatively narrow confidence interval (Table 1).

Moreover, we found no obvious indication of publication bias in funnel plots and Egger's test (Supplemental Figure S3).

By contrast, in NRS the quality of evidence was insufficient because most of them presented a high risk of bias due to uncontrolled confounders (Table 1). The heterogeneity of the results was quantitatively high (I^2: 99%), but we interpreted it as being qualitatively acceptable because HbA_{1c} in those using CSII was similar or lower than in those with MDI, with results presenting effect size with the same direction.

4.3.3 Severe hypoglycemia

In RCT, the pooled incidence rate ratio of severe hypoglycemia episodes on CSII *versus* MDI was 0.87 (95%CI: 0.55 to 1.37; 993 CYP; I^2:0%); corresponding values in NRS were 0.71 (95%CI: 0.63 to 0.81; 70204 CYP; I^2:57%) and did not differ according to the type of study (Figure 3). However, in NRS, the reduction of SH associated with CSII lost statistical significance in analyses restricted to studies with low risk of bias (Supplemental Figure S2).

The quality of evidence in RCT was low due to the wide confidence interval in the pooled incidence rate ratio (Table 1). Results from NRS had the same direction that those from RCT, but quality of evidence was much lower; according to the GRADE approach, evidence from NRS was insufficient because of very serious risk of bias resulting from important residual confounding (Table 1). Although in NRS the I^2 was 57%, we believe that there is no serious qualitative heterogeneity because most effect estimates across studies were null or favored CSII (Figure 3).

4.3.4 Diabetic ketoacidosis

The frequency of DKA episodes did not differ between CSII and MDI in both RCT (8 studies; risk ratio: 1.29; 95% CI: 0.62 to 2.69; 790 CYP, I^2 0%) and NRS (28 studies; risk ratio: 0.98; 95% CI: 0.75 to 1.29; 45399 CYP, I^2 63%) (Figure 4). Results did not change substantially after removing studies with high and intermediate risk of bias (Supplemental Figure S2), or across different types of NRS (Figure 4.3). The strength of evidence was downgraded in both RCT (moderate-level of evidence) and NRS (insufficient evidence) because of heterogeneity and imprecision of results (Table 1).

4.3.5 Time in target, below and above glycemic range

Two RCT reported data on the percentage of the TIR, TBR and TAR with no significant differences between CSII and MDI. Main pooled results were as follows: percentage of TIR (mean difference: 5.21; 95% CI: -2.04 to 12.46; 68 CYP, I^2 0%), percentage of TBR (mean difference: -1.81; 95% CI: -6.33 to 2.72; 68 CYP, I^2 0%), and percentage of TAR (mean difference: -3.88; 95% CI: -13.92 to 6.16; 68 CYP, I^2 0%) (Figure 5). Quality of evidence was insufficient because of very serious risk of bias and imprecision of effect estimates (Table 1).

4.3.6 Health-Related Quality of Life

The included studies used heterogeneous tools to assess HRQoL (Supplemental Table S4). Some studies measured HRQoL with validated and age-appropriated diabetes-related quality of life questionnaires, whereas others measured overall quality of life and focused on parental rather than children's quality of life. Because of the substantial heterogeneity of studies, we performed a meta-analysis with those that presented overall HRQoL mean (±SD) scores at the end of the follow-up. For RCT, SMD was 0.42 (95%CI: 0.07-0.76; 217 CYP; I^2:29%);

corresponding values for NRS were 0.35 (95%CI: 0.15-0.55; 699 CYP; I^2:33%) (Figure 6). In both RCT and NRS, strength of evidence was insufficient due to high risk of bias, inconsistent results across studies, and small number of studies.

4.3.7 Equity analysis

While 100% of the studies reported country/place of residence of CYP/families and 97% the individual's sex, only 38% reported their race/ethnicity, 26% the socioeconomic status, 20% parental occupation, 12% parental education/diabetes literacy, 4% social capital and 1% religion (Table 2). Most socioeconomic data correspond to baseline socio-demographic characteristics of CYP/families and very few studies included subgroup analyses aimed to establish if potential benefits of CSII vary according to the PROGRESS variables into a context of type 1 diabetes care in pediatric age.

Most of the existing literature corresponds to studies conducted in high-income countries that also included data on socially disadvantaged groups of CYP/families. However, some studies also included individuals belonging to racial minorities and immigration groups, with under/unemployed parents, lower educational level, and lower SES. We summarized the information available in both advantaged and disadvantaged groups about the effects of CSII on each significant glycemic outcome (Table 3). There was a suggestion of improvement of the glycemic outcomes globally, which was also observed across the disadvantaged groups, defined from race/ethnicity, parental occupation and educational level, and SES.

4.4 Discussion

In this systematic review and meta-analysis of the literature, we found moderate-level evidence from RCT that the CSII modestly lower HbA_{1c} compared with MDI among children and adolescents with type 1 diabetes. Results were in the same direction in NRS, although the level of evidence was lower. However, in both RCT and NRS, CSII did not show to improve other glycemic outcomes or HRQoL compared with MDI nor presented adequate strength of evidence. Equity data, when reported, suggest that individuals from disadvantaged groups can also benefit from CSII.

Our findings agree with those from recent meta-analyses of RCT (49–52,76,77,85), where children and adolescents using CSII *vs* MDI had lower mean HbA_{1c}, a tendency to fewer severe hypoglycemia episodes, and an improvement of quality of life. Our results did not substantially differ by patient's age. In addition, like RCT, most of the NRS showed a similar increase of HbA_{1c} values after the first year on CSII, which is probably associated with the early motivation for the use of a novel technology (5,86).

Although the pooled reduction of severe hypoglycemia episodes found in NRS was substantial (rate ratio: 0.71), it did not reach statistical significance when we analyzed only the few studies with low risk of bias. As regards the RCT, the failure of the CSII to show a reduction in hypoglycemia episodes could be due to the fact that the selection of most of participants in RCT was based on patient's preferences to wear rather than on pump's indication to "reduce hypoglycemia" (52). Obtaining favorable results reducing SH may need the use of low glucose suspend systems, which requires the adoption of CGM systems, which were not assessed in this meta-analysis.

HRQoL seemed to be slightly better in CYP on CSII, but the effect estimates were of small size and based on few studies, so they provided an insufficient level of evidence. A recently published meta-analysis reported results similar to ours, though based on a reduced number of studies (85). We meta-analyzed only those studies with data on overall or diabetes-specific HRQoL at the end of the follow-up, measured with similar scales (PedsQL, KINDL-R and DQoL). Consequently, the pooled results on HRQoL should be interpreted with caution because they were obtained in a selected subsample of studies and HRQoL was measured with heterogeneous tools.

For equity data in the existing literature, most information is derived from high-income countries, despite the evidence of a greater increase in the incidence of type 1 diabetes in countries with low-to-middle income levels (87,88). However, a few results from these studies correspond to young people belonging to disadvantaged groups and living in high-income countries - such as immigrants, ethnic minority groups, non-recipients of state assistance, whose parents have lower education level. Although current data reveal overall insufficient glycemic control, it seems that the socially disadvantaged groups achieved some improvement in the glycemic outcomes when on CSII therapy (32,89–91).

Unfortunately, we could only partially assess whether the effect of the CSII *vs* MDI varies across the socioeconomic status and, in particular, if the potential benefits of using CSII would accrue in most socially disadvantaged persons. The lack of standardized terminology and straightforward assessment of equity-relevant information in the literature restrained our ability to fully capture differences between social groups in the access to and effectiveness of the CSII.

Thus, our data should be interpreted with caution, as most of the studies are not conducted for this purpose (92–95).

Unlike previous systematic reviews, we also included NRS for three reasons. First, in observational studies with long follow-up, it is more likely that the effects of an enthusiastic environment for a new therapy (CSII) can be mitigated, especially because most CYP and caregivers are willing to receive more diabetes education when starting on CSII (96). Second, NRS may be more realistic as the clinical profile of the participants is intended to be broader and more representative of the potential candidates for CSII in the general young population (40). Third, by studying large registries, it is possible to capture the influence of inequality factors on the effectiveness of CSII (69). The drawback of using NRS is their higher risk of bias; notwithstanding this, the direction of the results has been very consistent in both RCT and NRS.

Current clinical guidelines consider CSII as an appropriate therapy for all CYP with type 1 diabetes (22,70). Of note, however, is that guidelines particularly consider this therapy for individuals with recurrent severe or nocturnal hypoglycemia, wide glycemic variability regardless of HbA_{1c}, suboptimal diabetes control, and early microvascular complications or elevated cardiovascular risk factors. Moreover, CYP with optimal metabolic control that aim to improve quality of life and/or treatment satisfaction are also considered candidates for CSII (39). It is worthy to point that most CYP with type 1 diabetes in the T1D Exchange Clinic Registry did not meet the targets for HbA1c suggested by diabetes medical societies clinical guidelines (8). Additionally, the International Society for Pediatric and Adolescent Diabetes on its latest guidelines was flexible to distinguish individual's glycemic target according to the access or not to advanced insulin

delivery technology (97). Our results, however, show that there is still insufficient evidence to recommend using the CSII without CGM integrated system based on a clinically relevant improvement in glycemic outcomes or HRQoL. Thus, in principle, recommendation for using CSII without the integration of CGM systems seems to be mostly based on patients' or family's preference.

Our study has two main limitations. First, information on glycemic outcomes beyond HbA_{1c} could not be retrieved; this is important because newest devices with automated insulin delivery add more information on glycemic variability by measuring TIR, which is considered the best predictor of short- and long-term clinical complications for people living with type 1 diabetes (27). However, TIR is preferably measured with CGM systems, which was not widely used in the studies reviewed, and makes it a promising outcome to be assessed in future reviews. Second, newest CSII with closed-loop systems have also been used very recently, and they have been shown to be safe for pediatric use (39,70); however, we did not include them in our review because studies on the close-loop pumps compare them against CSII only, without considering MDI therapy, and our main focus was the form of insulin delivery.

4.5 Conclusion

As conclusion, we found moderate-level evidence that the CSII, without integration of CGM systems, modestly lower HbA_{1c} when compared with MDI. More evidence is needed on the effect of the CSII *vs* MDI on other important glycemic outcomes and HRQoL. Future research on diabetes technology assessment should include individual and area-level socioeconomic information to enable a full equity-oriented analysis of the effectiveness of the CSII in CYP.

Table 1. Quality of evidence (GRADE approach) on the effect of the continuous subcutaneous insulin infusion (CSII) vs multiple-daily injections (MDI) of insulin on glycemic outcomes and health-related quality of life, in randomized controlled trials and non-randomized studies

Quality of evidence							Number of patients		Effect		Overall level of evidence
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	CSII	MDI	Relative (95% CI)	Absolute (95% CI)	
Glycated hemoglobin											
16	randomized trials	serious [a]	not serious [b] (I^2: 34%)	not serious	not serious	no evidence	489	493	-	MD **0.22%** (0.33 to 0.11) **lower**	⊕⊕⊕◯ MODERATE
64	non-randomized studies	very serious [c]	not serious [b] (I^2:99%)	not serious	not serious	no evidence	53033	72180	-	MD **0.45%** (0.52 to 0.38) **lower**	⊕◯◯◯ INSUFFICIENT †
Severe hypoglycemia											
12	randomized trials	serious [a]	not serious (I^2: 0%)	not serious	serious [d]	no evidence	508	485	Rate ratio **0.87** (0.55 to 1.37)	**-**	⊕⊕◯◯ LOW
38	non-randomized studies	very serious [c]	not serious [e] (I^2:57%)	not serious	not serious	no evidence	32148	38056	Rate ratio **0.71** (0.63 to 0.81)	**-**	⊕◯◯◯ INSUFFICIENT †
Diabetic ketoacidosis											
8	randomized trials	not serious	not serious (I^2: 0%)	not serious	serious [d]	no evidence	405	385	Risk Ratio **1.29** (0.62 to 2.69)	**-**	⊕⊕⊕◯ MODERATE
28	non-randomized studies	very serious [c]	serious [f] (I^2: 63%)	not serious	serious [d]	no evidence	22135	23264	Risk Ratio **0.98** (0.75 to 1.29)	**-**	⊕◯◯◯ INSUFFICIENT †

(Continued)

% of Time in target (TIR), below (TBR) and above (TAR) the glucose range											
2	randomized trials	very serious [a]	not serious (I^2:0%)	not serious	serious [d]	no evidence	34	14	-	**TIR:** MD **5.21%** (-2.04 to 12.46) **higher** **TBR:** MD **- 1.81%** (-6.33 to 2.72) **higher** **TAR:** MD **- 3.88** (-13.92 to 6.16) **higher**	⊕◯◯◯ INSUFFICIENT
Health-related quality of life											
4	randomized trials	serious [g]	serious (I^2:29%) [h]	not serious	not serious	no evidence	106	111	-	SMD **0.42** (0.07 to 0.76) **higher**	⊕◯◯◯ INSUFFICIENT
3	non-randomized studies	very serious [c]	serious (I^2:33%)	not serious	not serious	no evidence	290	409	-	SMD **0.35** (0.15 to 0.55) **higher**	⊕◯◯◯ INSUFFICIENT †

CI: Confidence interval; MD: Mean difference; SMD: Standardized mean difference; TIR: Time in range; TBR: Time below range; TAR: Time above range

† In NRS, evidence started as low quality. a. Lack of transparency of randomization, and selection bias; b. There is statistically significant heterogeneity in effect size, but most effect estimates suggest lower or similar glycated hemoglobin on CSII vs MDI; c. Due to potential residual confounding bias; d. The confidence interval is wide; e. There is statistically significant heterogeneity in effect size, but most effect estimates suggest fewer or similar severe hypoglycemia episodes on CSII vs MDI; f. Effect estimates do not have the same direction; g. Detection bias found in health-related quality of life outcome; h. There is moderate statistically significant heterogeneity in effect size and effects are not clinically relevant.

Table 2: Studies reporting PROGRESS (equity) factors and examples of terminologies used across studies. Values are presented as % and (number of studies).

PROGRESS Framework	PROGRESS factors				
	Report data	**Advantaged groups**	**Examples of terminologies**	**Disadvantaged groups**	**Examples of terminologies**
Place of Residence [a]	100% (99)	High-income countries 96% (95)	USA and Canada EU countries United Kingdom Israel Australia Japan Saudi Arabia Qatar	Low-to-middle-income countries 4% (4)	China Brazil Turkey
Race, ethnicity, culture, and language [b]	38% (38)	Majorities 6% (6)	Only majority group (100% sharing the same origin and background). Only Caucasians. Only White. Only families that fully speak/read the national language.	Minorities 32% (32)	Immigrants. Different social aspects including Black, African-American, Hispanic, Latino, Asian-British, Indian, Pakistani, Mixed population.
Occupation [c]	20% (20)	Better parental occupation and/or higher state assistance 17% (17)	Universal health insurance. State assistance. Donation or non-profit organization. Employee-funded insurance system. Fully costed by families. Fully private insurance	Worst parental occupation and/or unprivileged state assistance 3% (3)	Area deprivation score without health assistance. Number of caregivers
Sex [d]	97% (96)	More than 10% of difference between sexes 53% (53)	Unbalanced prescription between sexes	Less than 10% of difference between sexes 43% (43)	Balanced prescription between sexes

Religion [e]	1% (1)	Majority religious groups (0)	Not available	Minority religious group 1% (1)	Religion affiliation was accounted: Jewish and Bedouin
Education [f]	12% (12)	Higher educational level 1% (1)	Only higher education level	Lower educational level 11% (11)	Less than High School. Lower education level. Different levels of parental education. Lower deprivation score area with lower education
Socioeconomic Status (SES) [g]	26% (26)	Higher SES 1% (1)	Families that fully provide treatment	Lower SES 25% (25)	Lower SES accounted/inferred. Deprivation score/index/quintiles including lower SES groups. Annual household income including lower SES group. Hollingshead Four-factor Index of Social Status
Social Capital [h]	4% (4)	Wider set of relationships 3% (3)	Individuals that participated in a diabetes camp	No social relationships 1% (1)	Individuals without a systematic diabetes education program

a. Country where individuals reside (as per the World Bank database) (44); b. Self-identification racial or ethnic group, or different culture and language, including nationality status (32,91); c. Patterns of work that provide proper maintenance of treatment or attain better state assistance (44,91); d. Biological identification of boys and girls between groups (98,99); e. Mention of religious affiliation of spiritual beliefs or values (100); f. Assessment of informed educational level or approximation by health literacy and numeracy (89,101); g. Acquisition of information considering access to resources and privilege (32,89,90,101,102); h. Information from benefits obtained by individuals due to their social relationships, e.g.: to be member of a diabetes foundation, to participate in diabetes camp (99).

Table 3: Significant glycemic outcomes and their effects (improvement vs worsening) when using the continuous subcutaneous insulin infusion across studies assessed with the PROGRESS framework (number of studies) [a]

	HbA_{1c}	SH	DKA	TIR, TAR, TBR	HRQoL
Place of Residence	(91)	(60)	(50)	(4)	(26)
Advantaged group	55 vs 1	19 vs 3	9 vs 2	1 vs 0	15 vs 1
Disadvantaged group	1 vs 0	1 vs 0	0	No ob.	No ob.
Race, ethnicity, culture, and language	(33)	(18)	(17)	(2)	(10)
Advantaged group	4 vs 0	2 vs 1	0	No ob.	3 vs 0
Disadvantaged group	22 vs 0	3 vs 1	4 vs 0	0	3 vs 0
Occupation	(19)	(7)	(7)		(2)
Advantaged group	2 vs 0	0	0	No ob.	No ob.
Disadvantaged group	15 vs 0	5 vs 0	2 vs 0	No ob.	2 vs 0
Sex	(90)	(60)	(50)	(4)	(26)
Advantaged group	32 vs 0	8 vs 1	5 vs 1	1 vs 0	7 vs 0
Disadvantaged group	22 vs 1	11 vs 2	4 vs 1	0	8 vs 1
Religion					
Advantaged group	No ob.	No ob.	No ob.	No ob.	No ob.
Disadvantaged group	No ob.	No ob.	No ob.	No ob.	No ob.
Education	(11)	(5)	(5)		(3)
Advantaged group	No ob.	0	0	No ob.	0
Disadvantaged group	10 vs 0	1 vs 0	2 vs 0	No ob.	2 vs 0
SES	(26)	(11)	(11)		(3)
Advantaged group	1 vs 0	No ob.	No ob.	No ob.	No ob.
Disadvantaged group	17 vs 0	1 vs 0	2 vs 0	No ob.	1 vs 0
Social Capital	(3)	(1)	(1)		(3)
Advantaged group	2 vs 0	No ob.	No ob.	No ob.	1 vs 1
Disadvantaged group	1 vs 0	1 vs 0	1 vs 0	No ob.	No ob.

HbA_{1c}: glycated hemoglobin; SH: severe hypoglycemia; DKA: diabetic ketoacidosis; TIR: time in range: TAR: time above range; TBR: time below range; HRQoL: health-related quality of life; SES: Socioeconomic status; No ob.: no observations

a. Represent the total number of studies that assessed any of the glycemic outcomes according to different PROGRESS variables.

Figure 1: Flow of studies across the review

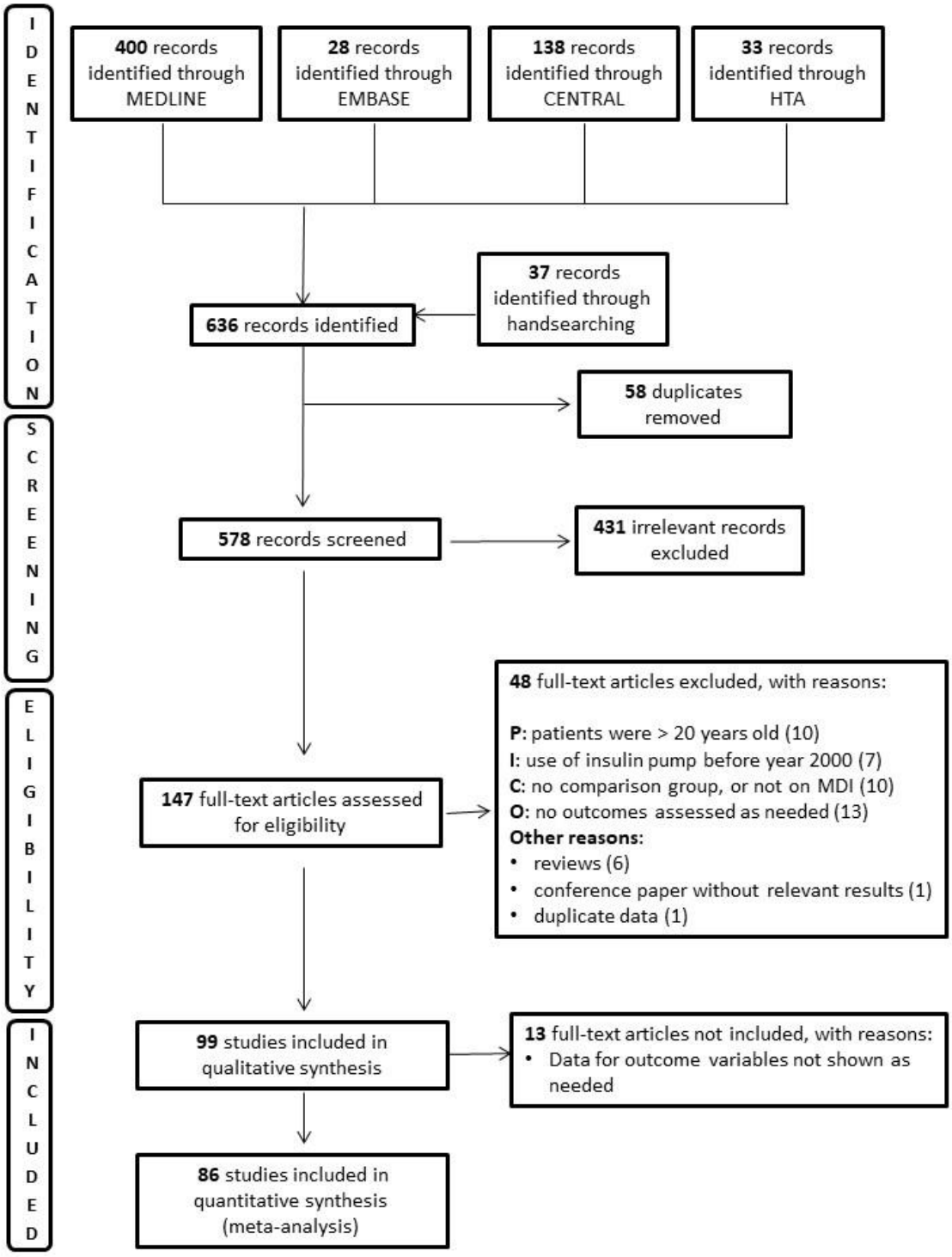
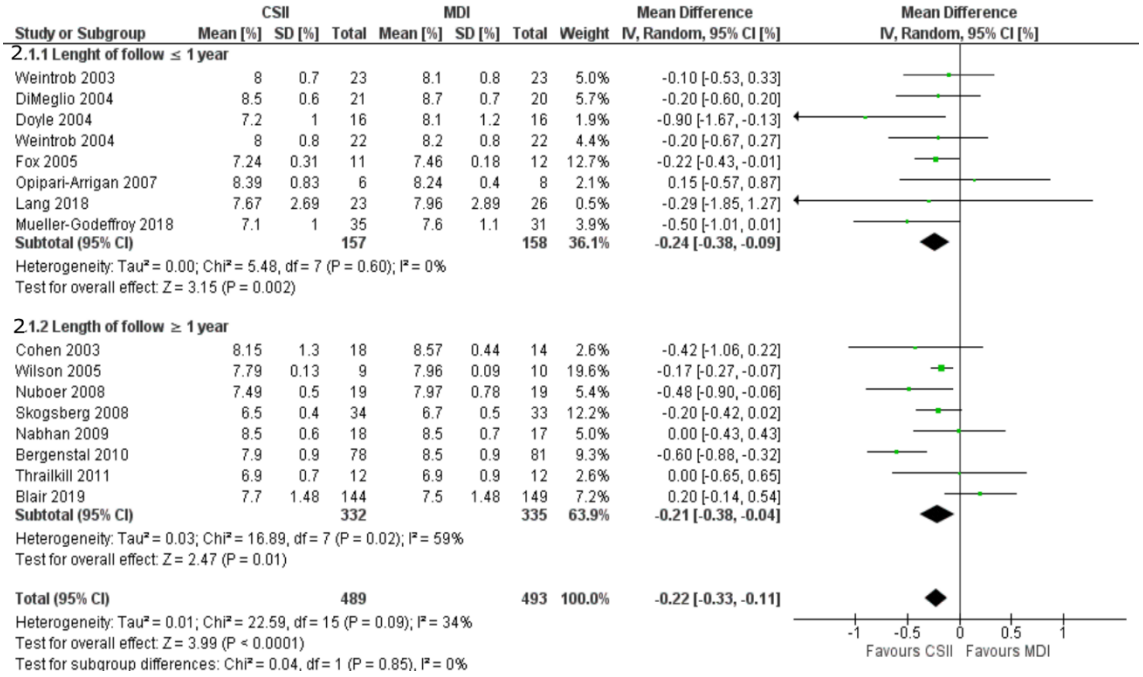
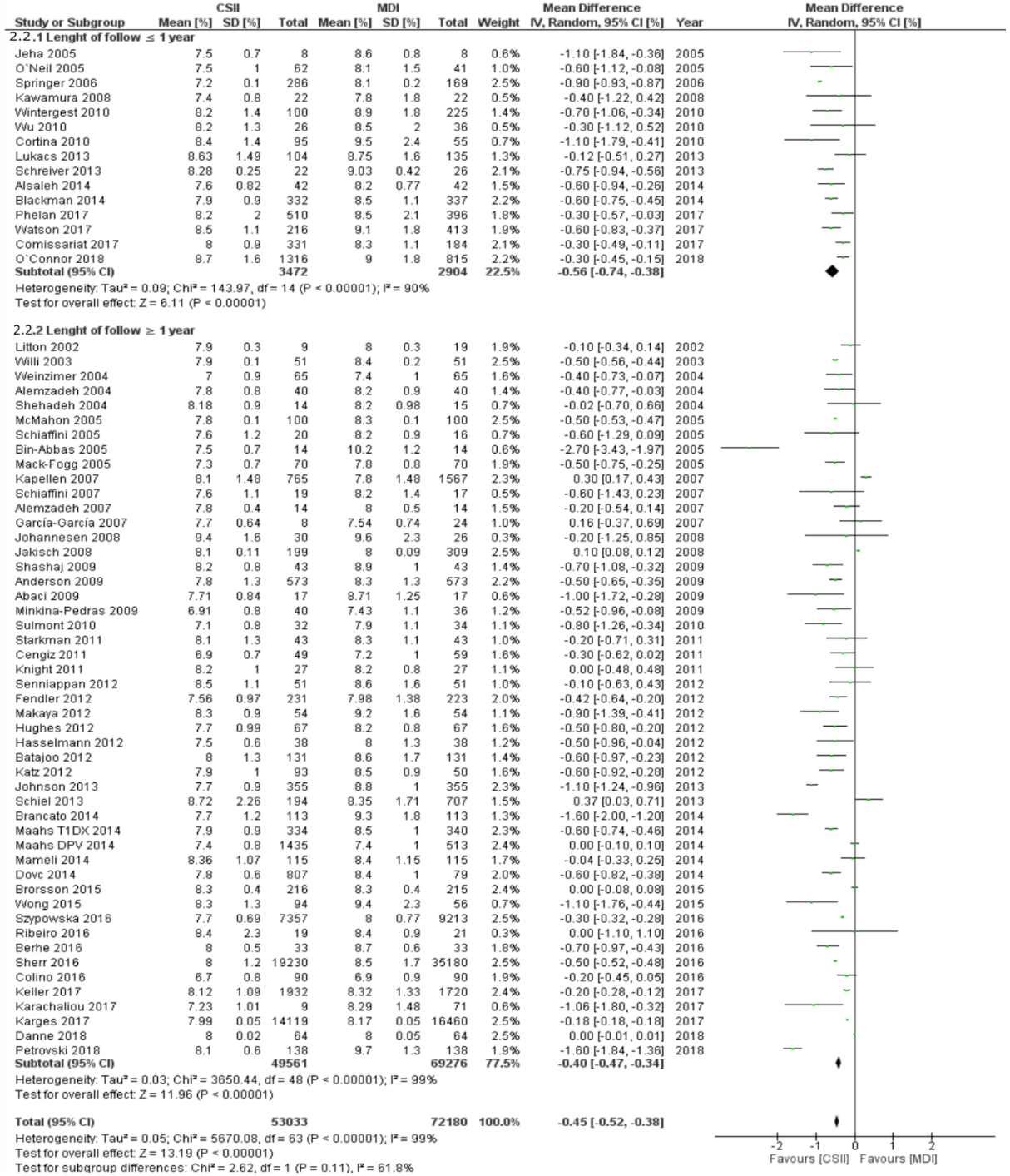


Figure 2. Forest plot comparing the effect of continuous subcutaneous insulin infusion (CSII) *versus* multiple-daily injections of insulin (MDI) on glycated hemoglobin (HbA_{1c}) in randomized controlled trials (RCT) (2.1) and in non-randomized studies (NRS) (2.2). Results are broken down by length of follow-up (2.1 and 2.2), and by type of NRS (2.3).

2.1: Randomized trials. Mean difference of HbA_{1c} (%)



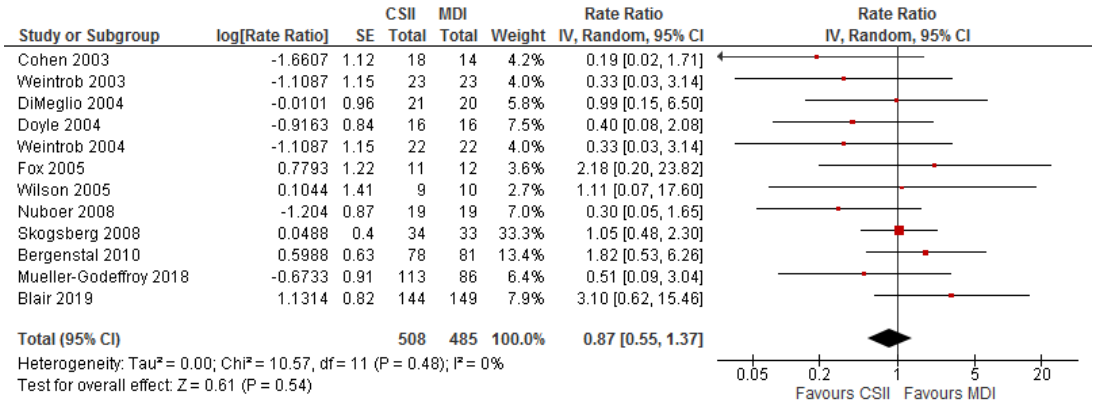
2.2: Non-randomized studies. Mean difference of HbA1c (%)



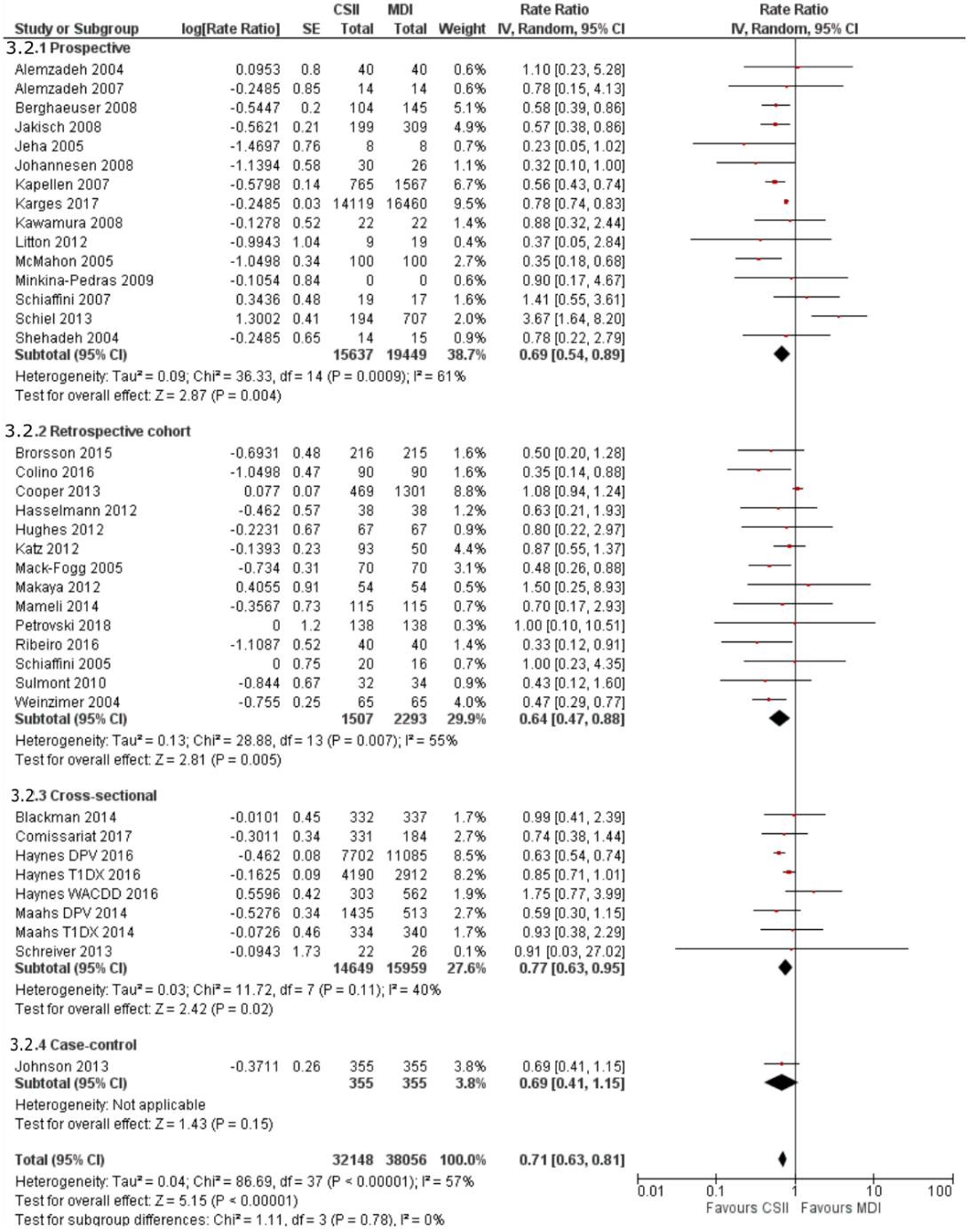
SD: standard deviation; IV: inverse variance; CI: Confidence interval; MD: Mean difference.

Figure 3. Forest plot comparing the effect of continuous subcutaneous insulin infusion (CSII) *versus* multiple-daily injections of insulin (MDI) on severe hypoglycemia (SH) in randomized controlled trials (RCT) (3.1) and in non-randomized studies (NRS) (3.2). Results in NRS are broken down by type of study.

3.1: Randomized trials. Incidence rate ratio of severe hypoglycemia



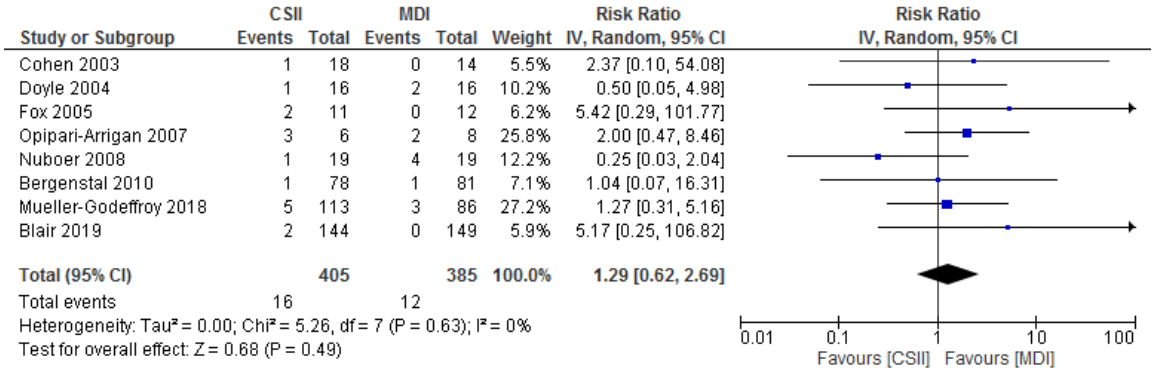
3.2: Non-randomized studies. Incidence rate ratio of severe hypoglycemia



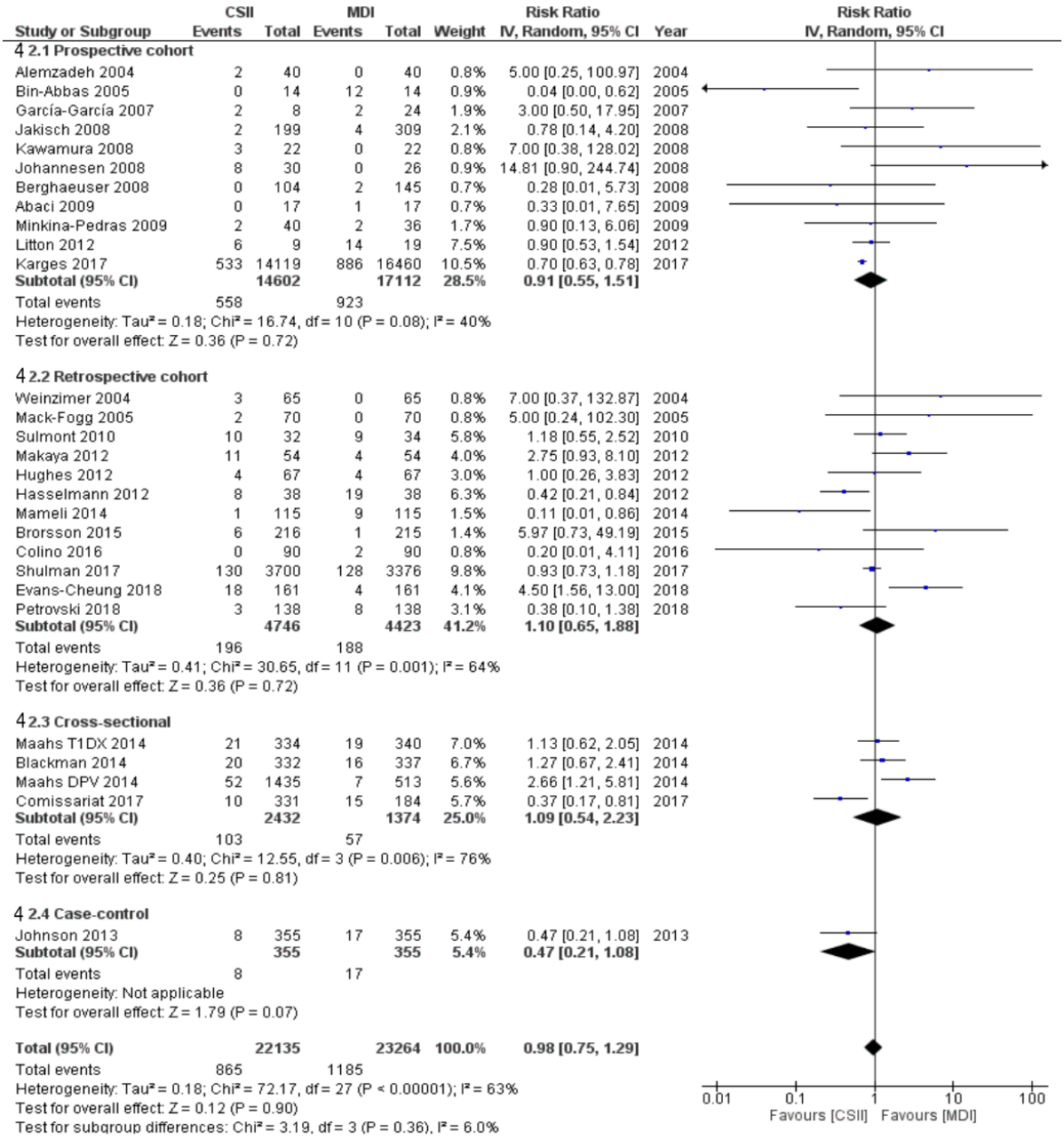
IV: inverse variance; CI: Confidence interval

Figure 4. Forest plot comparing the effect of continuous subcutaneous insulin infusion (CSII) *versus* multiple-daily injections of insulin (MDI) on diabetic ketoacidosis (DKA) in randomized controlled trials (RCT) (4.1) and in non-randomized studies (NRS) (4.2). Results in NRS are broken down by type of study.

4.1: Randomized trials. Risk ratio of diabetic ketoacidosis



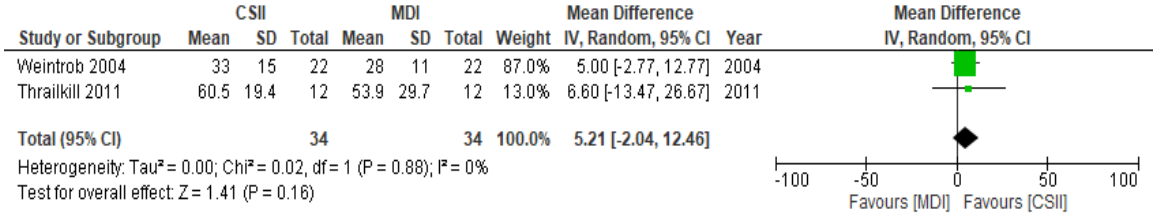
4.2: Non-randomized studies. Risk ratio of diabetic ketoacidosis



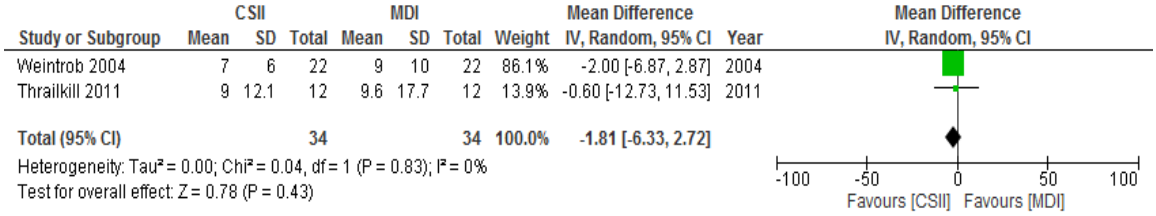
IV: inverse variance; CI: Confidence interval

Figure 5. Forest plot comparing the effect of continuous subcutaneous insulin infusion (CSII) *versus* multiple-daily injections of insulin (MDI) on the time spent in target glucose range (5.1), below range (5.2) and above range (5.3) in randomized controlled trials (RCT).

5.1: Time in target glucose range. Mean difference of % time



5.2: Time below target glucose range. Mean difference of % time



5.3: Time above target glucose range. Mean difference of % time

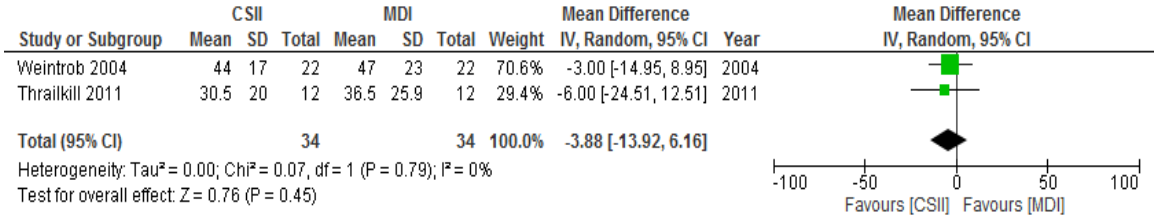
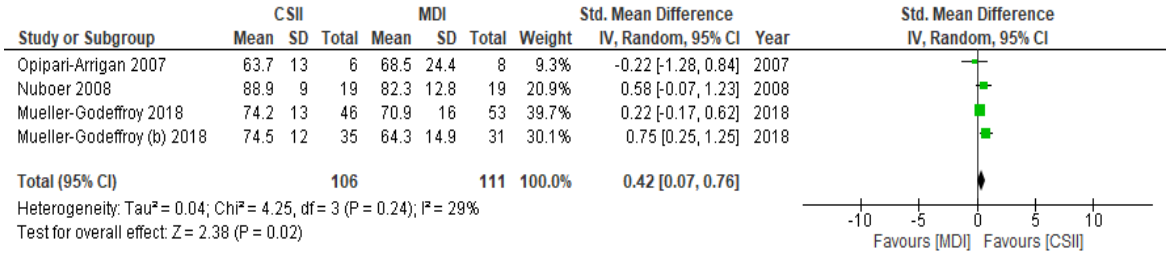


Figure 6. Forest plot comparing the effect of continuous subcutaneous insulin infusion (CSII) *versus* multiple-daily injections of insulin (MDI) on health-related quality of life (HRQoL) in randomized controlled trials (RCT) (6.1) and in non-randomized studies (NRS) (6.2)

6.1: Randomized trials. HRQoL standardized mean difference (%)



6.2: Non-randomized studies. HRQoL standardized mean difference (%)

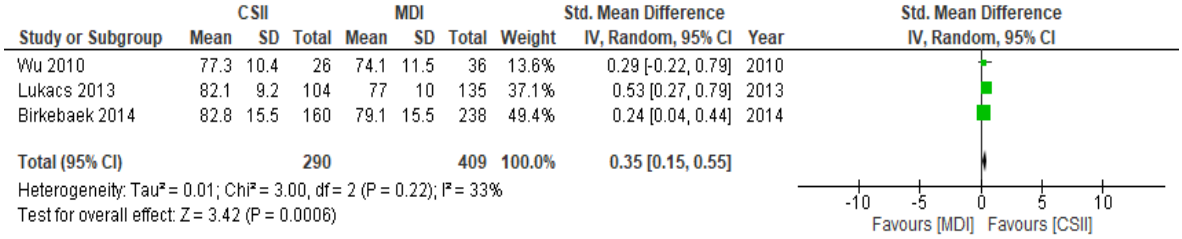


Table S1: Characteristics of the studies included in this review.

Authors, year of publication, reference	Reference
Study design / registration number / Funding/Year of data collection	Design
Country or region	Country
Number of patients assigned and that received each treatment (CSII:MDI); Sex (M:F); Age; Baseline characteristics including duration of T1D, HbA_{1c} [mean % (SD)] and HRQoL assessment tool; Other definition or comment	N and clinical characteristics
Community/ clinic based research	Setting
Continuous subcutaneous insulin infusion (CSII), including the use of adjunctive glucose monitor: model of device and insulin	Type of diabetes-related technology
Multiple daily insulin injections (MDI): injections and insulins	Type of conventional treatment comparator
A. Place of residence B. Race, ethnicity, culture and language C. Occupation D. Sex E. Religion F. Education G. Socioeconomic status H. Social capital	Inequality assessed at baseline
1. Glycated hemoglobin (HbA1c) at the end of the study: CSII vs. MDI [mean % (SD)], sig 2. Number of severe hypoglycemic (SH) episodes: CSII vs. MDI, sig 3. Number of patients with ≥ 1 diabetes ketoacidosis (DKA) episode: CSII vs. MDI, sig 4. Glycemic variability (GV): % of time in range (TIR), hypo and/or hyperglycemia: CSII vs. MDI, sig 5. HRQoL comparisons between CSII vs. MDI, sig	Outcomes
Time of follow-up	Follow-up

Cohen, 2003, (103)	Randomized cross-over trial; Supported by Tayco Diagnostica (1981) Ltd.; Year of data collection not informed.	Israel	16 (18:14) (6:10) 14.5-17.9 years HbA1c,%: CSII 8.58 (0.82) vs. MDI 8.48 (1.4) Tool: Diabetes Treatment Satisfaction Questionnaire (DTSQ) and the satisfaction subscale of the Diabetes Quality of Life Questionnaire (DQOLY) - At least 2 years duration, low C-peptide secretion (<0.6 ng/ml) and no other chronic disease. Excluded patients unable to detect hypoglycemia, with microvascular complication, or other significant disorder; Hypoglycemia was mild diurnal and nocturnal, or severe, events.	Ambulatory	Tayco, Disetronic, Burgdorf, Switzerland with short-acting analog insulin (Humalog®, Eli Lilly)	NPH and regular insulin before breakfast, regular insulin only before lunch and dinner, and NPH only at bedtime.	A. Israel B. NR C. NR D. F>M E. NR F. NR G. NR H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 8.15 (1.3) vs. 8.57 (0.44), NS **2. Number of SH episodes: CSII vs. MDI, sig:** 1 vs. 4, NS **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** 1 vs. 0, NS **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** Significant better satisfaction in CSII treatment. Overall HRQoL data NR.	1 year
Weintrob, 2003,(104)	Open randomized crossover trial. Supported by Minimed/ Agentek (1987) Ltd; 2002	Israel	46 (23:23) (10:13) 9.4-13.9 years Mean HbA1c: CSII 8.0 (1.1) % vs MDI 8.3 (0.7) % T1D duration: at least 2 years Tool: Diabetes Treatment Satisfaction Questionnaire (DTSQ) and the satisfaction subscale of the Diabetes Quality of Life Questionnaire for Youth (DQOLY). Participation was offered on a consecutive basis; of the 258 patients aged 9 to 14 years in the institute eligible for the study, the first 24 who expressed a desire to be included were enrolled. Crossover: 3.5 months of CSII to 3.5 months of MDI therapy, with a 2-week washout;	Ambulatory	Programmable external pump (MiniMed 508; MiniMed, Sylmar, CA) using lispro (Humalog; Eli Lilli).	Combined neutral protamine hagedorn (NPH) and regular insulin before breakfast, regular insulin before lunch and supper, and NPH at bedtime	A. Israel B. NR C. NR D. M=10, F =13 E. NR F. NR G. NR H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 8.0 (0.7) vs 8.1 (0.8), p=0.03 **2. Number of SH episodes: CSII vs. MDI, sig:** 1 vs. 3, NS **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** Zero vs zero, NS **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** Overall HRQoL scores NR. Significant difference between treatment groups in treatment satisfaction. There were no differences between treatment groups for any of the DQOLY subscales. Data	8 months

			Hypoglycemia was defined as mild and severe events.						
DiMeglio, 2004,(47)	Randomized trial; From Nov 1999 to April 2003	USA	42 (21:20) (17:25) < 5 years of age Diagnosis for > 12 months HbA1c: CSII 8.8 (0.6) vs MDI 8.8 (0.7) Patients on CSII received differentiated education One patient randomized to MDI dropped out before the baseline visit; Hypoglycemia was defined as severe events (with seizures).	Ambulatory	MiniMed 508 (Medtronic MiniMed, Northridge, Calif) with lispro insulin (Humalog, Eli Lilly, Indianapolis, Ind)	All were using lispro insulin as their short-acting insulin, 13 used neutral protamine Hagedorn (NPH) as their long-acting insulin, 4 used Lente, and 3 used ultralente.	A. Indiana, USA B. NR C. NR D. M=17, F=25 E. NR F. NR G. NR H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 8.5 (0.6) vs. 8.7 (0.7), NS **2. Number of SH episodes: CSII vs. MDI, sig:** 2.2 vs. 2.1, NS **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** 0 vs.0, NS **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** Assessed with SMBG **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	6 months
Doyle, 2004,(105)	Randomized trial Year of data collection not informed. Founding: Medtronic Minimed. Suppliers provided by Aventis Phramaceuticals, Novo Nordski Pharmaceuticals and LifeScan.	USA	32 (16:16) (14:18) Mean age, years: CSII 12.5±3.2 and MDI 13±2.8 HbA1c: CSII 8.1 (1.2) vs. 8.2 (1.1) Tool: Diabetes Quality of Life-Youth (DQOL-Y) for 8 patients in each group. Treated with insulin for at least 6 months; naïve to CSII and glargine; Hypoglycemia was defined as severe events.	Ambulatory	Medtronic MiniMed 508 or Paradigm 511 pumps with insulin aspart	Once-daily glargine and premeal/ snack insulin aspart	A. Connecticut, USA B. Differences between White, Hispanic and black C. NR D. M=14, F=18 E. NR F. NR G. NR H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 7.2 (1.0) vs 8.1 (1.2), <0.05 **2. Number of SH episodes: CSII vs. MDI, sig:** 2 vs. 5, NS **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** 1 vs 2, NS **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** No significant differences between groups – Data NR.	16 weeks

Weintrob, 2004, (106)	Randomized crossover study; Supported by MiniMed and Agentek, Tel Aviv; Enrollment: NR; Publication year: 2004	Israel	23 (22:22); (10:13); Median age:11.9 years (range 9 ¼ to 13 3/4); Median duration of diabetes: 6.0 years (range 2 ½ to 11 years); Mean HbA1c %: 8.9±1.0; CGMS was worn for 72 hours each time (1 month after entering in the study and at the end) Inclusion criteria were age 8 to 14 years, treatment with insulin for at least 2 years, C-peptide <0.6 ng/mL and absence of other health problems; Hypoglycemia was defined as blood glucose <70 mg/dL.	Ambulatory	MiniMed 508; Insulin Lispro	Combined NPH and regular insulin before breakfast, regular insulin before lunch and supper, and NPH at bedtime	A. Israel B. NR C. NR D. 10 boys and 13 girls E. NR F. NR G. NR H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 8.0 (0.8) vs. 8.2 (0.8), NS **2. Number of SH episodes: CSII vs. MDI, sig:** 1 vs. 3, NS **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** Zero vs. zero, NA **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** - TIR, %: 33 (15) vs. 28 (11), NS - Hypo, %: 7 (6) vs. 9 (10), NS - Hyper, %: 44 (17) vs. 47 (23), NS **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	7 ½ months
Fox, 2005,(42)	Randomized trial From Jan 2001 to Sep 2003.	USA	23 (11:12) (13:9) 1- 6 years old Diabetes duration (months): CSII 15.3 ±3.4 vs MDI 19.7±4.1 HbA1c, %: CSII 7.4 (0.5) vs MDI 7.6 (0.3) At least 6 months of diagnosis Hypoglycemia was defined as mild/moderate (blood glucose below 70 mg/dL).	Ambulatory	Medtronic MiniMed 508	Two or three shots per day using NPH insulin and rapid-acting analog	A. Florida, USA B. NR C. NR D. M=13, F=9 E. NR F. NR G. NR H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 7.24 (0.31) vs. 7.46 (0.18), NS **2. Number of SH episodes: CSII vs. MDI, sig:** 2 vs. 1, NS **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** 2 vs 0, NS **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	6 months
Wilson, 2005, (107)	Randomized open-label feasibility trial Supported by the Lucile Packard Foundation for Children's Health, Medtronic	California, USA	19 (9:10); (7:12); Mean Age: 3.6 (±1.0) years; For all groups HbA1c, %: 8.0 (0.8); Duration of diabetes: 1.4y; Tool: Diabetes Quality of Life (DQOL) questionnaire for parents of toddlers: CSII: 2.3±0.3 vs. MDI 2.3±0.6 Continuous glucose monitoring profiles were obtained using the continuous glucose monitoring	Ambulatory	Medtronic MiniMed 508 pump with diluted lispro insulin	Not specified	A. California, USA B. NR C. NR D. M=7, F=12 E. NR F. Parental education: 15.7 ±2.8 years (range 8.5–22) G. NR H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** Estimated: 7.79 (0.13) vs 7.96 (0.09), NS **2. Number of SH episodes: CSII vs. MDI, sig:** 1 vs 1, NS **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** Zero vs zero, NS **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** Absolute data not shown. **5. HRQoL comparisons between CSII vs. MDI, sig:** Δ CSII: -0.24±0.25 vs Δ MDI -0.8±0.19, p=0.03	1 year

	MiniMed, Abbott, the Precision Xtra by MediSense; Enrollment started in May 2001		system (CGMS), (Medtronic MiniMed).				Differences between groups were not significant.	
Opipari-Arrigan, 2007, (108)	Randomized controlled trial; Enrollments in 2002 and 2003	USA	16 (8:8), 14 (6:8) completed the study; (9:7); Mean age: 4.4 ±0.7 years; HbA1c %: CSII 8.26 (1.37) vs. MDI 7.98 (0.76); Tools: Pediatric Quality of Life Inventory (PedsQL), Diabetes Module (PEDSQL 3.0) - diabetes symptoms: CSII 55.7±10.4 vs. 62.0±21.8 At least 1 year of T1D; Hypoglycemia was defined as severe episodes.	Ambulatory	Animas infusion pump (Animas Corporation, West Chester, PA, USA); Insulin not specified	One child: NPH, regular and lispro and changed to NPH and lispro. One child switched from NPH and lispro to glargine and lispro The remaining received NPH and lispro insulin	A. All from USA B. 100% Caucasian C. NR D. 9 boys and 7 girls E. NR F. NR G. randomization not based on SES H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 8.39 (0.83) vs. 8.24 (0.4), NS **2. Number of SH episodes: CSII vs. MDI, sig:** 0 vs. 25, NS **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** 3 vs. 2, NS **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** - TIR, %: 32 vs. 34.3, NS - Hypo, %: 6.3 vs. 5.8, NS - Hyper, %: 61.7 vs. 60, NS **5. HRQoL comparisons between CSII vs. MDI, sig:** - Diabetes symptom: CSII 63.7±13.0 vs. MDI 68.5±24.4, p<0.05	6 months
Nuboer, 2008, (109)	Open-label, Randomized, prospective parallel study preceded by a run-in phase; Publication year: 2008	Netherlands	38 (19:19); (17:21); Mean age: 10y; HbA1c (after run in): CSII: 7.66 (0.56) vs. MDI: 7.98 (0.57); Duration in years: CSII 5.6±3.3 and MDI 4.7±2.9 years; Tool: Pediatric Quality of Life Inventory (PedsQL 4.0) in parents and in children – baseline CSII in children: 79.4±11.3 vs. MDI 79.2±9.5 Inclusion criteria: T1D, daily insulin administration for 1 yr or longer, random C-peptide < 200 pmol, HbA1c > 8.0%, a history	Ambulatory	H-tron Disetronic insulin pump (Roche, Switzerland); Insulin aspart	Insulins aspart, regular, NPH and glargine.	A: The Netherlands B: 90% Caucasians C: five children were recipients of state medical assistance (3 on CSII) D: 17 boys and 21 girls E: NR F: NR G: NR H: NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 7.49 (0.50) vs. 7.97 (0.78), p<0.05 **2. Number of SH episodes: CSII vs. MDI, sig:** 2 vs. 4, p<0.05 **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** 1 vs 4, NS **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** 88.8±9.0 vs. 82.3±12.8, NS After completion of the randomization, all children were on CSII by preference with both PEDsQL scores maintaining a higher score from the baseline.	14 months

			of repeated symptomatic hypoglycemias, age 4-16 years, and attendance of a regular school; Hypoglycemia was considered as severe episodes.						
Skogsberg, 2008, (110)	Open, randomized, parallel, multicenter trial Supported by R+D Center, county of Gävleborg`, Sweden, 'The Swedish Children`s Diabetes Foundation', Novo Nordisk, and Roche Diagnostics. From December 2001 to April 2004	Sweden	72 (34:33) 67 (34:33) completed the whole study (42:30) 7–17 yr of age; Age at start for CSII (11.8y) and for MDI (12.3y) Time of diagnosis: CSII 12.2 ±2.0 days and MDI 10.4 ± 1.7 d HbA1c: CSII 8.2 (0.4) vs. MDI 8.4 (0.5) 45 pubertal, 27 prepubertal. Tool: All patients completed the Diabetes Treatment Satisfaction Questionnaire (DTSQ). Hypoglycemia was defined as the perceived episodes.	Ambulatory	H-Tron (Roche, Burgdorf, Switzerland) Insulin aspart (NovoRapid; Novo Nordisk)	Pen: Natural protamine hagedorn [NPH] insulin twice daily and rapid-acting insulin, aspart, three to –four times daily	A. Sweden B. NR C. NR D. M=42, F=30 E. NR F. NR G. NR H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 6.5 (0.4) vs. 6.7 (0.5), NS **2. Number of SH episodes: CSII vs. MDI, sig:** 13 vs. 12, NS **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** Zero vs zero, NS **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** Data for overall DTSQ NR in scores. Treatment satisfaction was found to be significantly higher in CSII group.	24 months
Nabhan, 2009, (111)	Randomized Prospective Study; Enrollment from Nov 1999 to Nov 2003	USA	35 (18:17); (17:18); Mean age: 3.7±0.8y; Duration of T1D: 1.6±0.6y; Mean HbA1c: 8.9±0.6%; Tool: Parenting Stress Index (PSI) and Child Behavior Checklist (CBCL). Children < 5 years of age with a history of T1DM for at least 12	Ambulatory	Not specified	Not specified	A. USA B. NR C. NR D. boys 17, girls 18 E: NR F: NR G: NR H: NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 8.5 (0.6) vs. 8.5(0.7), NS **2. Number of SH episodes: CSII vs. MDI, sig:** NA **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NA **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA	12 months

			months; The study was originally planned as a randomized crossover study, but was changed to allow families who started on CSII the choice to remain on pump therapy.				**5. HRQoL comparisons between CSII vs. MDI, sig:** No HRQoL data.	
Bergenstal, 2010, (112)	Multicenter randomized trial (STAR3); Novo Nordisk, LifeScan, Bayer, and Becton Dickinson. The manuscript was written with the aid of the sponsor. Randomization from Jan 2007 to Dec 2008	30 diabetes centers in USA and Canada	156 children (78:81); (87:69); Age: 7-18 years (CSII: 11.7±3.0 y; MDI: 12.7±3.1 y); HbA1c: CSII: 8.3±0.6%; MDI: 8.3±0.5%; Eligibility: between the ages of 7-70 years, received multiple daily injections during the previous 3 months, had HbA1c 7.4-9.5%, and had been under the care of the principal investigator for at least 6 months. Hypoglycemia was defined as an episode requiring assistance and confirmed by documentation of a value ≤ 70 mg/dl.	Ambulatory	MiniMed Paradigm REAL-time System, Medtronic; Insulin aspart	Insulin glargine (Lantus, Sanofi-Aventis) and insulin aspart.	A. USA B. Hispanic, White and other C. with intent to differentiate between student and employed (did not assess parent employment status) D. CSII: 59% male; MDI: 53% male E. NR F. NR G. NR H.NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 7.9 (0.9) vs. 8.5 (0.9), p<0.001 **2. Number of SH episodes: CSII vs. MDI, sig:** 7 vs. 4, NS **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** 1 vs. 1, NS **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	1 year
Bergenstal, 2011, (113)	Randomized clinical trial (STAR3); Supported by Medtronic, Novo Nordisk and LifeScan and Becton Dickinson	30 diabetes center in USA and	128 pediatric patients (65:63); Sex: not reported; Age: pediatric patients ranged from ages 7-18 years; Mean Hb1Ac: : 8.3%; This is a study to examine the effects of crossing over from MDI therapy to sensor-augmented pump (SAP) for 6 months and the effects of 18 months´ sustained use of SAP. Pediatric subjects were an arm of the study.	Ambulatory	SAP (Paradigm REAL-Time System, Medtronic MiniMed) with insulin aspart	Insulins aspart and glargine.	A. USA and Canada B. Hispanic, White and other C. NR D. NR E. NR F. NR G. NR H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 8.1 vs. 8.3, p<0.05 **2. Number of SH episodes: CSII vs. MDI, sig:** Not specified within the pediatric arm **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** Not specified within the pediatric arm **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	18 months

	Published in 2011							
Thrailkill, 2011, (114)	Prospective, randomized, pilot trial Enrollment between April 2005 and Feb 2009	USA	12 (12:12), comprehensive data available for 19 subjects; (11:13); Mean age: 12.1 y (8-18 years old); HbA1c %: CSII 11.2 (2.1) vs. MDI 11.7 (2.6); Tool: self-report questionnaire assessing participant satisfaction with the assigned treatment. Continuous glucose monitoring system (CGSM) was used to obtain 72h-period to compare GV between treatments. Newly diagnosed T1D, without history of DKA; Hypoglycemia was assessed as life-threatening condition (loss of consciousness or seizures)	Ambulatory	Pump model: IR 1250 (Animas Corp., West Chester, PA, USA); Insulin: aspart and lispro	Glargine and aspart; NPH and aspart.	A. USA B. 75% non-Hispanic white on pump and 97.7% non-Hispanic white on MDI C. children recipients of state medical assistance D. 58.3% female on pump and 50% female on MDI E. NR F. NR G. NR H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 6.9 (0.7) vs. 6.9 (0.9), NS **2. Number of SH episodes: CSII vs. MDI, sig:** 0 vs. 0, NS **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** Zero vs. zero, NA **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** - TIR, %: 60.5 (19.4) vs. 53.9 (29.7), NS - Hypo, %: 9.0 (12.1) vs. 9.6 (17.7), NS - Hyper, %: 30.5 (20) vs. 36.5 (25.9), NS **5. HRQoL comparisons between CSII vs. MDI, sig:** HRQoL data NR. Significant difference between treatments regarding treatment satisfaction.	12 months
Rubin, 2012, (115)	STAR 3 is a randomized 12-minth clinical trial. Funded by Medtronic MiniMed. Enrolled from Jan 2007 to Dec 2008	USA and Canada	Pediatric group: 147 (77:70) 56% male Mean age: 12.2±3.1 years Mean duration of T1D: 5.0±3.4 years Mean Hba1c: 8.3±0.5% This study was part of the STAR 3 trial where likely factors to affect patient acceptance of sensor-augmented pump therapy were studied: PEDsQL (Psychosocial health Summary Score), and Overall Preference. Patients included with Hba1c between 7.4-9.5% only.	Ambulatory	MiniMed Paradigm REAL-Time System (Medtronic, Northridge,CA)	Glargine and insulin aspart, with insulin pens. CGM device in MDI group was the Guardian REAL-Time Clinical, Medtronic.	A. USA and Canada B. 89% were non-Hispanic white C. NR D. 56% male E. NR F. NR G. NR H. NR	**1. Glycated hemoglobin (HbA1c) at the end of the study: CSII vs. MDI [mean % (SD)], sig:** NA **2. Number of severe hypoglycemic (SH) episodes: CSII vs. MDI, sig:** NA **3. Number of patients with ≥ 1 diabetes ketoacidosis (DKA) episode: CSII vs. MDI, sig:** NA **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** - Diabetes-specific HRQoL: measures of hypoglycemia fear improved significantly during the study in the CSII group.	52 weeks

Slover, 2012, (116)	Randomized clinical trial (STAR3); Medtronic. Enrolled from Jan 2007 to Dec 2008.	USA and Canada	156 (78:78); (85:71); Age (range) years: CSII: 12.1 (7-17) MDI: 12.6 (7-17); Mean HbA1c: CSII 8.26±0.55% and MDI 8.30±0.53%; Duration of T1D, years: 7-12 years: CSII: 3.8±2.4; MDI: 4.2±2.6 13-18 years: CSII:5.8±3.5; MDI: 6.7±4.2; Participants should be naïve to CSII and have baseline HbA1c values ≥7.4% and ≤9.5%; Hypoglycemia was measured through SAP	Ambulatory	MiniMed Paradigm REAL-Time System with insulin aspart.	Insulin glargine in combination with either lispro or aspart.	A. USA and Canada B. NR C. NR D. 55% male E. NR F. NR G. NR H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** Results not presented as required, A1C values showed significant ($p < 0.05$) treatment group differences favoring SAP therapy. **2. Number of SH episodes: CSII vs. MDI, sig:** Results presented as area under the curve, NA as required. **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NA **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	One year
Lang, 2018, (117)	Randomized trial; Sep 2014 to Dec 2016	China	79 (23:56); (42:37); Age ranged from 5-14 years old; HbA1c: CSII: 13.57±4.02 % and MDI: 12.87±3.97%; Duration of T1D not reported; Inclusion criteria was not specified; The sample was stratified in three groups: 1- MDI receiving aspart and detemir once/day: 2 – MDI receiving aspart and detemir twice/day; 3- CSII; Criterion of hypoglycemia was not specified.	Ambulatory	Not specified	Not specified	A. China B. NR C. NR D. 53% girls E. NR F. NR G. NR H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 7.67 (2.69) vs. 7.96 (2.89), NS **2. Number of SH episodes: CSII vs. MDI, sig:** Not specified as required **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NA **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	6 months
Mueller-Godeffroy, 2018, (118)	Multicenter open randomized controlled trial; funded by the German Research Foundation and	18 German pediatric diabetes	211 (106:105) → data analyzed for 90:89 (113:86) Age CSII: 11.3±2.7 y; MDI: 11.9±2.8y Median DM1 duration: CSII 3.3±2.9 y; MDI: 3.6±3.0y HbA1c, %: CSII 7.3±0.9; MDI: 7.8±1.3 Tool: Diabetes-specific and generic HRQoL module were assessed from the KINDL-R.	Ambulatory	Not specified	Not specified	A. Germany B. NR C. NR D. female>male E. NR F. NR G. Higher SES with CSII therapy H. NR	**1. Glycated hemoglobin (HbA1c) at the end of the study: CSII vs. MDI [mean % (SD)], sig:** 6-7y: 7.0 (0.5) vs. 7.1 (0.7), NS 8-11y: 7.1 (1.0) vs. 7.6 (1.1), NS 12-16y: 7.3 (1.0) vs 7.8 (1.3),NS **2. Number of severe hypoglycemic (SH) episodes: CSII vs. MDI, sig:** 2 vs. 3, NS **3. Number of patients with ≥ 1 diabetes ketoacidosis (DKA) episode: CSII vs. MDI, sig:**	6 months

	additional financial support by Roche Diagnostics. Between 2011 and 2014		All children and adolescents aged 6-16 being treated with MDI with an indication for shift to CSII were eligible. Exclusion criteria: T2D less than 6mo, remission phase and insufficient literacy.					5 vs. 3, NS **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** - 8 to 11yo: 74.2±13 vs. 70.9±16, p<0.05 - 12 to 16yo: 74.2±13.0 vs. 70.9±16.0, NS - Treatment satisfaction: Significant differences were found for CSII.	
Blair, 2019, (119)	Multicenter, randomized trial, with recruitment between May 2011 and Jan 2017; UK national Institute for Health Research; device and suppliers provided with discount by Roche.	England and Wales	293 (144:149); (153:140) Median age: 9.8 years (IQ 5.7-12.3 y); Mean HbA1c: 11.6 (4.5)% Duration of T1d: 14 days from the diagnosis; Tool: Diabetes module of PedsQL (Pediatric Quality of Life Inventory). Only patients with a new diagnosis of T1D were recruited. Patients with a sibling with the disease and those who could have affected glycemic control were ineligible. SH was considered when associated with altered consciousness.	Ambulatory	Device was not mentioned. Insulin aspart.	Insulin glargine or detemir, and aspart.	A. UK B. self-report: White British, Black British, Asian British, Indian, Pakistani, Mixed and other C. NR D. M>F E. NR F. NR G. deprivation score was higher in CSII group H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 7.7 (1.48) vs. 7.5 (1.48), NS **2. Number of SH episodes: CSII vs. MDI, sig:** 6 vs. 2, NS **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** 2 vs. zero, NS **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** Child reported scores at 12 mo. for 71% of individuals (104:104), with an adjusted mean difference of 3.1 (95%CI -0.6 to 6.8) favored CSII, NS. Parents (not children) reported superior PedsQL score for those patients treated with CSII.	One year
Litton, 2002, (120)	Prospective cohort; Data collection not specified; Publication year: 2002	USA	28 (9:19); (15:13); < 5 years of age (mean age of diagnosis: 18.6±3.1 months). Pump therapy started at a mean age of 34.1±4.5 months; HbA1c: CSII vs MDI (9.5±0.4 vs. 8.0±0.3); Criteria for selection (CSII): children who had diabetes for at least 6 months and developed (1) recurrent episodes of moderate or severe hypoglycemia, (2)	Ambulatory	Model of Insulin pump not reported; Insulin: Humalog	3 to 4 injections of insulin per day with a mixture of long-acting (NPH or Lente) and short-acting (Humalog or regular) insulin.	A. North Carolina, USA B. NR C. Y: one patient did not receive pump because insurance health did not cover it. D. M 15, F 13 E. NR F. NR G. NR H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 7.9 (0.3) vs. 8.0 (0.3), p<0.001 **2. Number of SH episodes: CSII vs. MDI, sig:** 1 vs. 6, p<0.05 **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** 6 vs. 14, NS **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	12.7±1.6 months

			persistent marked eleveations in HbA1c (≥9%), (3) unpredictable and erratic swings in blood glucose or (4) recurrent DKA; Among children who did not qualify for the study, reasons were since inadequate parental supervision, adequate diabetic control using MDI, and no coverage of health insurance for insulin pump.					
Willi, 2003, (121)	Prospective cohort, published in 2003	USA	51 (51:51); (18:33); Mean age: 7.2±3.4 years; Mean HbA1c: 8.35 ±0.15; Mean duration of T1D: 4.0±2.6 years; Pump protocol encompassed clinical criteria and family interest.	Ambulatory	Not specified	Not specified	A.USA B.NR C. Public and private assistance D. F>M E.NR F.NR G. % of single parent household H.NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 7.9 (0.1) vs. 8.4 (0.2), p<0.01 **2. Number of SH episodes: CSII vs. MDI, sig:** NA as required **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NA **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	24 months
Alemzadeh, 2004, (122)	Prospective cohort; First author was a member of the medical advisory board of Medtronic / MiniMed during the time of the study; Follow started between July 2001	Wiscosin, USA	80 (40:40); (26:54); Age: CSII: 14.7 ±1.9 y; MDI: 14.6±2.0 y; HbA1c: CSII (8.4±1.1) vs MDI (8.5±1.1); Duration of diabetes: CSII (6.2±3.1 years) vs. MDI (7.2±3.0 years); Before initiation, all patients were on mealtime lispro and long-acting Humulin U (ultralente) insulin and applied principles of adjustment of insulin to carbohydrate ratio; Severe (<50 mg/dL) and moderate (<60 mg/dL) hypoglycemia were assessed.	Ambulatory	MiniMed, Northridge CA (USA), or Disetronic, St Paul MN (USA)	Premeal lispro + BID ultralente	A. USA B. all white children C. NR D. CSII: 67.5 % F; MDI: 67.5% M E. NR F. NR G. NR H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 7.8 (0.8) vs. 8.2 (0.9), p<0.002 **2. Number of SH episodes: CSII vs. MDI, sig:** 3.3 vs. 3.0, p<0.05 **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** 2 vs zero, NS **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	One year

	and Sep 2002.							
Shehadeh, 2004, (123)	Multicenter prospective cohort, Published in 2004	Israel and Slovenia	15 enrolled, 14 finished the study. (14:15); (8:7); Mean age: 3.8±1.2 years; Mean duration of disease not available; Mean HbA1c, %: 8.82±0.98; Tool: Diabetes Treatment Satisfaction Questionnaire (DTSQ) and a modification of the Diabetes Quality of Life Measure for parents. Insulin pump was suggested for children (< 6 years) who had diabetes for at least 6 months.	Ambulatory	MiniMed 508 pump; NovoRapid insulin	Not specified	A. Israel and Slovenia B. NR C. NR D.M>F E.NR F.NR G.NR H.NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 8.18 (0.9) vs. 8.2 (0.98), p<0.05 **2. Number of SH episodes: CSII vs. MDI, sig:** 4 vs. 5, NS **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** Zero vs. zero **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** Significant differences in the DTSQ score in favor of the CSII.	12 months
Weinzimer, 2004, (124)	Retrospective Cohort; Since 1995	USA	65 (65:65); (37:28); Mean age: 4.5±1.4 years (range: 1.4-6.9); Mean duration of T1D: 1.8±1.2 years (range: 0.3-5.2); HbA1c %: 7.4±1.0; Inclusion: children before 7 years of age; CSII was requested by the parents. Hypoglycemia was defined as severe episodes.	Ambulatory	Not specified	Not specified	A. USA B. 89% were White, 5% Black and 4% Hispanic. C. Maternal employment status: 26 stayed at home and 38 had a full-time employment outside the home D. 37 M and 28 F E. NR F. NR G. NR H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 7.0 (0.9) vs. 7.4 (1.0), p=0.006 **2. Number of SH episodes: CSII vs. MDI, sig:** 24 vs. 50, p=0.02 **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** 3 vs. zero, NA **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	Mean duration of 30 months
Bin-Abbas, 2005, (125)	Prospective cohort; Between Oct 2002 and June 2004; Supported by MiniMed Medtronic	Saudi Arabia	14 (14:14); (7:7); Mean age: 12.8±4.3 years; Mean Hba1c %: 10.2±1.2; Mean duration of T1D: 6±4.3 years; Selection criteria to start on CSII included HbA1c > 8.5% and recurrent episodes of hypoglycemia; SH defined as	Ambulatory	MiniMed 508 with insulin lispro	NPH and regular insulin	A. Saudi Arabia B. NR C. NR D. 50%/ 50% E. NR F. NR G. NR H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 7.5 (0.7) vs. 10.2 (1.2), p<0.001 **2. Number of SH episodes: CSII vs. MDI, sig:** 0 vs. 3, p<0.001 **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** 0 vs. 12, p<0.05	1 year and 8 months

			values < 40 mg/dL with coma or seizures.					**4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	
Jeha, 2005, (126)	Prospective cohort. Partly founded by Medtronic MiniMed and Novo Nordiski. Year of data collection not disclosed.	USA	10 children (10:10) → 8 analyzed; (2:8); Average age: 3.65±1.34 years; Duration of T1D: 1.9± 1.4 years; Mean Hba1c: 8.6±0.8 %; CGMS (Medtronic MiniMed, Northridge, USA) to determine blood glucose variability. Tool: Short form of the Parenting Stress Index (PSI). It was a sample of convenience where 10 families were approached to be in the study and none refused. They were selected based on age and duration of disease.	Ambulatory	Paradigm insulin pump (Medtronic Minimed) with aspart insulin (Novo Nordiski)	NPH and Lispro insulin (Eli Lilly)	A. Texas, USA B.NR C.NR D. F>M E.NR F.NR G.NR H.NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 7.5 (0.7) vs. 8.6 (0.8), p<0.05 **2. Number of SH episodes: CSII vs. MDI, sig:** 2 vs. 9, p=0.01 **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NA **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** (NA as required) - TI glucose 60-150 mg/dL, %: 35 vs. 28, NS - Hypo (<60 mg/dL), %: 2 vs. 6, p=0.01 - Hyper (>300 mg/dL), %: 7 vs. 20, p=0.01 **5. HRQoL comparisons between CSII vs. MDI, sig:** No data score for HRQoL. No significant differences for PSI.	6 months
Mack-Fogg, 2005, (127)	Retrospective chart review; Published in 2005	Rochester, USA	70 patients (all of them on CSII); (36:34); Mean age 9.1±2.89 years; HbA1c: 7.8±0.8 %; Chart review of patients who began CSII prior to the age of 12 years and who had been using CSII for at least 6 months.	Ambulatory	Not specified	Prior to initiation of CSII, insulin therapy consisted of two to four insulin injections per day (combination of lispro, NPH and ultralente)	A. USA B. NR C. NR D. M>F E. NR F. NR G.NR H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 7.3 (0.7) vs. 7.8 (0.8), p<0.0001 **2. Number of SH episodes: CSII vs. MDI, sig:** 15 vs. 32, p<0.06 (NS) **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** 2 vs. zero, NS **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	336 ±58 days
McMahon, 2005, (128)	Prospective cohort; Enrollment from Feb 1999 to Dec 2002	Western [illegible]	100 patients (100:100); (41:59); Mean age at the start of pump: 12.5 ±3.8 years; Mean duration of diabetes: 5.1±3.8 years; Mean HbA1c: 8.3%;	Ambulatory	Minimed 507C, Medronic and for those less than 10 years of age, Minimed 508, Medtronic. Insulin: NR	NPH insulin prior to the start of pump therapy.	A. Perth, Australia B. NR C. NR D. boys:41, girls: 59 E. NR F. NR G. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 7.8 (0.1) vs. 8.3 (0.1), p<0.001 **2. Number of SH episodes: CSII vs. MDI, sig:** 11 vs. 33 **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** Zero vs zero, NA	24 months

			Tool: DQOL – self-efficacy with diabetes treatment Criteria to start on pump: recurrent severe hypoglycemia, poor control despite compliance with therapy and after requested of the patient or caregiver; Severe hypoglycemia was presented for two groups (< and > 12 years old)				H. NR	**4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** 173.9±4.1 vs. 159.3±4.1, p<0.05	
O´Neil, 2005, (129)	Cross-sectional	USA	103 (62:41) (50:53) Mean age: 12.2±1.9 years Duration of T1D: 5.6y Mean Hba1c: 7.7±1.2% Quality of life was assessed using a modified diabetes-specific measure of quality of life.	Community (Summer Camp)	Not specified	Not specified	A. USA B. Mostly non-Hispanic white C. NR D. F>M E. NR F. NR G. NR H. Summer camp	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 7.5 (1.0) vs. 8.1 (1.5), p<0.05 **2. Number of SH episodes: CSII vs. MDI, sig:** NA **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NA **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** No differences were observed between participants using either therapies.	One week
Schiaffini, 2005, (130)	Retrospective cohort; Published in 2004	Italy	36 children (20:16); (10:26); Mean age: 13.4±2.9 years; Diabetes duration: 5.5±2.1 years; Mean HbA1c %: CSII 8.5±1.8 vs. MDI 8.9±1.7; Patients enrolled had changed their previous insulin regimen at least one year before the study.	Ambulatory	Medtronic MiniMed 508 or Disetronic H-tron and D-tron; Insulin: fast-acting analogue (lispro or aspart)	Insulin glargine and human soluble before meals	A. Italy B. NR C. NR D. F>M E. NR F. NR G. NR H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 7.6 (1.2) vs. 8.2 (0.9), p<0.01 **2. Number of SH episodes: CSII vs. MDI, sig:** 4 vs. 3, NS **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NS (no data) **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	12 months
Berhe, 2016, (131)	Cross-sectional with data collected 1 year before and 1 year	USA	33 patients (33:33) (16:17) Mean Age: 4.6±1.5 years Mean duration of T1D: 3.4±1.2 years Baseline Hba1c: 8.7±0.6%	Ambulatory	Device: MiniMed (Medtronic, Northridge, CA), Animas (Animas Corp, West Chester, PA, and Cozmo	Two to three injections per day (short and intermediate-acting insulin)	A. USA B. NR C. NR D. F>M E. NR F. NR G. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 8.0 (0.5) vs. 8.7 (0.6), p<0.001 **2. Number of SH episodes: CSII vs. MDI, sig:** 0 vs. 5.9 p<0.001	1 year

	after CSII initiation.		No specific criteria for inclusion and exclusion, except for patients in honeymoon phase.		(Smiths Medical, St Paul, MN). Short-acting insulin.		H. NR	**3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** 0 vs. 0, NS **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	
Springer, 2006, (132)	Database review recorded from Jan 2003 to Sep 2003	USA	455 (286:169); (243:212); Mean age: 11.8±3.9 years; Mean duration of T1D: 4.9±3.1 years Mean HbA1c: 7.6±1.4; Consecutive patients who had a visit logged in the database, included after accomplished exclusion criteria (age> 18 years, Asian race, or due to lack of information/missing data)	Ambulatory	Not specified	Not specified	A. USA B. Caucasian, African-American and Hispanic C. NR D.M>F E.NR F.NR G. Stratified in income groups: median income was higher in the pump-treated patients. H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 7.2 (0.1) vs 8.1 (0.2), p<0.001 **2. Number of SH episodes: CSII vs. MDI, sig:** NA **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NA **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	Cross-sectional
Alemzadeh, 2007, (133)	Prospective cohort; Supported by grants from Medtronic MiniMed Co. (Northridge, CA) and Novo Nordisk Pharmaceuticals, Inc. (Princeton, NJ); Enrollment not mentioned.	Wisconsin, USA	14 patients (14:14); (6:8); Age (range): 2.2-5.5 years old; Duration of T1D (range): 1.0-3.3 years; HbA1c %: 8.0±0.5 Use of a CGMS to measure blood glucose levels. Tool: TAPQoL, an instrument for measuring parents´ perceptions of HRQoL. Data were collected retrospectively for 1 year prior to CSII initiation and prospectively for the 1 year of CSII therapy. Criteria: recurrent episode of hypoglycemia and erratic blood glycemia swings that did not resolve with insulin adjustments.	Ambulatory	Medtronic MiniMed (Northridge, CA, USA)	Mealtime Aspart (Novolog, Novo Nordisk, Princeton, NJ) and bedtime glargine (Lantus, Sanofi-Aventis, Bridgewater, NJ)	A. USA B. NR C. NR D. 6 boys and 8 girls E. NR F. NR G. NR H.NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 7.8 (0.4) vs. 8.0 (0.5), NS **2. Number of SH episodes: CSII vs. MDI, sig:** 2 vs. 3, NS **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** Zero vs. zero **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** measured in number of events and/or mean values. **5. HRQoL comparisons between CSII vs. MDI, sig:** No significant differences were found.	2 years

García - García, 2007, (134)	Prospective cohort, from Oct 2003 to Mar 2004	Spain	32 (8:24); 13:19; Mean age, years: 12.5±2.4; Mean HbA1c, %: CSII (7.6±0.6); MDI (7.8±0.7); Mean duration of T1D: 5.7 years; Inclusion criteria: DM1 before 14 years of age, at least 2 years duration of follow-up in the service, previous intensive treatment with more than four glycemic analyses a day, good parental supervision, and clinical indication with poor metabolic control.	Ambulatory	Disetronic Htron, with insulin lispro.	Glargine and lispro	A. Spain B. NR C.NR D. F>M E.NR F.NR G.NR H.NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 7.70 (0.64) vs. 7.54 (0.74), NS **2. Number of SH episodes: CSII vs. MDI, sig:** Zero vs 1, NS **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** 2 vs. 2, NS **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	24 months
Kapellen, 2007, (135)	Prospective cohort from Dec 2005	Germany and Austria	1567 (765:1567),indication of CSII for dawn phenomenon: 765 patients; 54.5% female; Mean age: 12.2±4.2 years; Mean duration of T1D: 5.2 years; Mean HbA1c, %: 8.1±1.76; Indication for CSII: dawn phenomenon (27.4%), reduction of hypoglycemia (20%), improvement of hyperglycemia (18.1%), failure of injection therapy and personal issues.	Ambulatory	Not specified	Not specified	A. Germany and Austria B. NR C. NR D. F>M E.NR F.NR G.NR H.NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 8.0 (1.48) vs. 7.8 (1.48), p<0.01 (assessed indication for dawn phenomenon, SD was an estimation) **2. Number of SH episodes: CSII vs. MDI, sig:** 75 vs. 134, NS **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NA **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	Three years
Schiaffini, 2007, (136)	Prospective Cohort. Year of data collection not disclosed.	Italy	36 (19:17) (18:18) Age: 9-18 years old T1D duration: CSII 5.8; MDI 5.7 y Hba1c: CSII 8.3; MDI 8.5 Inclusion criteria: Hba1c>8% Groups were marched for pubertal age.	Ambulatory	Device not mentioned. Rapid-acting insulin	60% of patients with NPH and Regular	A. Italy B. NR C. NR D. male> female on CSII E. NR F. NR G. NR H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 7.6 (1.1) vs. 8.2 (1.4), p<0.05 **2. Number of SH episodes: CSII vs. MDI, sig:** 11 vs. 7, NS **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NA **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	24 months

Berghaeuser, 2008, (137)	Prospective multicenter analysis, Sep 2007	Germany and Austria	249 (104:145); 45% female; Mean age: 3.2 years (range: 0.4-16.7 years); Mean HbA1c, %: CSII (8.47±1.54); MDI (9.23±1.76); Patients aged 18 years or younger who started CSII with 4wk after presentation of newly diagnosed T1D. They were matched with patients on MDI.	Ambulatory	Device not reported; Insulin analog	NPH; 45% used short-acting insulin as mealtime.	A. Germany and Austria B. NR C. NR D. M>F E.NR F.NR G.NR H.NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** Information NA as required **2. Number of SH episodes: CSII vs. MDI, sig:** 35 vs. 84, p=0.009 **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** 0 vs. 2, NS **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	12 months
Jakisch, 2008, (138)	Prospective cohort; Dataset of June 2006	Germany	Baseline: 868 (434:434); 3-y follow-up: 508 (199:309); (48%M: 52% F); Mean age at inclusion: 10.9 years; Mean duration of T1D: 3.3 y (MDI) and 3.5 y (CSII); Mean HbA1c at baseline: CSII (7.5±0.05) and MDI (7.5±0.05); Initiation on CSII or MDI treatment was based on a joint decision by the patient, the family and the diabetes care team. Medical indications for CSII were metabolic criteria.	Ambulatory	Not specified	Not specified	A. Germany B.NR C.NR D.52% female E.NR F.NR G.NR H.NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 8.1 (0.11) vs. 8.0 (0.09), NS **2. Number of SH episodes: CSII vs. MDI, sig:** 34 vs. 60, p <0.0001 **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** 2 vs. 4, p=0.0007 **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	3 years
Johannesen, 2008, (139)	Open intention-to-treat study; MiniMed (Denmark) provided the insulin pumps. Year of data collection not disclosed.	Denmark	56 (30:26); (31:25); Mean age, years: CSII (15.6±1.9) and MDI (16.2±2.3); Duration of T1D, years: CSII (6.7±3.9) and MDI (7.8±4.0); Mean Hba1c%: CSII (9.5±1.5) and MDI (9.7±1.6); Tool: "validated" diabetes-related QoL questionnaire. An open intention-to-treat study.	Ambulatory	Device was not specified; Insulin Actrapid	Short-acting insulin preparation (Actrapid) and NPH at bedtime	A. Denmark B.NR C.NR D.M>F E.NR F.NR G.NR H.NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 9.4 (1.6) vs 9.6 (2.3), NS **2. Number of SH episodes: CSII vs. MDI, sig:** 4 vs. 11, NS **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** 8 vs. 0, NS **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** No significant difference.	12 months

Kawamura, 2008, (140)	Prospective intervention study, from June 2004 to May 2005	Japan	22 (22:22); (4:18); Mean age: 14.2±2.6 years; Mean duration of T1D: 7.5±3.8 years; Mean HbA1c: 7.8±1.8%; Tool: the Insulin Therapy Satisfaction Questionnaire (ITR-QOL). Patients enrolled were at an age of 6-18 years, with daily insulin requirement of 0.7-1.5 U/kg/day, HbA1c <12% and practicing SBMG.	Ambulatory	MMT 508 MiniMed Insulin Pump, with NovoRapid insulin.	Basal-bolus with regular human insulin or rapid-acting insulin and intermediate/ long-acting insulin	A. Japan B.NR C.NR D.F>M E.NR F.NR G.NR H.NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 7.4 (0.8) vs. 7.8 (1.8), NS **2. Number of SH episodes: CSII vs. MDI, sig:** 7 vs. 8, NS **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** 3 vs. zero, NS **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** Scores for 13/23 items in the questionnaire showed improvement following the CSII therapy.	48 weeks
Weinzimer, 2009, (141)	Short-term prospective longitudinal study. Funding: Abbott Diabetes Care provided the FreeStyle Navigator. Year of data collected not informed.	USA	45 (24:21) 40% female Mean age: 10.7 years Mean duration of T1D: CSII 4.9; MDI 3.4 y HbA1c: CSII 7.1; MDI 7.8% Inclusion criteria were age, and t1D > 1 year. Patients used the Navigator glucose readings during the study; and in the end completed a CGM satisfaction scale.	Ambulatory	Device and insulin not specified.	Glargine plus short-acting insulin	A. USA B. 93% Caucasians, not related to the use of CSII C. NR D. M>F used CSII E. NR F. NR G. NR H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 7.0 vs. 7.6, NS **2. Number of SH episodes: CSII vs. MDI, sig:** NA **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NA **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** - TIR, %: 52 (13) vs. 46 (17), NS - Hypo (<70mg7dL), %: 3.4 (3.8) vs. 4.9 (7.2), NS - Hyper (>180 mg/dL), %: 45 (15) vs. 49 (18), NS **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	26 weeks
Abaci, 2009, (142)	Prospective cohort; Enrollment between 2002 and 2006	Turkey	17 (17:17); (9:8); Mean ±SD age: 15.53±1.8 years; Mean ± SD duration of T1D: 6.8 ±4.0 years; HbA1c %: 8.7±1.2	Ambulatory	8 patients used Medtronic-MiniMed (Minimed, Sylmar, CA, USA), 3 patients Disetronic H-Tron (Disetronic Medical Systems AG, Burgdorf, Swizterland), 5 patients Dana	Basal insulin NPH and corrections with lispro or aspart	A. Turkey B. NR C. NR D. 9 males and 8 females E. NR F. NR G. NR H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 7.71 (0.84) vs. 8.71 (1.25), NS **2. Number of SH episodes: CSII vs. MDI, sig:** 2 vs. 0, NS **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** 0 vs. 1, NA **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA	4 years

				Diabcare (Korea), and one patient Deltec Cosmo (Smith Medical, MD, USA); Insulin lispro (Humalog, Lilly, Indianapolis, IN, USA) or aspart (NovoRapid, NovoNordisk, Baysvaerd, Denmark).				**5. HRQoL comparisons between CSII vs. MDI, sig:** NA	
Anderson, 2009, (143)	Retrospective cohort; Reviews from June 2000 to July 2008	Australia	573 (573:573); (300:273); Mean age in years: June 2000 (11.3), June 2004 (12.1), June 2008 (12.4); Duration of T1D in years: June 2000 (3.9), June 2004 (4.3) and June 2008 (4.7); Mean HbA1 %: June 2000 (8.6±1.4), June 2004 (8.8±1.4) and June 2008 (7.6±1.4); The aim was to compare the A1c achieved while using an easy bolus insulin calculation card (ezy-BICC), mixed insulin injections and CSII	Ambulatory	No device reported; Ultra-rapid-acting insulin	Self-mixed rapid-acting insulin and intermediate insulin twice each day before breakfast and dinner.	A. Australia B. NR C. Purchase of an insulin pump has to be paid for by the family D. 52.3% boys E.NR F. NR G. Y H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 7.8 (1.3) vs. 8.3 (1.3), p<0.001 **2. Number of SH episodes: CSII vs. MDI, sig:** NA **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NA **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	From 2000 to 2008
Minkina-Pedras, 2009, (144)	Prospective cohort. Recruitment from 2001-2007.	Poland	76 patients (40:36) 31:45 Mean age: CSII 6.5; MDI 7.1 y Mean duration of T1D: CSII 2.6; MDI 1.5 y HbA1c: CSII 7.10; MDI: 7.16% Availability of CSII treatment was related to the nationwide health-care programme. Groups were matched by age, gender and baseline parameters.	Ambulatory	Roche (H-Tron and D-Tron, Accu Check Spirit) and Medtronic (MiniMed 508, Paradigm 712). Insulin Aspart and Lispro.	Short or rapid-acting insulin, along with NPH insulin or long-acting analog (glargine)	A. Poland B. NR C. NR D. female > male E. NR F. NR G. NR H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 6.91 (0.8) vs. 7.43 (1.1), p<0.05 **2. Number of SH episodes: CSII vs. MDI, sig:** 2.85 vs. 2.85, NS **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** 2 vs. 2, NS **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	42 months

Shashaj, 2009, (145)	Longitudinal retrospective study, enrollment between June 2000 and Sep 2002	Italy	43 (43:43); comprehensive data for 16 pubertal patients (27:13); Mean age: 12±4 years; Mean duration of T1D: 5.9±3.8 years; Mean HbA1c: 8.9±1.4%; Inclusion criteria: age <18 years, On MDI treatment for at least 1 year before starting CSII; C-peptide secretion deficiency before start on CSII.	Ambulatory	Device not specified, insulin in pump was a rapid-acting analog of human insulin (lispro or aspart)	Regular and NPH insulins	A. Italy B. NR C. NR D. M>F E. NR F.NR G.NR H.NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** Prepubertal: 8.0 (0.8) vs. 8.8 (1.5), NS Pubertal: 8.2 (0.8) vs. 8.9 (1.0), p<0.05 Postpubertal: 7.9 (0.8) vs. 9.1 (1.7), p<0.05 **2. Number of SH episodes: CSII vs. MDI, sig:** NA **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NA **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	12 months
Cortina, 2010, (146)	Cross-sectional.	USA	150 (95:55) (74:76) Mean age: 15.4 years Mean duration of T1D: 6.0 years Mean HbA1c: 8.8% Tools: Children´s depression inventory; diabetes-specific psychological factors. All patients receiving care at the diabetes center initially started therapy on NPH/Regular or MDI; diabetes center with no selection criteria to switch to CSII.	Ambulatory	Not specified	Not specified	A. USA B. Mostly white (95.4%) C. 95% with private insurance D. 53% female E. NR F. Parental higher education level on CSII G. NR H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 8.4 (1.4) vs. 9.5 (2.4) **2. Number of SH episodes: CSII vs. MDI, sig:** NA **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NA **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** CSII users were more prone to engage in more frequent glucose meters, had less negative feelings around glucose meters, and took on more responsibility for diabetes management.	Cross-sectional
Sulmont, 2010, (147)	Retrospective cohort, published in 2009	France	66 (32:34); 6 dropouts on CSII therapy; No differentiation between boys and girls; Age at diagnosis, years: CSII (3.2±1.5); MDI (3.8±1.6); Duration of T1D, years: CSII (6.9±2.1); MDI (9.6±2.9); Mean HbA1c: CSII (10.3±1.1); MDI (11.2±2.0); This study reports long-term metabolic control in patients diagnosed before they were 6 years of age. Criteria to switch to CSII were poor metabolic	Ambulatory	Not specified	2 to 4 subcutaneous daily injections with regular and NPH insulins which were switched to rapid and long-acting insulin analogs when available.	A.France B. NR C.NR D.NR E.NR F.NR G.NR H.NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 7.1 (0.8) vs. 7.9 (1.1), p=0.011 **2. Number of SH episodes: CSII vs. MDI, sig:** 3 vs. 8, p=0.016 **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** 10 vs. 9, NS **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	Eight years

			control (HbA1c>8%), severe or frequent hypoglycemia, personal issues.					
Wintergest, 2010, (148)	Retrospective cohort from 2008	USA	701 (100 on CSII; 225 on MDI); 51% male; Mean age: 13.5±4.3 years; Mean HbA1c, %: 9.0±2.0; Duration of T1D: NR; Excluded patients whose diagnosis was at the previous 6 months.	Ambulatory	Not specified	Not specified	A. USA B. Caucasia, African-American and other C. Private or public insurance D. M>F E. NR F.NR G. Private or public insurance H.NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 8.2 (1.4) vs. 8.9 (1.8), NS **2. Number of SH episodes: CSII vs. MDI, sig:** NA **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NA **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	Cross-sectional
Wu, 2010, (149)	Cross-sectional.	USA	62 patients (26:36) 60% female Average age: 14.2 years old Average T1D duration: 4.2 years Mean Hba1c: 8.4% Tool: DQOL (Diabetes Quality of Life). Children included with 6 months previous diagnose. Data from three different centers.	Ambulatory	Not specified	Not specified	A. USA B. Mostly Caucasians (no mentions related with CSII pump) C. NR D. F>M E. NR F. NR G. Middle/upper-middles class – deprivation score not related with the use of CSII H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 8.2 (1.3) vs. 8.5 (2.0), NS **2. Number of SH episodes: CSII vs. MDI, sig:** NA **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NA **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** 77.3±10.4 vs. 74.1±11.5, NS	Cross-sectional
Cengiz, 2011, (150)	Retrospective cohort, between Sep 2006 and April 2009; NIH.	USA	108 patients (49:59); (46:62); Mean age: 10.0±0.4 years; Mean HbA1c: 9.8%; Of the 108 patients included, 19 switched to CSII at approximately 3 months and an additional 30 by 12 months.	Ambulatory	Not specified	A mixture of NPH insulin and rapid-acting insulin analogue at breakfast with separate injections of rapid-acting insulin analogue and	A. USA B. NR C. NR D. 57% female E. NR F. NR G. NR H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 6.9 (0.7) vs. 7.2 (1.0), NS **2. Number of SH episodes: CSII vs. MDI, sig:** 0 vs. 6 events **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** Zero vs. zero **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA	12 months

						detemir at dinner.		**5. HRQoL comparisons between CSII vs. MDI, sig:** NA	
Knight, 2011, (151)	Prospective follow-up; Published in 2011	Australia	27 (27:27); (14:13); Mean age at enrollment: 12.6±2.7 years; Mean HbA1c: 8.2±0.8%; Duration of T1D: not informed; Patients with T1D were reassessed 24 months after commencing CSII. No reason was informed regarding indication of CSII.	Ambulatory	Not specified	Not specified	A. Australia B. NR C.NR D.M>F E.NR F.NR G.NR H.NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 8.2 (1.0) vs. 8.2 (0.8), NS **2. Number of SH episodes: CSII vs. MDI, sig:** NA **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NA **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	Two years
Starkman, 2011, (152)	Chart review, with data collected from Jan 2006 to Aug 2009.	USA	43 (43:43); (25:18); Average age at start therapies, years: CSII (12.3±3.5); MDI (10.2±3.5); Average duration of T1D: 50.8±34.8 months; HbA1c, %: CSII (7.7±0.8); MDI (8.3±0.9); Analyses of data of patients with over 1 year of diabetes duration at the time of MDI initiation and were changed to CSII.	Ambulatory	Not specified	Not specified	A.USA B.NR C.NR D. M>F E.NR F.NR G.NR H.NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 8.1 (1.3) vs. 8.3 (1.1), NS **2. Number of SH episodes: CSII vs. MDI, sig:** NA **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NA **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	1 year
Batajoo, 2012, (153)	Retrospective observational study; Between 1999 and 2009	New York, USA	131 (131:131); (72:59); Mean age at transition to CSII: 10.2±3.9 years; Mean HbA1c %: 8.6±1.7; Mean duration of T1D: 3 years±3.9 years; Patients were transitioned from MDI to CSII and data were collected from 6 months prior then 30 months after initiation. No indication for CSII was specified.	Ambulatory	Not specified	Not specified	A. USA B. NR C. NR D. 55% male E. NR F. NR G. NR H.NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 8.0 (1.3) vs. 8.6 (1.7), NS **2. Number of SH episodes: CSII vs. MDI, sig:** NA **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NA **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	36 months

Fendler, 2012, (154)	Prospective observational study; from Jan 2002 to Dec 2010; Foundation for Polish Science	Poland	454 (231:223); (255:199); Mean age at enrollment in years (range): 10.2 (7.17-13.15) for CSII and 14.13 (10.82-16.18) for MDI; Mean HbA1c: 7.2 for CSII and 7.4 for MDI; Mean duration of T1D in years (range): 2.43 (1.47-5.21) for CSII and 2.46 (0.70-5.53) for MDI; The decision to introduce CSII was based on patient´s or their parents´, and on clinical judgement.	Ambulatory	Pumps manufactured by Medtonic (Paradigm series), Roche (Accu-Chek) and Deltec (Cozmo), with insulin analogues or human insulin. No patient with SAP.	Various combinations of long-acting analogues, NPH insulin, short-acting analogues or human insulin.	A. Poland B.NR C. All the cost was reimbursed by a non-profit org or by the National Health Fund. D.56% male E.NR F.NR G. All the cost was reimbursed by a non-profit org or by the National Health Fund. H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 7.56 (0.97) vs. 7.98 (1.38), p=0.002 **2. Number of SH episodes: CSII vs. MDI, sig:** NA **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NA **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	Mean follow-up: 3.05±1.74 years
Hasselmann, 2012, (155)	Cohort with data collected retrospectively between Jan 2003 and Jul 2010.	France	76 (38:38) (40:36) Mean age: CSII 9.0; MDI: 8.7 y T1D duration: CSII 2.7; MDI: 2.4 y HbA1c: CSII 9.1; MDI: 8.8 Inclusion criteria to CSII as per ISPAD 2007.	Ambulatory	Not specified	Short and long-acting insulin.	A. France B. NR C. NR D. % male > female on CSII E. NR F. NR G. NR H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 7.5 (0.6) vs. 8.0 (1.3), p<0.05 **2. Number of SH episodes: CSII vs. MDI, sig:** 5 vs. 8, NS **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** 8 vs. 19, p<0.05 **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	Three years
Hughes, 2012, (156)	Retrospective cohort (2005-2010)	Ireland	67 (67:67); Male > Female; Age ranged 1 to 16 years; Mean HbA1c: 8.7%; Mean duration of T1D: NR; Potential reasons to commence CSII include poor metabolic	Ambulatory	Not specified	Not specified	A. Ireland B. NR C. NR D. Most male E. NR F. NR G. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 7.7 (0.99) vs. 8.2 (0.80), p<0.05 **2. Number of SH episodes: CSII vs. MDI, sig:** 4 vs. 5, NS **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** 4 vs. 4, NS	4 years

			control (elevated HbA1c>9%, wide blood glucose variability; recurrent nocturnal hypoglycemia and desire for increased flexibility.				H. NR	**4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	
Katz, 2012, (157)	Retrospective longitudinal. Data collected during two different waves (2004-2006 and 2005-2009).	USA	255 (93:50). Remaining patients were on NPH. 51.4% were female Median age: 12.2 years old Median duration of T1D: 4.4 years Mean HbA1c: 8.3% Three different groups were assessed: NPH (BID), MDI (basal-bolus), and CSII (on pump).	Ambulatory	Not specified	Basal insulin analog (detemir or glargine)	A. USA B. White more prone to be on CSII C. NR D. F=M E. NR F. NR G. NR H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 7.9 (1.0) vs. 8.5 (0.9) **2. Number of SH episodes: CSII vs. MDI, sig:** 50 vs. 31, p<0.05 **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NA **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	Median follow-up: 1.2 years (range: 0.2-3.4y)
Makaya, 2012, (158)	Retrospective cohort, published in 2012	UK	54 (54:54); (22:32); Mean age: 12.9 years; Mean HbA1c,%: 9.2±1.6; Mean duration of T1D: NR; Patients included were at least on 12 months on MDI just before started CSII. Criteria for CSII according to NICE guidelines, and most of them started for high HbA1c, or due to inability to cope with MDI.	Ambulatory	Not specified	Not specified	A.UK B.NR C.NR D.F>M E.NR F.NR G.NR H.NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 8.3 (0.9) vs. 9.2 (1.6), p=0.007 **2. Number of SH episodes: CSII vs. MDI, sig:** 3 vs. 2, NS **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** 11 vs. 4 episodes, NS **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	24 months
Senniappan, 2012, (95)	Retrospective case-controlled survey, with data collection between 2006 and 2008	UK	102 (51:51); (54:48); Mean Age, years: CSII (11.3±3.5); MDI (10.9±3.6); Mean duration of T1D, years: CSII (5.1±3.0); MDI (3.6±3.4); Mean HbA1c, %: CSII (8.6±1.3); MDI (9.2±1.8); Inclusion criteria: age less than 18 years; on CSII therapy for at least 12 months. The patients were matched with controls on	Ambulatory	Not specified	Not specified	A.UK B. ethnicity was taken into account. C. parents in highest employment tertile showed a non-significant lowering in glycemic outcomes D.M>F E.NR F. children with the least educated parents showed a	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 8.5 (1.1) vs. 8.6 (1.6), p=0.02 **2. Number of SH episodes: CSII vs. MDI, sig:** NA **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NA **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	24 months

			MDI. Primary indications for CSII were poor metabolic control, recurrent hypoglycemia and quality of life issues.				significant rise in HbA1c levels G. parents in the highest income tertile showed a non-significant trend toward a lowering in HbA1c levels H. NR		
Thompson, 2012, (159)	Cross-sectional. Collected data in 2010.	England	325 (159:157) (170:155) Mean age: 10.6y Average duration of T1D: 4.5 y Median Hba1c: 7.8% Children on CSII had to accomplish Kauffman level 5 competence structures.	Ambulatory	Not specified	Not specified	A. England B. White British mostly on pump C. NR D. male > female E. NR F. NR G. NR H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** Lower Hba1c values on CSII assessed with a multiple regression analysis **2. Number of SH episodes: CSII vs. MDI, sig:** NA **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NA **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	Cross-sectional
Cooper, 2013, (160)	A retrospective cohort from a population-based register; Data between 2000 and 2011	Australia	1770 patients (469:1301); (920:850); Age at diagnosis: 8.6 (±4.1) years; Duration of T1D: 6.1 (±4.2) years; Mean HbA1c level per year between 8.0% and 8.5%; Proportion of subjects on each treatment was stratified in age groups and calendar year (2000-2011): By 2011, 32% (0-6 years age group), 26% (6-12 years age group), and 32% (12-18 years age group) were on CSII.	Ambulatory	Not specified	A combination of short- and intermediate-acting insulins with or without a short-acting analogue at afternoon tea; and a combination of short- and intermediate-acting insulins in the morning with a short-acting analogue at dinner and a long-acting analogue (detemir) at night-time.	A. Western Australia B. NR C. NR D. M>F E. NR F. NR G. Y H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** No comparisons between regimens **2. Number of SH episodes: CSII vs. MDI, sig:** 322 vs. 545, NS **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NA **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	4.8 years (range: 0.25-12.15 years)

Froisland, 2013, (161)	Cross-sectional. Data from the Norwegian Childhood Diabetes Registry. Data collected from Apr 2010 to March 2011.	Norway	898 (503:395) (462:736) Mean age: 13.3 y MeanT1D duration: 4.9 y Mean HbA1c: 8.5% Tool: DIABKIDS questionnaires DCGM-37 and DDM-10.	Ambulatory	Not specified	Predominantly using insulin analogues.	A. Norway B. Only assessed families that fully speak and read in Norwegian C. Pump is fully reimbursed by social security system. D. F>M E. NR F. NR G. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** NA as required **2. Number of SH episodes: CSII vs. MDI, sig:** NA as required **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NA as required **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA as required **5. HRQoL comparisons between CSII vs. MDI, sig:** There were no significant association between mode of insulin delivery and any of the DDM-10 scales.	
Hilmi, 2013, (100)	Retrospective cohort, between 2000-2008	Israel	168 (88:80); (93:75); Average age: 10.2±4.4 years in Bedouin group and 9.6±3.8 years in the Jewish group; HbA1c at baseline not specified; Patients with T1D aged 1-18 years who were diagnosed at a single center during 2000-2008 with a clinical follow-up more than one year.	Ambulatory	Not specified	Not specified	A. Israel B. Bedouin and Jewish C. NR D. 55.4% male E. Bedouin and Jewish F.NR G. Socioeconomic inference H.NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** HbA1c levels compared by ethnicity (>3y of disease), p<0.01: - Bedouin: 10.58±1.95 % - Jewish: 8.94±1.55 % **2. Number of SH episodes: CSII vs. MDI, sig:** NA **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** Data not shown as required, NS **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	At least one year
Johnson, 2013, (162)	Case-control; Jan 1999 – Jan 2011	Australia	710 (355:355); (341:369); Age at pump start: 11.5±3.5 years; Duration of T1D: 4.1±3.0 years; Hba1c at start: 8.0±1.0 %; Only patients who commenced insulin pump therapy at least 6 months after diagnosis and with a minimum of 6 mo of data on their pump therapy were included.	Ambulatory	Not specified	Not specified	A. Australia B. NR C. Pumps are funded through private health insurance, or by donation. The cost of the consumables is subsidized by the government. D.F>M E.NR F.NR G. NR H.NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 7.7 (0.9) vs. 8.8 (1.0), p<0.01 **2. Number of SH episodes: CSII vs. MDI, sig:** 25 vs. 36, p=0.013 **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** 8 vs. 17, p=0.003 **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	Data until 7 years of follow-up

Lukacs, 2013, (163)	Cross-sectional. Year of data collection not disclosed.	Hungary	239 (104:135) (124:115) Mean age: CSII 13.3; MDI: 13.4 y Mean duration of T1D: CSII 6; MDI 5.7 y Mean Hba1c: CSII 8.6; MDI 8.7% Assessment of the pediatric Quality of Life Inventory, generic core scales and the Diabetes Module. Patients recruited from a Diabetes Summer Camp and eligible when they had more than 2 years of disease.	Community (Summer Camp)	Not specified	Not specified	A. Hungary B. All white patients C. NR D. male>female E. NR F. NR G. NR H. From a diabetes camp	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 8.63 (1.49) vs. 8.75 (1.60) **2. Number of SH episodes: CSII vs. MDI, sig:** NA **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NA **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** 82.1±9.2 vs. 77±10, p<0.001	Cross-sectional.
Schiel, 2013, (164)	Prospective cohort, published in 2013	Germany	901 (194:707); (432:469); Mean age: 11.5±4.0 years; Mean duration of T1D: 4.0±3.6 years; Mean HbA1c, %: 8.61±2.12; All patients were included in the study. SH were assessed across only one month.	Ambulatory	Not specified	Not specified	A. Germany B. NR C.NR D.F>M E.NR F.NR G.NR H.NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 8.72 (2.26) vs. 8.35 (1.71), NS **2. Number of SH episodes: CSII vs. MDI, sig:** 12 vs. 12, NS **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NA **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	Six years
Schreiver, 2013, (165)	Cross-sectional observational cohort, enrollment between Jan and Dec 2010	Germany	48 (22:26); (22:26); Mean age: 12.9±3.3 years; Mean duration of T1D: 63.4 ±44.2 months; Mean HbA1c: 8.52±1.1%; All children at the institution were eligible for the study. Including criteria: age 6-18y, duration of disease > 1 year, intensive insulin treatment with either MDI or CSII with a constant mode of therapy for at least 6 months; Severe	Ambulatory	Device not specified; insulin: short-acting insulin	A combination of short and long-acting, short and intermediate-acting, normal and long-acting, or short, normal and long-acting insulins.	A. Germany B.NR C.NR D.F>M E.NR F.NR G.NR H.NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 8.28 (0.25) vs. 9.03 (0.42), NS **2. Number of SH episodes: CSII vs. MDI, sig:** 0.59 vs. 0.77, NS **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NA **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	Cross-sectional (3 days CGM control)

			hypoglycemia was defined as glycemic value < 50 mg/dL						
Alsaleh, 2014, (166)	Cross-sectional. Year of collection not disclosed.	England	42 (42:42) (25:17) Age 5-17 years old Duration of T1D ranged from 19 to 151 months Mean Hba1c: 8.2% Face-to-face interviews regarding health and clinical outcomes, home and family life, school life, and psycho-social impacts.	Ambulatory	Device not specified Insulin Aspart and lispro	Short-acting/intermediate-acting and long-acting insulin	A. England B. NR C. NR D. male>female E. NR F. NR G. NR H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 7.6 (0.82) vs. 8.2 (0.77), p<0.05 **2. Number of SH episodes: CSII vs. MDI, sig:** NA **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NA **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** No structured scale used.	6 months
Birkebaek, 2014, (167)	Cross-sectional study from the Danish Registry for Diabetes in Childhood and Adolescence. Year of collection: 2009	Denmark	700 (295:405) (340:360) Age: 8-17 years Range of T1D duration: 0.36-14.5 y Baseline Hba1c: CSII: 7.82; MDI 8.17 Tool: PEDsQL DM To be included in the study, patients had to be treated with either CSII or MD, and parents and children had to have completed the survey.	Ambulatory	Not specified	Not specified	A. Denmark B. NR C. NR D. F>M E. NR F. NR G. NR H NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 7.95 vs. 8.26, p=0.004 **2. Number of SH episodes: CSII vs. MDI, sig:** NA **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NA **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** 82.8±15.5 vs. 79.1±15.5, p=0.02	Cross-sectional
Blackman, 2014, (168)	Data from two different but overlapping cohorts:	USA	(a) 669 (332:337); (384:285) <6 yr old; HbA1c: CSII 7.9 (0.9) vs MDI 8.5 (1.1); T1D duration ≥1 yr; Clinic-reported SH was assessed.	(a) Ambulatory	(a) not specified (b) not specified	(a) MDI basal/bolus method: 332 (50%) (b) not specified	(a): A. USA B. White non-Hispanic (534) Black non-Hispanic (35) Hispanic or Latino (52) Other (42) C. NR D. M 384, F 285 E. NR	(a) **1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 7.9 (0.9) vs 8.5 (1.1), p<0.001 **2. Number of SH episodes: CSII vs. MDI, sig:** 9.9 vs. 10.1, NS **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** 20 vs 16, NS	(a) no follow-up

	(a) cross-sectional study; August 2012 (b) retrospective longitudinal study (the T1D Exchange clinic registry); enrollment from Sep 2010		(b) 1904 (92:1812); Info only concerning the 92 patients on CSII: (M 52: F 40); Median age: 9 yr; HbA1c (%): CSII 8.2 vs MDI 8.4; Obs: the longitudinal cohort was reduced to children who changed from injection to pump therapy before they were 6 yr old (N=92).	(b) Ambulatory			F. Less than high school (15: 20%) High school (178: 33%) Associate (73: 56%) Bachelor (182: 57%) Master (121: 62%) Professional/doctorate (48: 69%) G. Annual household income: <$35 000 (114: 35%) $35 000–<$50 000 (58: 33%) $50 000–<$75 000 (104: 57%) $75 000–<$100 000 (87: 52%) $100 000 or more (154: 66%) H. NR (b) A: USA B. White non-Hispanic 82; Non-White 10 C. Private 77 No insurance/ non-private insurance 15 D. F 40, M 52 E. NR F. High school diploma/GED or less 14 Associate of bachelor degree 49 Master, professional, or doctorate degree 29 G. NR H. NR	**4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA (b) **1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** Hba1c was lower in pump users compared with injection users (p<0.001) **2. Number of SH episodes: CSII vs. MDI, sig:** NA **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NA **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	(b) A period between ages 1 and <6 yr
Branca to, 2014, (169)	Retrospective cohort (Chart Review);	Italy	113 (113:113); (53:60); Mean age at pump: 9.6±5.0 years; Mean HbA1c %: 9.3±1.8; Duration of T1D (range): 1-726 days;	Ambulatory	Not specified	Not specified	A. Italy B. NR C. NR D. 53 males and 60 females E. NR F. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 7.7 (1.2) vs. 9.3 (1.8), p<0.0001 **2. Number of SH episodes: CSII vs. MDI, sig:** NA **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NA	Mean follow-up: 4.0±1.8 years (1.0-

	From Jan 2004 to Sep 2013		Inclusion criteria: interval between onset and insulin pump commencement of < 2years, use of CSII for > 1 year, and use of CGM for < 4 weeks/year				G. CSII intended to be offered equally H. NR	**4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	8.0 years)
Cherubini, 2014, (170)	Multi-center, observational, cross-sectional, performed between Feb 2008 and Feb 2009.	Italy	577 patients (271:306) (252:325) Mean age: CSII 14.1; MDI: 14.2 y T1D duration: CSII 6.4; MDI: 5.3 y Mean Hba1c, %: CSII: 8.0; MDI 8.1 HRQoL was assessed by the Insulin Delivery System Rating Questionnaire (IDSRQ). To be included patients must be using CSII or MDI at least 6 mo before recruitment.	Ambulatory	Not specified	Not specified	A. Italy B. NR C. NR D. F>M E. NR F. Higher parental educational level on CSII G. NR H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 8.0 vs. 8.1, NS **2. Number of SH episodes: CSII vs. MDI, sig:** NA as required. **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NA as required. **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** CSII had a significantly higher score than the MDI group	Cross-sectional
Dovc, 2014, (171)	Prospective registry, between 2000 and 2011; Supported by the Slovenian National Research Agency grants.	Slovenia	886 (807:79); Sex NR Median age was 12.7 years in 2001 and 7.5 years in 2010; Median time of disease when started on CSII: 8.8 years in 2001 and 0.59 years in 2010; Data on the entire pediatric T1D population.; Selection of the therapy was performed according the ISPAD guidelines.	Ambulatory	Not specified	Not specified	A. Slovenia B.NR C.NR D. different analyses for HbA1c regarding sex E.NR F. NR G.NR H.NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 7.8 (0.6) vs. 8.4 (1.0), p<0.001 **2. Number of SH episodes: CSII vs. MDI, sig:** Data were not specified by modality of treatment **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** Data were not specified by modality of treatment **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	Median follow-up of 5.0 years
Fredheim, 2014, (172)	National registry (2006-2009); Supported by the Nordic Diabetes Registries	Denmark - - -	11,908 children (3395:8513); -Denmark:2322 (394:1928) - Iceland: 113 (3:110) - Norway:2738 (1314:1424) - Sweden:6735 (1684:5051); (M 6314: F5594); Mean onset age: 7.7±3.9 years; Mean duration of T1D: 6.1±3.6 years;	Ambulatory	Not specified	Not specified	A. Nordic countries B. Nordic vs. non-Nordic C. NR D. 53% were boys E. NR F. NR G. NR H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** Data were not specified by modality of treatment, but by ethnic groups (being Nordic and non-Nordic), by country (p<0.0001): - Denmark: 8.3 (1.3) vs. 8.6 (1.3) - Iceland: 8.2 (1.4) vs. 8.1 - Norway: 8.4 (1.3) vs. 8.7 (1.6) - Sweden: 8.0 (1.3) vs. 8.1 (1.5) **2. Number of SH episodes: CSII vs. MDI, sig:** NA	Three years

	(Denmark, Iceland), the Iceland Thorvaldsen´s Foundation (Island) and the Swedish Board of Health and Welfare (Swediabkids)		The study cohort comprehended data from four national pediatric registries. Patients were diagnosed with T1D according to WHO criteria.					**3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NA **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	
Maahs, 2014, (74)	Cross-sectional analyses of two diabetes registries (a) T1DX: data are obtained through a combination of clinic and participant report; enrollment from Sep 2010 to Aug 2012; supported by the Leona M. and Harry B. Helmsley	USA, Germany and Austria	**(a)** 674 (334:340); (391:283); Median age 4.9 years; Median duration of diabetes: 2.0 years; Mean HbA1c %: 8.2±1.0; Data are obtained through 52 medical centers; SH events resulted in seizures/loss of consciousness **(b)** 1948 (1435:513); (1032:916); Median age 5.0 years; Median duration of diabetes: 1.8 years; Mean HbA1c %: 7.4±0.9; More than 90% of German and more than 70% of Austrian children with diabetes are included in the registry.	Ambulatory	Not specified	Not specified	A. (a) USA (b) Germany and Austria B. (a) Language was a barrier (b) Turkish background C. (a) having private insurance had higher HbA1c D. Y E. NR F. (a) higher education had higher HbA1c G. (a) higher income with higher HbA1c H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** **(a)** 7.9 (0.9) vs. 8.5 (1.0), p<0.001 **(b)** 7.4 (0.8) vs. 7.4 (1.0), p<0.01 **2. Number of SH episodes: CSII vs. MDI, sig:** **(a)** 9 vs. 10, NS **(b)** 23 vs. 14 , NS **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig: (a)** 21 vs. 19 , NS **(b)** 52 vs. 7, p=0.01 **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	(a) 1 year (b) 1 year

	Charitable Trust (b) DPV: prospective longitudinal standardized computer-based documentation system (between 2011 and 2012); supported by the German BMBF Competence Network DM								
Mameli, 2014, (173)	Retrospective multicenter cohort, with data collected between Jan 2011 and Dec 2011	Italy, Canada and Spain	115 (115:115); (63:52); Mean age:13.5±3.8 years; Mean duration of T1D: 6.3±3.4 years; Mean HbA1c: 8.54±1.12 %; Inclusion criteria were: age 5-20 years at the time of collection and use of CSII for at least 5 years or more.	Ambulatory	Not specified	Not specified	A. Italy, Canada and Spain B.NR C.NR D.M>F E.NR F.NR G.NR H.NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 8.36 (1.07) vs. 8.40 (1.15), p=0.02 **2. Number of SH episodes: CSII vs. MDI, sig:** 3 vs. 4, NS **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** 1 vs. 9, p=0.01 **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	One year
Al Hayek, 2015, (174)	Cross-sectional. From June 2013 to Feb 2014	Saudi Arabia	187 (36:151) (92:95) Mean age: 15.3 years old Mean duration of T1D: 7.1 years	Ambulatory	Not specified	Not specified	A. Saudi Arabia B. NR C. NR D. male > female E. NR F. NR G. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** Data not assessed according to therapies **2. Number of SH episodes: CSII vs. MDI, sig:** NA **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NA	Cross-sectional

			Patients were selected according to their availability during routine visits to the outpatient clinic. Adolescents were asked to complete the Arabic-translated FOH (Fear of Hypoglycemia) and Screen for Child Anxiety-related disorders (SCARED) questionnaieres.				H. NR	**4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** Patients on CSII had significantly lower levels of worry, panic disorder, separation anxiety disorder, and significant school avoidance than patients on MDI	
Brorsson, 2015, (175)	Retrospective case-control study, from Jan 2005 to Dec 2009; Supported by grants from the Swedish Child Diabetes Foundation, the Swedish Diabetes Association Research Foundation and funding for care research from Upsala University.	Sweden	431 patients (216: 215); (225:206); Mean age (range) years: 10.7 (1.9-17) for CSII and 10.8 (1.1-16.9) for MDI; Mean HbA1c %: 8.4; Duration of T1D (range) years: 4.6 (0.1-15.3) for CSII and 4.1 (0.3-12.4) for MDI; Inclusion criteria were to have an insulin requirement of more than 0.5U/kg/day, complete follow-up data, neither to use CGM during the entire period nor long-acting insulin together with CSII.	Ambulatory	Not specified	Direct-acting insulin analogs and a majority with long-acting analogs.	A. Sweden B.NR C.NR D.M>F E.NR F.NR G.NR H.NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 8.3 (0.4) vs 8.3 (0.4), NS **2. Number of SH episodes: CSII vs. MDI, sig:** 6 vs. 13, $p<0.05$ **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** 6 vs. 1, $p<0.01$ **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	24 months

Olsen, 2015, (176)	Prospective Observational study from a national registry-based study. Data collection from 2005-2011.	Denmark	3339 (1493:1846) (1721:3111) Mean age not mentioned. Patients were divided into age groups (<5y, 5-10y, 10-15y, 15-18y) Mean HbA1c presented only in graphs. Initially all children treated with pump were allocated to the case group: a control group was selected from the remaining children on MDI.	Ambulatory	Not specified	Not specified	A. Denmark B. > Danish C. NR D. > male E. NR F. NR G. NR H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** A mean significant difference of -5.29 mmol/mol in the CSII group **2. Number of SH episodes: CSII vs. MDI, sig:** NA **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NA **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	Mean 5.1 year
Wong, 2015, (177)	Prospective cohort, Published in 2010	USA	150 → 135 concluded and 127 did not switch treatment (85:42); 73:77; Mean age: 15.5±1.4 years; Duration of T1D: 6.1±3.9 years; Mean HbA1c, %: 8.8±1.9; All participants received similar diabetes education, and had a similar number of regular visits. Exclusion criteria included inability to understand spoken and written English. Families were invited to participate as a consecutive and convenience sampling	Ambulatory	Not specified	Not specified	A. USA B. White, Black, Hispanic and Asian C. Insurance status D. F>M E.NR F. Parental education G. amount of caregivers H.NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 8.3 (1.3) vs. 9.4 (2.3), p<0.05 **2. Number of SH episodes: CSII vs. MDI, sig:** NA **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NA **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	Until two years
Colino, 2016, (178)	Retrospective longitudinal study; Between 2003 and 2012	Spain	90 patients (all switched to pump); (52:38); Mean age 10.5 y, at the beginning of the pump treatment, there were 21 preschoolers, 28 prepubertal and 41 pubertal; Mean HbA1c (%): 6.9 (6.5-7.4); T1D duration: 4.3 (2.1-8.7) years; Data were collecting by reviewing charts retrospectively for 1 year before and a min of 1 year after CSII started.	Ambulatory	Not specified	51% were treated with detemir, 36% with glargine and 11% with NPH, and 1 patient was only using regular insulin	A. Spain B. All Caucasians C. Spanish Public Health Care System without restrictions D. 58% male E. NR F. NR G. NR H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 6.7 (0.8) vs. 6.9 (0.9), p<0.05 **2. Number of SH episodes: CSII vs. MDI, sig:** 6 vs. 17, p<0.05 **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** 0 vs. 2, NS **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	Median follow-up: 3.5±1.8 years

Haynes, 2016, (73)	Cross-sectional analysis of three diabetes registry databases (2011 – 2012) 21 (a): T1DX – US Type 1Diabetes Exchange 21 (b): DPV – German/Austrian Diabetes Patienten Verlaufsdokumentation 21 (c): WACDD – Western Australian Children Diabetes Database	USA,	**(a)** 7,102 (2878:4224); (3551:3551); Mean age 12.7±3.4 years; Mean HbA1c %: 8.6±1.4 **(b)** 18,787 (11032:7755); (9769:9018); Mean age: 12.8±3.6 years; Mean HbA1c %: 8.0±1.4 **(c)** 865 (562:303); (450:415); Mean age 13.4±3.4 years; Mean HbA1c %: 8.2±1.3	Ambulatory	Not specified	Not specified	A. USA, Germany, Austria and Australia B. NR C. NR D. (a) 50% male (b) 52% male (c) 52% male E. NR F. NR G. NR H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** NR as required **2. Number of SH episodes: CSII vs. MDI, sig:** (a) 188 vs. 324, P<0.05 (b) 274 vs. 307, p<0.05 (c) 24 vs. 7, p<0.05 **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NR **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	12 months
Ribeiro, 2016, (179)	Retrospective cohort, with data collection between	Brazil	40 (40:40); (19:21); Age: 14.2±2.35 years; Mean duration of T1D: 7.0 years;	Ambulatory	Not specified	Not specified	A. Brazil B. NR C. NR D. 46% male E.NR F.NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 8.4 (2.3) vs. 8.4 (0.9), NS **2. Number of SH episodes: CSII vs. MDI, sig:** 5 vs. 15, p=0.02	One year

	2011-2012		Mean HbA1c,%: CSII (8.9±2.5) and MDI (9.1±2.0); Inclusion criteria: duration of diabetes min 2 years; patient had been using MDI for at least 6 months, and later CSII for at least other 6 months; Severe hypoglycemia defined as episodes that required help from other person.				G.NR H.NR	**3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** zero **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	
Sherr, 2016,(30)	Retrospective Data from three registries (2011-2012) A. DPV (Prospective Diabetes Follow-up Registry) B. T1DX (T1D Exchange) C. NPDA (National Pediatric Diabetes Audit)	Germany and Austria (DPV), USA (T1DX) and England and Wales (NPDA)	54410 patients (19230:35180); 53% male, 47% female; Median Age by registry (IQR): DPV: 12.1 (8.6-14.8) years T1DX: 12.2 (9.2-15.0) years NPDA: 12.9 (9.9-15.0) years; Duration of diabetes by registry (IQR): DPV: 2.9 (0.3-6.1) years T1DX: 3.0 (1.0-6.0) years NPDA: 4.1 (1.8-7.0) years; Mean ± SD HbA1c (%), by registry: DPV: 8.0 (1.6) T1DX: 8.3 (1.4) NPDA: 8.9 (1.6); Participants included if they had a history of T1D, aged < 18 years, had information on the insulin delivery modality, and had attended at least one office visit during 2011 and 2012; Limitation: the period of pump use was not reported.	Ambulatory	Not specified	Not specified	A.Y B. Pump use was lower in ethnic minorities. C.NR D.M>F E.NR F.NR G. Relation with SES and outcomes H.NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 8.0 (1.2) vs. 8.5 (1.7), p<0.001 **2. Number of SH episodes: CSII vs. MDI, sig:** NA **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NA **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	One year

Szypowska, 2016,(71)	Prospective, multicenter, standardized diabetes patient registry; supported by the AstraZeneca, Boehringer Ingelheim, DexCom Inc. Diabetes Foundation UK, Foundation Hannoversche Kinderheilanstalt, Lilly Diabetes Excellence Centre, Medtronic Europe, Medtronic Foundation, Sanofi. 2016	19 European countries (39 centers) and 7 countries outside Europe	16 570 (7357: 9213); (8534:8036); Age 0-18 y (Median: 14y); Median diabetes duration: 5.3 y; HbA1c, %: CSII 7.7±0.69 vs. MDI 8.0±0.77; Datasets were aggregated over the most recent year of treatment for each patient.	Ambulatory	Not specified – Insulin pump usage was defined as at least one visit with pump therapy	Not specified	A. 77% of participants from European countries and 23% children from countries outside Europe (Israel, Brazil, Turkey). Use of CSII in European countries (45.8%) and in countries outside Europe (39.3%). B. NR C. Cost of CSII covered by: Health care system: 75%; Shared by heath care and family: 16%; Fully by family: 9% D. 51.5% M, 48.5% F E. NR F. NR G. It´s mentioned but they did not differentiate between groups H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 7.7 (0.69) vs. 8.0 (0.77), p<0.001 **2. Number of SH episodes: CSII vs. MDI, sig:** NA **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NA **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	Median follow: 5.3 years

Viner, 2016,(180)	Prospective cohort; From Jan 2008 to Dec 2013	United Kingdom	384 patients (207:158) – 12 patients were on two injections per day regimen; (191:193); Mean age: 13.3±2.5 years; Mean time followed in the clinic: 4.0 ±1.65 years; Multilevel models for change in HbA1c centered on age of 9 years: around half of the sample maintained HbA1c on 7.5% with minimal change across adolescence.	Ambulatory	Not specified	Not specified	A. UK B. White or British and non-white C. NR D. 50.4% female E. NR F. NR G. By quintiles: from most to least deprived H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** Not specified (analyses by interaction between variables on equity) **2. Number of SH episodes: CSII vs. MDI, sig:** NA **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NA **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	Mean follow: 4.0 years
Comissariat, 2017, (101)	Cross-sectional survey from a registry; From Feb 2015 to May 2016	USA	515 children (331:184); (278:273); Mean age ± SD: 5.2±1.2 years; HbA1c % Mean ± SD: 8.1±1.0; Mean ± SD duration of diabetes: 2.4±1.0 years; Diabetes diagnostic for at least 1 year; retrospective assessment for SH and DKA	Ambulatory	Not specified	Not specified	A.USA B. White non-Hispanic 78%, Black non-Hispanic 6%, Hispanic 11%, Other 6% C. NR D. Female 46% E.NR F. Level of parent education G. Annual household income ≥75,000: 62% among pump users and 36% among non-users H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 8.0 (0.9) vs. 8.3 (1.1), p<0.001 **2. Number of SH episodes: CSII vs. MDI, sig:** 20 vs. 15, NS **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** 10 vs. 15, NS **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	Three months
Gesuita, 2017, (181)	Cross-sectional multicenter study, from Jan 2008 to Feb 2009	Italy	768 (658:110); (428:340); Age: 0-4yo:5.7%, 5-9yo:19.2%, 10-17yo:75.1%; HbA1c: <7.5%: 28.1%, >7.5%: 71.9%; Mean duration of T1D: ≤5 years: 64.6%, 6-10 years: 10.7%, 11-16 years: 24.7%; Data were obtained from VIPKIDS (eValuation of Insulin Pump treatment in KIDS), with patients recruited being on MDI or CSII therapy at least for 6	Ambulatory	Not specified	Not specified	A. Italy B. NR C. Mother and father´s occupation level: unemployed, low, medium or high level of occupational position D. 56% male E.NR F. Parents´ educational level G. Hollingshead Four-factor Index of Social Status (SES)	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** CSII: 26% HbA1c <7.5%; MDI: 41% HbA1c <7.5% **2. Number of SH episodes: CSII vs. MDI, sig:** NA as required **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NA as required **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	No follow

			months, from 14 Italian Diabetes Pediatric Centers.				H.NR		
Karachaliou, 2017, (182)	Observational retrospective data from a follow-up from Jan 2011 to Dec 2012	Greece	80 (9:71); (45:44); Mean age: 12.05±5.15 years; Mean duration of T1D: 4.9±3.88 years; Mean HbA1c%: 8.02±1.09; This study examined the direct costs for T1D therapy from the public sector perspective.	Ambulatory	Not specified	Not specified	A. Greece B.84% Greek, 16% immigrant C.NR D.M>F E. NR F.NR G. Public reimbursement policies are the same throughout the country H.NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 7.23 (1.01) vs 8.29 (1.48), p=0.059 **2. Number of SH episodes: CSII vs. MDI, sig:** NA **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NA **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	2 years
Karges, 2017, (75)	Population-based prospective cohort study; Supported by the Competence Network DM and the German Center for Diabetes Research; Between Jan 2011 and Dec 2015	446 diabetes centers in Germany, Austria and	30579 patients (14119:16460); (16299:14280); Mean age 14.1±4.0 years; Mean HbA1c %: CSII 7.9±1.3 vs. MDI 8.2±1.7; Duration of diabetes: CSII 6.6±3.9 years vs. MDI 5.9±4.0 years; Patients were eligible for inclusion if they had a clinical diagnosis of T1D; exclusion criteria were younger than 6 months at diagnosis, being 20 years or older, having diabetes duration less than 1 year, using 3 or fewer daily insulin injections, and being using continuous glucose monitoring.	Ambulatory	Not specified	Not specified	A. Germany, Austria and Luxembourg B. migration background was considered C. NR D. M>F E. NR F.NR G. NR H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 7.99 (0.05) vs. 8.17 (0.05), p<0.001 **2. Number of SH episodes: CSII vs. MDI, sig:** 1437 vs. 2135, p<0.001 **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** 533 vs. 886 events, p<0.001 **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	5 years
Keller, 2017, (183)	Observational follow-up from 2009 to 2014	France	4293 (45% on pump =1932; 40% on basal-bolus =1720); (2205:2088); Age: 5.7-19.3 years; Mean duration T1D: 1.0-17.9 y; Mean HbA1c: 8.23 ±1.27 %;	Community (Diabetes Camp)	Not specified	Fast and long-acting insulins, and pre-mixed insulins.	A. France B. NR C. NR D. M>F E.NR F.NR G.NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 8.12 (1.09) vs. 8.32 (1.33), p<0.0001 **2. Number of SH episodes: CSII vs. MDI, sig:** NA **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NA	Five years

			Tool: The Diabetes Quality of Life for Youth questionnaire (DQOLY). The study was conducted in children and adolescents with T1D who attended diabetes summer camp between 2009 and 2014, and with less than a year of diabetes duration.			H. Diabetes Summer Camp	**4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** Patients on CSII had significantly worst health perception than patients on MDI.	
Phelan, 2017, (184)	Cross-sectional analysis of prospectively collected data from the Australasian Diabetes Data Network registry. 2015	Australia	3279 patients (1428:1219) - the remaining 564 were on two injections a day 52% male Mean age: 12.8 years Mean duration of T1D: 5.7 years Mean Hba1c: 8.3%	Ambulatory	Not specified	Insulin regimens were classified as twice-daily (BD) and at least three injections time a day (MID)	A. Australia B. NR C. Pumps are provided for those with private health insurance. D. male > female E. NR F. NR G. NR H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** - <6y: 7.8 (1.9) vs. 7.9 (2.0) - 6-10y: 7.6 (1.8) vs. 7.9 (2.0) - 10-14y: 8.2 (2.0) vs. 8.5 (2.1) - 14-18y: 8.3 (2.1) vs. 8.6 (2.2) **2. Number of SH episodes: CSII vs. MDI, sig:** NA **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NA **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	Cross-sectional
Shulman, 2017, (185)	Population-based cohort, data collected from Nov 2006 to March 2013	Canada	7076 (3700:3376); (3620:3456); Age groups: CSII (46.4% on 6th-13th birthday), MDI (71.2% ≥13th birthday); Duration of T1D: CSII (63.8% < 5 years); MDI (58.5% ≥5 years); Mean HbA1c for pump users: 58.2% between 7.5-9.0%; Data from administrative health databases were used that contain records of initial and annual renewal applications for pump funding. To be eligible, individuals must be < 19 years of age, have a diagnosis of T1D and have been on MDI for at least 1 year. The comparison	Ambulatory	Not specified	Not specified	A. Canada B. NR C. NR D. M>F E.NR F.NR G. Low-income families may be discontinuing pump therapy due to high burden of paying for the portion of pump supplies that is not reimbursed by the government funding program. H.NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** NA **2. Number of SH episodes: CSII vs. MDI, sig:** NA **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** 130 vs. 128, NS **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	2 years

			group was also part of a registry of individuals who were not on pump.						
Watson, 2017, (186)	Retrospective chart review in 2012	USA	729 (216 on CSII; 413 on MDI; 100 on BID); (354:375); Mean age: 12.5±3.7 years; Mean HbA1c: 8.7±1.7%; Mean duration of T1D: not reported; Exclusion criteria included patients diagnosed at ≤ 6 months of age, those not seen within the prior 12 months, and age≥ 18 years.	Ambulatory	Not specified	Not specified	A. USA B. White, black and other C. Insurance private or public: pump was used by 36% of private compared with only 18% of public patients. D. F>M E. NR F.NR G. Insurance private or public and the number of households H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 8.5 (1.1) vs. 9.1 (1.8), p<0.001 **2. Number of SH episodes: CSII vs. MDI, sig:** NA **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NA **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	Cross-sectional
Auzanneau, 2018, (187)	Cross-sectional data from the DPV Registry for 2015/16; supported by the German center for Diabetes Research.	Germany	29284 patients (13353:15931); (15462:13822); Median age: 13.4 (9.8-16.2) y; T1D duration: 4.0 (1.3-7.5) y; Median Hba1c: 7.62% Clinical data were aggregated for the years 2015 and 2016 and stratified by sex and area deprivation quintiles. The aim was to assess area deprivations (income, employment, education, municipal/district revenue, social capital, environment and security) and the indicators of diabetes care (like the use of CSII) and the outcomes (HbA1c and rates of SH and DKA).	Ambulatory	Not specified	Not specified	A. Germany B. 21.6% with migration background C. assessed by area deprivation D. M>F E. NR F. assessed by area deprivation G. assessed by area deprivation H. Involvement in a diabetes education program	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** NA as required **2. Number of SH episodes: CSII vs. MDI, sig:** NA as required **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NA as required **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	Cross-sectional
Danne, 2018, (188)	Retrospective data from the German/Austrian DPV	Germany and Austria	2529 patients (660:1869); Comprehensive data for 64 patients in each group. Mean age, y: 11.5±5.1 for CSII and 12.0±2.8 for MDI;	Ambulatory	Tubeless insulin pump (Omnipod Insulin Management System)	Not specified	A. Germany and Austria B. NR C. NR D. F>M E. NR F. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 8.0 (0.02) vs. 8.0 (0.05), NS **2. Number of SH episodes: CSII vs. MDI, sig:** NA	Three years

	registry, with collected data from 2012 and 2016; Diabetes foundation grants		Mean HbA1c, %: 7.5±1.2 for CSII and 7.6±1.3 for MDI; T1D duration, y: 3.2±3.7 for CSII and 4.1±3.2 for MDI; This analysis examined glycemic control in youth with T1D who switched from MDI to CSII and compared them to who continued MDI therapy over a 3-year time period.				G. NR H. NR	**3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NA **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	
Evans-Cheung, 2018, (189)	Retrospective data collected between 2002 and 2013	United Kingdom	161 (161:161); (70:91); Median age at CSII start: 11.9 (1.1-17.6) years; Median Hba1c pre-CSII, %: 9.0 (5.5-15.9); The aim was to assess HbA1c values and hospitalization rates (representing DKA and SH episodes) before, during and after CSII therapy.	Ambulatory	Not specified	Not specified	A. UK B. NR C. NR D. F>M E. NR F. NR G. NR H. NR	**1. HbA1c: CSII vs. MDI [median % (range)], sig:** 8.3 (5.4-14.4) vs. 9.0 (5.5-15.9), NS **2. Number of SH episodes: CSII vs. MDI, sig:** NS **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** 18 vs. 4, p<0.05 **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	Median follow-up: 2.3 (0-8.1) years
O´Connor, 2018, (190)	Retrospective cohort with data collected from 2011 and 2016; supported by the Institute for Translational Health Science Rising Star Program.	Seattle, USA	2131 patients (1316:815); 52.5% male; Mean HbA1c: 8.9±1.8 %; Mean age: 11.4±4.3 years; To be included: at least 4+ visits during study period. The aim was to assess health disparities with the use of CSII.	Ambulatory	Not specified	Not specified	A. USA B. Classified as non-Hispanic white, Hispanic, non-Hispanic Black, Asian/Pacific Islander, American Indian/Alaska Native C. NR D. M>F E. NR F. NR G. health insurance type (private, government, or charity/self-pay) as a proxy for income H. NR	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 8.7 (1.6) vs. 9.0 (1.8) **2. Number of SH episodes: CSII vs. MDI, sig:** NA as required **3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** NA as required **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA	Cross-sectional
Petrovski, 2018, (191)	Prospective cohort from 2016 to 2017	Qatar	138 patients (138:138); (62:76); Mean age: 9.8±3.4 years; Mean Hba1c: 9.7(1.3)% Mean T1D duration: 2.4±1.9 y;	Ambulatory	MiniMed Veo and 640G (a sensor augmented-pump); insulin not specified.	Not specified	A. Qatar B. Insulin pumps and sensors are reimbursed according to the nationality C. NR D. F>M	**1. HbA1c: CSII vs. MDI [mean % (SD)], sig:** 8.1(0.6) vs. 9.7 (1.3), p<0.05 **2. Number of SH episodes: CSII vs. MDI, sig:** 1 vs. 1, NS	One year

Patients who started on CSII were prospectively followed during one year, using a standardized protocol. Criteria to start on CSII: inadequate glycemic control with MDI, recurrent hyperglycemia, dawn phenomenon, recurrent severe hypoglycemia, frequent DKA, erratic blood glucose, lifestyle flexibility. Patients were excluded if CSII use were transitory (less than 3 months).	E. NR F. NR G. NR H. NR	**3. Number of patients with ≥ 1 DKA episode: CSII vs. MDI, sig:** 3 vs. 8, $p<0.05$ **4. GV: % of TIR, hypo and/or hyperglycemia: CSII vs. MDI, sig:** NA **5. HRQoL comparisons between CSII vs. MDI, sig:** NA

Table S2: Risk of bias assessment for randomized clinical trials (56) **on the effect of continuous subcutaneous insulin infusion (versus multiple daily injections of insulin) on glycemic outcomes and health-related quality of life (HRQoL). Glycemic outcomes include glycated hemoglobin, severe hypoglycemia, diabetic ketoacidosis, and the percentage of time that the glucose level was in the target range (TIR) of 70 to 180 mg/dL (3.9 to 10.0 mmol/L), in hyperglycemia and in hypoglycemia.**

Overall assessment: **Low risk of bias** All criteria met (low risk for each domain); or unclear risk in one domain **Intermediate risk of bias:** high risk of bias in one domain; or unclear risk in two domains, and the judgment that this was unlikely to have biased the results; **High risk of bias:** high risk of bias for one domain); or two criteria unclear, and the judgment that this was likely to have biased the results. N/A: Not available because HRQoL was not measured.

Author, Year (#)	A: Random sequence generation (Selection bias)	B: Allocation concealment (Selection bias)	C1: Blinding of participants and personnel (Performance bias)	D1: Blinding of glycemic outcomes assessment (Detection bias) D2: Blinding of HRQoL assessment (Detection bias)	E1: Incomplete glycemic outcome data (Attrition bias) E2: Incomplete HRQoL data (Attrition bias)	F: Selective reporting (Reporting bias)	G1: Overall assessment for glycemic outcomes G1: Overall assessment for HRQoL data
Cohen, 2003	?	?	?	+ +	? ?	+	− −
Weintrob, 2003	?	?	?	+ +	+ +	+	− −
DiMeglio, 2004	+	+	?	+ N/A	+ N/A	+	+ N/A
Doyle, 2004	+	+	?	+ +	+ ?	+	+ ?
Weintrob, 2004	?	?	?	+ N/A	? N/A	+	− N/A
Fox, 2005	+	+	?	+ N/A	+ N/A	+	+ N/A
Wilson, 2005	+	+	?	+ ?	? ?	+	? −

Opipari-Arrigan, 2007	+	+	?	+ −	? ?	+	? −
Nuboer, 2008	+	+	?	+ +	+ +	+	+ +
Skogsberg, 2008	+	+	?	+ +	+ +	+	+ +
Nabhan, 2009	+	?	?	+ N/A	+ N/A	+	? N/A
Bergenstal, 2010	?	+	?	+ N/A	+ N/A	+	? N/A
Bergenstal, 2011	?	?	?	+ N/A	? N/A	+	− N/A
Thrailkill, 2011	+	+	?	+ ?	+ +	+	+ ?
Rubin, 2012	?	?	?	+ ?	+ +	+	− −
Slover, 2012	?	?	?	? N/A	+ N/A	+	− N/A
Lang, 2018	?	+	?	+ N/A	+ N/A	+	? N/A
Mueller-Godeffroy, 2018	+	+	?	+ +	+ +	+	+ +
Blair, 2019	+	+	?	+ ?	+ ?	+	+ ?

Table S3: Risk of bias assessment for non-randomized studies (62) **on the effect of continuous subcutaneous insulin infusion (versus multiple daily injections of insulin) on glycemic outcomes and health-related quality of life (HRQL).**

Overall assessment: **Low risk of bias:** All criteria met (low risk for each domain); or unclear risk in one domain **Intermediate risk of bias:** high risk of bias in one domain; or unclear risk in two domains, and the judgment that this was unlikely to have biased the results; **High risk of bias:** high risk of bias for one domain); or two criteria unclear, and the judgment that this was likely to have biased the results. **N/A:** for Q1, Q2 and Q3: not applicable, because study does not include a comparison group; for Q5: not applicable, because assessor cannot be blinded; for Q7 and Q8: not applicable, because it is a cross-sectional study or only one groups was followed over time.

Author, Year (#)	Study design (case-control, cohort, cross-sectional)	Q1: Selection bias	Q2: Selection bias	Q3: Selection bias	Q4: Performance bias	Q5: Detection bias	Q6: Detection bias	Q7: Attrition bias	Q8: Attrition bias	Q9: Reporting outcomes	Q10: Reporting adverse effects	Q11: Confounding	Q12: Confounding	Q13: Confounding	Q14: Overall Assessment
Litton, 2002 (120)	Cohort	+	+	+	?	N/A	+	+	+	+	+	?	-	-	-
Willi, 2003 (121)	Cohort	?	?	N/A	+	N/A	?	?	?	+	?	?	?	?	?
Alemzadeh, 2004 (122)	Cohort	+	+	+	+	N/A	+	+	+	+	+	?	-	?	-
Shehadeh, 2004 (123)	Cohort	-	-	N/A	?	N/A	?	?	?	+	+	-	-	-	-
Weinzimer, 2004 (124)	Cohort	-	?	N/A	?	N/A	?	?	+	+	+	?	-	-	-

Bin-Abbas, 2005 (192)	Cohort	?	?	N/A	+	N/A	+	?	?	+	+	+	−	−	−
Jeha, 2005 (126)	Cohort	?	?	N/A	?	N/A	+	?	?	+	?	+	−	−	−
Mack-Fogg, 2005(127)	Cohort	−	−	?	+	N/A	?	?	?	+	+	?	−	−	−
McMahon, 2005 (128)	Cohort	−	?	N/A	?	N/A	−	?	?	+	+	−	−	−	−
O'neil, 2005 (129)	Cross-sectional	N/A	N/A	N/A	+	N/A	?	N/A	N/A	+	−	−	−	−	−
Schiaffini, 2005 (130)	Cohort	+	+	+	+	N/A	−	+	+	+	+	?	−	−	−
Berhe, 2006 (131)	Cross-sectional	N/A	N/A	N/A	+	N/A	−	+	+	+	+	+	−	−	−
Springer, 2006 (132)	Cross-sectional	?	?	?	?	N/A	?	?	?	?	?	?	?	?	?
Alemzadeh, 2007 (133)	Cohort	+	+	N/A	+	N/A	+	+	+	+	+	+	−	?	?
García-García, 2007 (134)	Cohort	+	+	+	?	N/A	+	+	?	+	+	−	−	−	−
Kapellen, 2007 (135)	Cohort	+	+	+	+	N/A	?	?	?	+	?	?	?	?	?
Schiaffini, 2007 (136)	Cohort	+	+	+	+	N/A	?	−	+	+	+	+	+	+	?
Berghaeuser, 2008 (137)	Chart-review	+	+	+	?	N/A	+	?	?	+	+	+	−	−	?
Jakisch, 2008 (138)	Cohort	+	+	+	+	N/A	?	−	−	+	+	−	+	+	?
Johannesen, 2008 (139)	Cohort	+	+	+	+	N/A	+	+	+	+	+	+	+	+	+
Kawamura, 2008 (140)	Cohort	−	−	N/A	?	N/A	+	?	?	+	+	−	−	−	−
Weinzimer, 2008 (141)	Cohort	+	+	+	+	N/A	+	+	+	+	−	+	−	−	−
Abaci, 2009 (142)	Cohort	?	?	N/A	+	N/A	+	?	?	+	+	?	−	−	−
Anderson, 2009 (143)	Cohort	?	?	N/A	+	N/A	+	+	+	+	?	?	−	+	−

Minkina-Pedras, 2009 (144)	Cohort	+	+	+	+	N/A	+	+	+	+	+	+	+	+	+	
Shashaj, 2009 (145)	Cohort	−	−	N/A	?	N/A	−	?	?	?	?	−	?	?	−	
Cortina, 2010 (146)	Cross-sectional	N/A	N/A	N/A	+	N/A	−	N/A	N/A	−	−	−	−	−	−	
Sulmont, 2010 (147)	Cohort	+	+	?	+	N/A	?	+	−	+	+	−	−	−	−	
Wintergest, 2010 (148)	Cohort	?	?	?	?	N/A	?	?	?	?	?	−	−	−	−	
Wu, 2010 (149)	Cross-sectional	+	−	−	+	N/A	−	N/A	N/A	+	−	−	−	−	−	
Cengiz, 2011 (193)	Cohort	?	?	+	+	N/A	?	+	?	+	+	+	−	−	−	
Knight, 2011 (151)	Cohort	−	−	N/A	?	N/A	?	?	?	+	?	−	?	−	−	
Starkman, 2011 (152)	Chart-Review	?	?	?	−	N/A	?	−	?	?	?	−	−	−	−	
Batajoo, 2012 (153)	Cohort	?	?	N/A	+	N/A	?	?	+	+	?	+	?	?	?	
Fendler, 2012 (154)	Cohort	+	+	+	+	N/A	+	+	+	+	?	+	+	+	+	
Hasselmann, 2012 (155)	Cohort	+	+	+	+	N/A	−	+	+	+	+	+	+	+	?	
Hughes, 2012 (194)	Cohort	?	?	N/A	?	N/A	?	?	?	+	+	−	−	−	−	
Katz, 2012 (157)	Cohort	+	+	+	+	N/A	?	−	−	−	+	−	−	−	−	
Makaya, 2012 (158)	Cohort	−	−	N/A	?	N/A	?	?	?	+	+	−	−	−	−	
Senniappan, 2012 (95)	Case-control	+	+	+	+	N/A	?	+	?	?	?	+	+	+	?	
Thompson, 2012 (159)	Cross-sectional	+	+	+	+	N/A	?	N/A	N/A	+	−	+	−	−	−	
Cooper, 2013 (160)	Cohort	+	?	+	?	N/A	?	?	?	+	+	?	+	+	?	
Froisland, 2013 (195)	Cross-sectional	+	+	+	+	N/A	?	−	+	+	+	?	+	+	?	

Hilmi, 2013 (100)	Cohort	?	−	−	?	N/A	?	?	?	+	?	−	−	−	−
Johnson, 2013 (162)	Case-control	+	+	+	?	N/A	?	+	+	+	+	+	+	+	?
Lukacs, 2013 (163)	Cross-sectional	N/A	N/A	N/A	+	N/A	−	N/A	N/A	−	−	+	−	−	−
Schiel, 2013 (164)	Cohort	+	+	+	+	N/A	?	+	?	+	?	?	?	?	?
Schreiver, 2013 (165)	Cross-sectional	+	+	−	−	N/A	+	+	?	+	?	−	−	−	−
Alsaleh, 2014 (166)	Cross-sectional	?	?	?	N/A	N/A	?	N/A	N/A	+	−	−	−	−	−
Birkebaek, 2014 (167)	Cross-sectional	+	+	+	+	N/A	−	N/A	N/A	+	?	+	+	+	−
Blackman, 2014 (168)	Cross-sectional	+	+	+	+	N/A	?	+	?	+	+	+	+	+	?
Brancato, 2014 (169)	Cohort	?	?	N/A	+	N/A	?	+	+	+	?	+	?	?	?
Cherubini, 2014 (170)	Cross-sectional	?	?	?	N/A	N/A	?	?	?	+	−	−	−	−	−
Dovc, 2014 (171)	Cohort	?	?	−	+	N/A	?	?	−	+	?	?	−	−	−
Fredheim, 2014 (172)	Cohort	+	+	+	+	N/A	?	+	+	+	+	+	+	+	+
Maahs, 2014 (74)	Cross-sectional	+	+	?	+	N/A	?	?	?	+	+	+	?	?	?
Mameli, 2014 (173)	Cohort	−	−	N/A	?	N/A	?	?	?	+	+	−	+	−	−
Alhayek, 2015 (174)	Cross-sectional	N/A	N/A	N/A	+	N/A	?	N/A	N/A	−	−	−	−	−	−
Brorsson, 2015 (175)	Case-control	?	?	+	+	N/A	?	+	+	+	+	+	+	+	?
Olsen, 2015 (176)	Cohort	+	+	+	+	N/A	?	+	+	+	−	+	+	+	?
Wong, 2015 (177)	Cohort	+	?	?	?	N/A	?	+	?	?	?	?	+	+	?
Colino, 2016 (178)	Cohort	?	?	N/A	+	N/A	?	?	?	+	+	+	+	+	?

Haynes, 2016 (73)	Cross-sectional	+	+	?	+	N/A	?	+	+	?	+	+	+	+	+	
Ribeiro, 2016 (179)	Cohort	−	−	N/A	?	N/A	?	?	?	+	+	−	−	−	−	
Sherr, 2016 (30)	Cohort	+	?	?	−	N/A	?	?	?	+	+	?	−	−	−	
Szypowska, 2016 (71)	Cohort	+	+	+	+	N/A	?	+	?	+	?	+	+	?	?	
Viner, 2016 (180)	Cohort	+	+	+	+	N/A	?	+	+	+	+	+	+	+	+	
Comissariat, 2017 (196)	Cross-sectional	+	+	?	+	N/A	?	?	?	+	+	?	?	?	?	
Gesuita, 2017 (181)	Cross-sectional	+	+	+	+	N/A	?	?	?	+	+	?	?	?	?	
Karachaliou, 2017 (182)	Cohort	?	?	?	?	N/A	?	?	?	+	?	?	?	?	?	
Karges, 2017 (75)	Cohort	+	?	?	+	N/A	?	?	?	+	+	?	+	+	?	
Keller, 2017 (197)	Cohort	?	?	?	?	N/A	?	?	?	+	?	?	−	−	−	
Phelan, 2017 (184)	Cross-sectional	+	−	−	+	N/A	?	N/A	N/A	+	−	+	−	−	−	
Shulman, 2017 (185)	Cohort	+	+	+	?	N/A	?	+	?	?	?	?	−	−	−	
Watson, 2017 (186)	Chart-Review	+	+	+	?	N/A	?	?	?	+	?	?	?	?	?	
Auzanneau, 2018 (187)	Cross-sectional	+	+	+	?	N/A	?	+	+	+	+	+	+	+	+	
Danne, 2018 (188)	Cohort	+	+	+	?	N/A	?	−	+	−	?	−	+	+	−	
Evans-Cheung, 2018 (189)	Cohort	?	?	?	+	N/A	?	?	?	+	+	+	?	?	?	
O´Connor, 2018 (190)	Cross-sectional	+	+	+	+	N/A	?	+	+	−	?	+	+	+	?	
Petrovski, 2018 (191)	Cohort	?	?	?	+	N/A	?	?	?	+	+	+	?	?	?	

Legend:

Q1: Do the inclusion/exclusion criteria vary across the comparison groups of the study*?*

Q2: Does the strategy for recruiting participants into the study differ across groups?

Q3: Is the selection of the comparison group inappropriate, after taking into account feasibility and ethical considerations?

Q4: Does the study fail to account for important variations in the execution of the study from the proposed protocol?

Q5: Was the outcome assessor not blinded to the intervention or exposure status of participants?

Q6: Were valid and reliable measures, implemented consistently across all study participants used to assess inclusion/exclusion criteria, intervention/exposure outcomes, participant health benefits and harms, and confounding?

Q7: Was the length of follow-up different across study groups?

Q8: In cases of high loss to follow-up (or differential loss to follow-up), was the impact assessed (e.g., through sensitivity analysis or other adjustment method)?

Q9: Are any important primary outcomes missing from the results?

Q10: Are any important harms or adverse events that may be a consequence of the intervention/exposure missing from the results?

Q11: Are results believable taking study limitations into consideration?

Q12: Any attempt to balance the allocation between the groups or match groups (e.g., through stratification, matching, propensity scores).

Q13: Were important confounding variables not taken into account in the design and/or analysis (e.g., through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment such as instrumental variables)?

Q14: Interpretation of information

Table S4: Health-related quality of life (HRQoL) and treatment satisfaction with continuous subcutaneous insulin infusion (CSII) versus multiple-daily injections (MDI) in randomized controlled trials (RCT) and non-randomized studies (NRS).

Reference	Design	Tool and definitions	Score				Overall findings
			Baseline	CSII	MDI	Statistical significance	
Cohen, 2003 (103)	Randomized controlled trial	DTSQ	20.5±3.6 ¥	32±6.5	21.8±3.7	P<0.05	No data for overall HRQoL, only for the satisfaction subscale.
		DQoLY – only for satisfaction subscale	77.4±16.1 ¥	82.7±13	76.4±14.3	P<0.05	A higher score represents better treatment satisfaction.
Weintrob, 2003 (104)	Randomized controlled trial	DTSQ	21.4±3.3 ¥	30.6±3.7	21.9±3.8	P<0.01	No data for overall HRQoL, only for satisfaction subscale.
		DQoLY – satisfaction subscale	71.9±14.5 ¥	74.8±13.5	73.5±14.0	NS	A higher score represents better treatment satisfaction.
Doyle, 2004 (105)	Randomized controlled trial	DQoLY	-	-	-	NS	Data not shown.
Wilson, 2005 (107)	Randomized controlled trial	DQOL for parents of toddlers	CSII: 2.3±0.3 vs. MDI 2.3±0.6	Δ CSII: -0.24±0.25	Δ MDI -0.8±0.19	p=0.03 for differences from baseline. Differences between groups NS.	Final scores for both therapies not reported.
Opipari-Arrigan, 2007 (108)	Randomized controlled trial	PEDsQL (Diabetes Module) – completed by the parents.	CSII 55.7±10.4 vs. MDI 62.0±21.8	63.7±13.0	68.5±24.4	p<0.05	A higher score represents better quality of life.
Nuboer, 2008 (109)	Randomized controlled trial	PEDsQL – completed by all parents and almost the totality of the children	CSII 79.4±11.3 vs. MDI 79.2±9.5	88.8±9.0	82.3±12.8	NS	A higher score represents better quality of life.
Skogsberg, 2008 (110)	Randomized controlled trial	DTSQ	-	-	-	P<0.05	No data for overall HRQOL DTSQ not shown in scores
Thrailkill, 2011 (114)	Randomized controlled trial	Self-reported treatment satisfaction questionnaire	-	-	-	-	Scores not given

Rubin, 2012 (198)	Randomized controlled trial	PedsQL version 4.0 (children and caregivers) Psychosocial Health Summary Score and Physical Health Summary Score Diabetes-specific HRQOL was assessed using the Hypoglycemia Fear-Scale II (HFS-II) Treatment satisfaction was assessed using the Insulin Delivery System Rating Questionnaire (IDSRQ)	Psychosocial: CSII 78.38±14.59 vs. MDI 78.76±10.27 Physical: CSII 86.99±12.99	Psychosocial: ΔCSII: 3.39 Physical: ΔCSII: 2.53	Psychosocial: ΔMDI: 3.64 Physical: ΔMDI: 1.41	Psychosocial: P<0.01 Physical: NS	Final scores not reported. Higher scores indicate better HRQoL. There were no significant between-arm differences in change in HRQL.
Mueller-Godeffroy, 2018 (118)	Randomized controlled trial	Children and adolescent Diabetes-specific HRQoL (DHRQoL) measured using a specific module of the KINDL-R; KINDL-R is a generic instrument for assessing Health-Related Quality of Life in children and adolescents aged 3 years and older. Adolescents and their caregivers completed the Diabetes Treatment Satisfaction Questionnaire (DTSQ)	Children 8-11y: CSII 68.1±14.9 vs. MDI 61.8±15.2 Adolescents 12-16y: CSII 70.6±11.9 vs. 67.8±16.9	Children 8-11y: 74.5±12 Adolescents 12-16y: 74.2±13.0	Children 8-11y: 64.3±14.9 Adolescents 12-16y: 70.9±16.0	Children 8-11y: P<0.05 Adolescents 12-16y: NS	Higher scores indicate better HRQoL
Blair, 2019 (119)	Randomized controlled trial	PEDsQL	NR	Δ CSII: 3.1 (95%CI: -0.6 to 6.8)	NR	NS	Final scores not reported. An adjusted mean difference of 3.1 (95%CI -0.6 to 6.8) favored CSII, NS.
Shehadeh, 2004 (123)	Cohort	DTSQ and a modification of the Diabetes Quality of Life Measure for parents.	-	-	-	Significant values favoring CSII	Data score available for parental quality of life.
Jeha, 2005 (126)	Cohort	PSI – assess the overall level of parenting stress experienced.	Pre-CSII: 66	62	66	NS	No data score for overall HRQoL
McMahon, 2005 (128)	Cohort	DQOL	Pre-CSII: 159.3±4.1	173.9±4.1	159.3±4.1	P<0.05	Significant value accounted for self-efficacy with diabetes treatment

O'Neil, 2005 (129)	Cross-sectional	HRQoL was assessed using a modified diabetes-specific measure of quality of life, consisting of diabetes life satisfaction scale, disease impact scale and a disease-related worries scale	-	Impact scale:54.9±12.9 Worries scale:20.3±7.0 Satisfaction scale:62.5±9.9 Self-rated health: 3.4±0.6	Impact scale:54.2±13.7 Worries scale:21.6±9.0 Satisfaction scale:59.1±12.3 Self-rated health:3.3±0.6	NS	No data for overall HRQoL. For impact scale, higher scores indicate lower HRQoL; For Worries scale, higher scores indicate lower HRQoL; For Satisfaction scale, higher scores indicate higher HRQoL.
Alemzadeh, 2007 (133)	Cohort	TAPQoL – A questionnaire used to assess parent's perception of HRQoL in preschool children.	-	-	-	No significant differences were found for any of the subscales.	No data as needed for the scores on HRQoL.
Johannesen, 2008 (139)	Open intention-to-treat	"Validated" QoL questionnaires, categorized intro four groups: "Diabetes affecting daily life", "Worries regarding diabetes", "Satisfaction in daily life", and "General aspects". Authors did not specify the questionnaire.	-	-	-	NS	No data for overall HRQoL.
Kawamura, 2008 (140)	Prospective intervention study	ITR-QoL – effects pre and post-CSII	-	-	-	Data Scores for 13/23 items in the questionnaire showed improvement following the CSII therapy.	No data for overall HRQoL.
Cortina, 2010 (146)	Cross-sectional	Children's Depression Inventory	-	-	-	-	This was not considered a HRQoL questionnaire. CSII users were more prone to engage in more frequent glucose meters, had fewer negative feelings around glucose meters, and took on more responsibility for diabetes management.
Wu, 2010 (149)	Cross-sectional	DQOL (Diabetes Quality of Life).	75.5±11.0 ¥	77.3±10.4	74.1±11.5	NS	Higher scores indicate better HRQoL.
Froisland,2012 (195)	Cross-sectional	DIABKIDS questionnaires DCGM-37 (measurement of six dimensions of HRQoL) and DDM-10 (two dimensions specific to diabetes)	Total Score: 78±14 ¥	-	-	DCGM-37 scales were not associated with mode of insulin therapy. DDM-10 scales did not present any	No significant differences in scores were found between users of an insulin pump and multi-injection treatment.

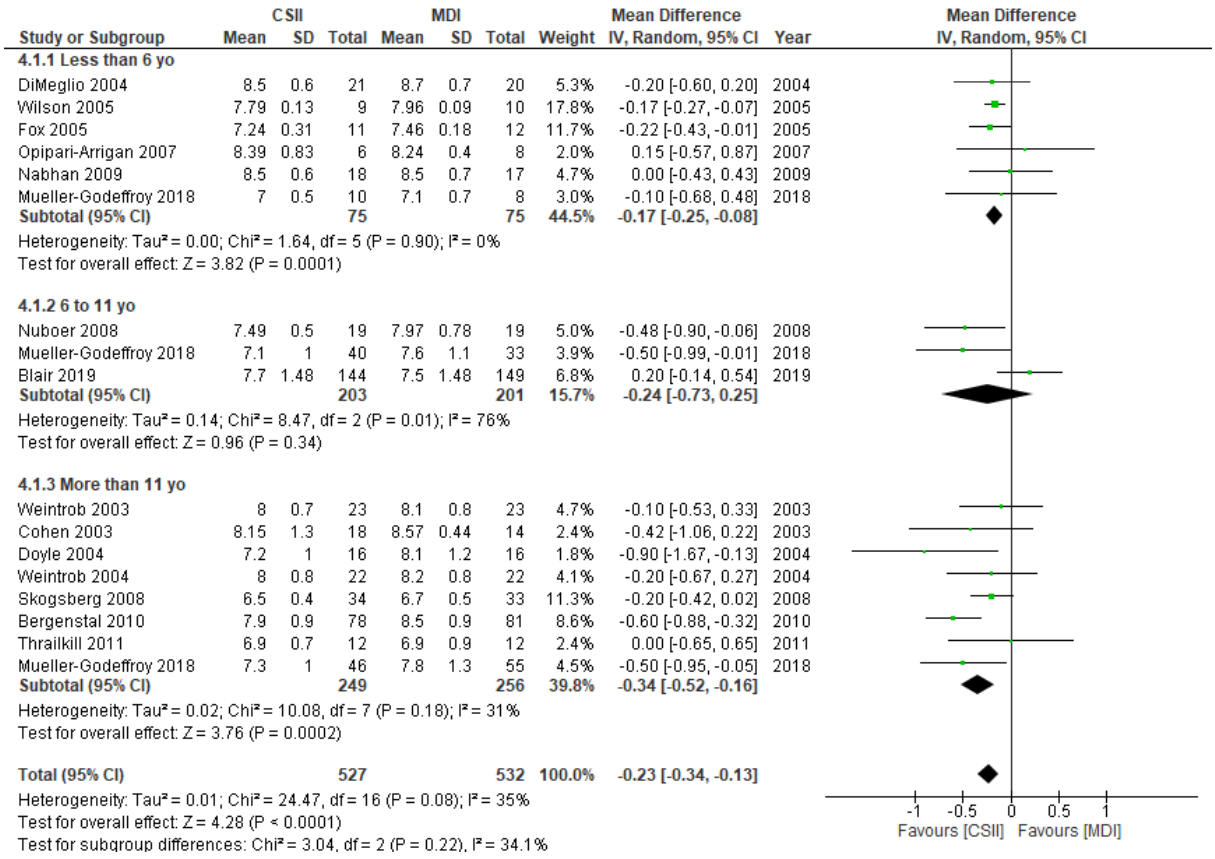
						significant associations between therapies.	
Lukacs, 2013 (163)	Cross-sectional	PedsQL 4.0 Generic Core Scale (GCS) and the PedsQL Diabetes Module (DM)	No data	82.1±9.2	77.0±10.0	P<0.001	GCS was considered the main score for HRQoL. Higher scores indicate better HRQoL.
Alsaleh, 2014 (166)	Cross-sectional	Face-to-face interviews regarding health and clinical outcomes, home and family life, school life, and psycho-social impacts.	-	-	-	Administration of insulin via pump rather than injections was generally preferred.	No data for overall of HRQoL.
Birkebaek, 2014 (167)	Cross-sectional	PedsQL 3.0 Diabetes Module (PedsQL DM) and the PEDsQL 4.0 generic Core Scales (PedsQL GCS) aiming for child self-report treated for more than one year	CSII 81.2±5.7 vs. MDI 79.9±5.7	82.8±15.5	79.1±15.5	P=0.02	Total scale score was considered the main score for HRQoL, in children treated for more than one year. Higher scores indicate better HRQoL.
Cherubini, 2014 (170)	Cross-sectional	IDSRQ - assesses HRQOL based on patients' perception of their insulin delivery system. This tool was correlated with the DQOLY.	-	-	-	The CSII group had significantly higher level of treatment satisfaction and perceived clinical efficacy, and a lower level of daily activity interference than the MDI group.	No data for overall HRQoL.
Al Hayek, 2015 (174)	Cross-sectional	FOH and SCARED	-	-	-	Patients on CSII had significantly lower levels of worry, panic disorder, separation anxiety disorder, and significant school avoidance than patients on MDI.	They were not considered HRQoL questionnaires.
Keller, 2017 (183)	Cohort	DQoLY	-	-	-	Patients on CSII had significantly worst health perception than patients on MDI.	No data for overall HRQoL.

¥ Baseline score on HRQoL questionnaire was presented for the entire sample without differentiating between treatment arms .**DTSQ:** Diabetes Treatment Satisfaction Questionnaire; **DQoLY:** Diabetes Quality of Life for Youth Questionnaire; **DQOL:** Diabetes Quality of Life Instrument; **PedsQL:** Pediatric Quality of Life Inventory; **PSI:** Parental Stress Inventory; **ITR-QoL:** Insulin therapy satisfaction questionnaire, **IDSRQ:**

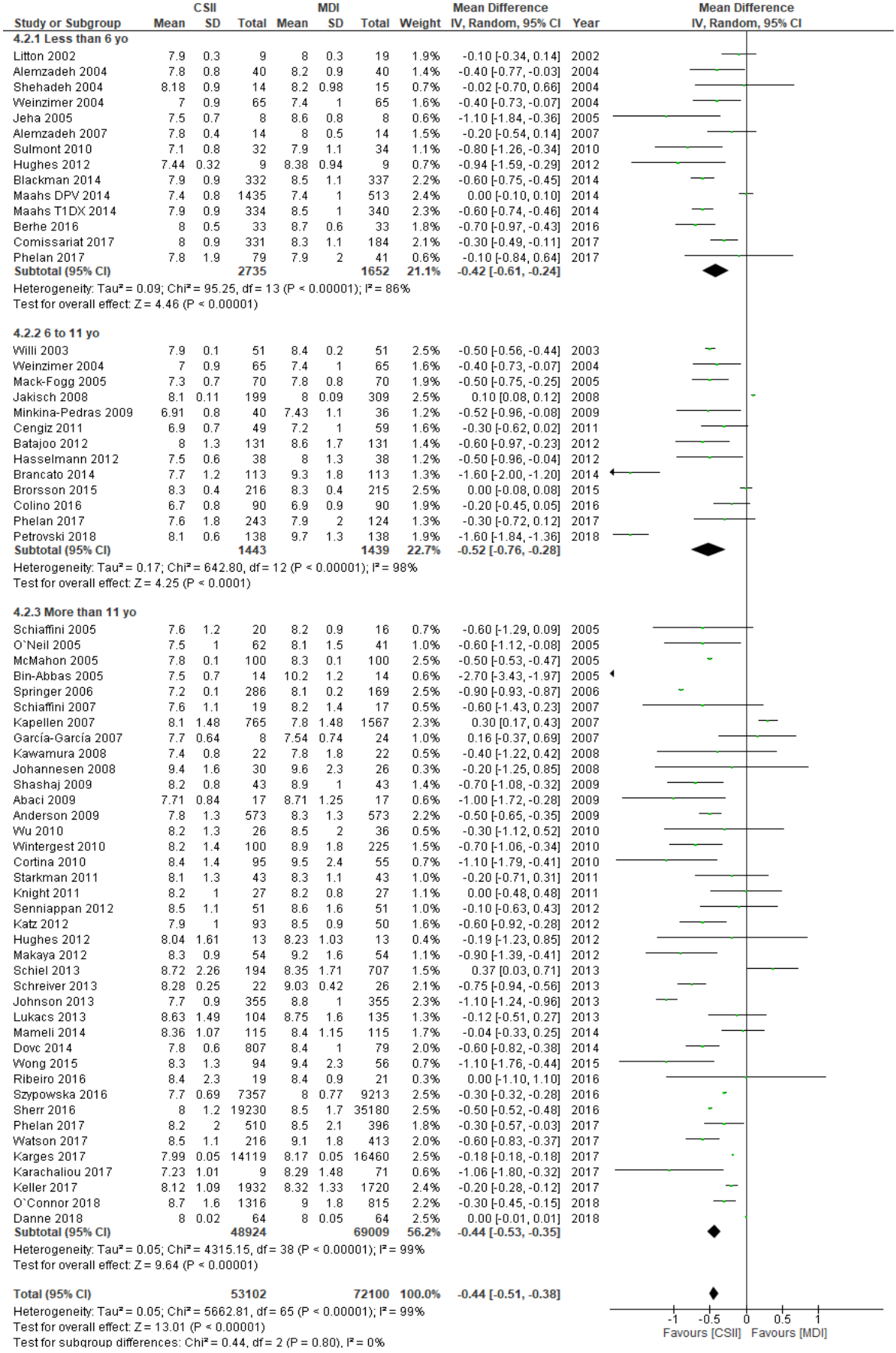
Insulin Delivery System Rating Questionnaire; **FOH:** fear of hypoglycemia; **SCARED:** Screen for Child Anxiety-related disorders; **RCT**: Randomized controlled trial; **NRS**: Non-randomized studies; **HRQoL**: Health-related quality of life; **NS**: non-significant.

Figure S1: Forest plot comparing the effect of continuous subcutaneous insulin infusion (CSII) versus multiple-daily injections of insulin (MDI) on glycated hemoglobin (HbA1c) in randomized clinical trials (RCT) (S1.1) and in non-randomized studies (NRS) (S1.2). Results are broken down by group of age.

S1.1: Randomized trials. Mean difference of HbA_{1c} (%)



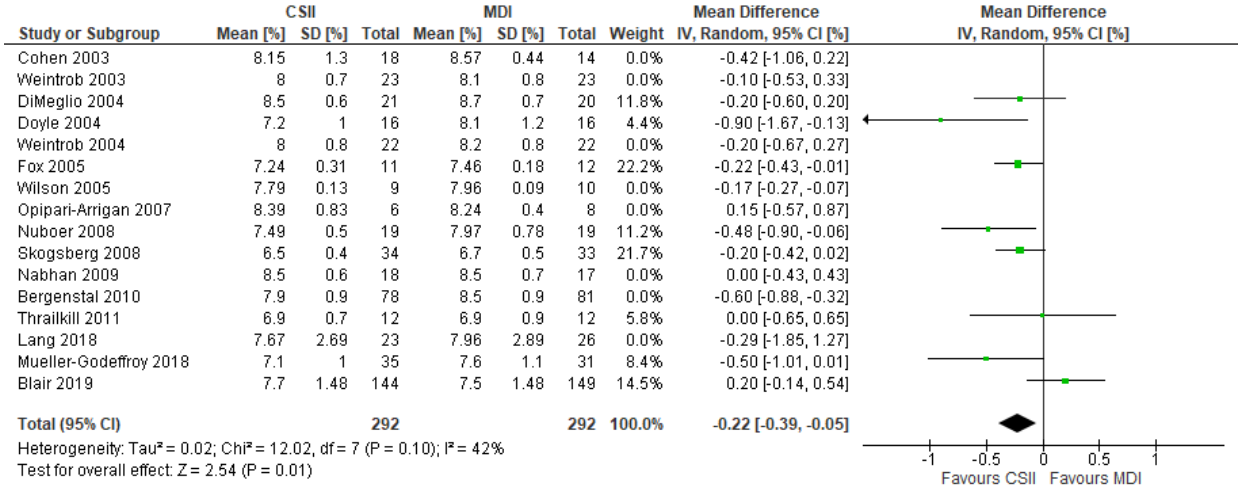
S1.2: Non-randomized studies. Mean difference of HbA_{1c} (%)



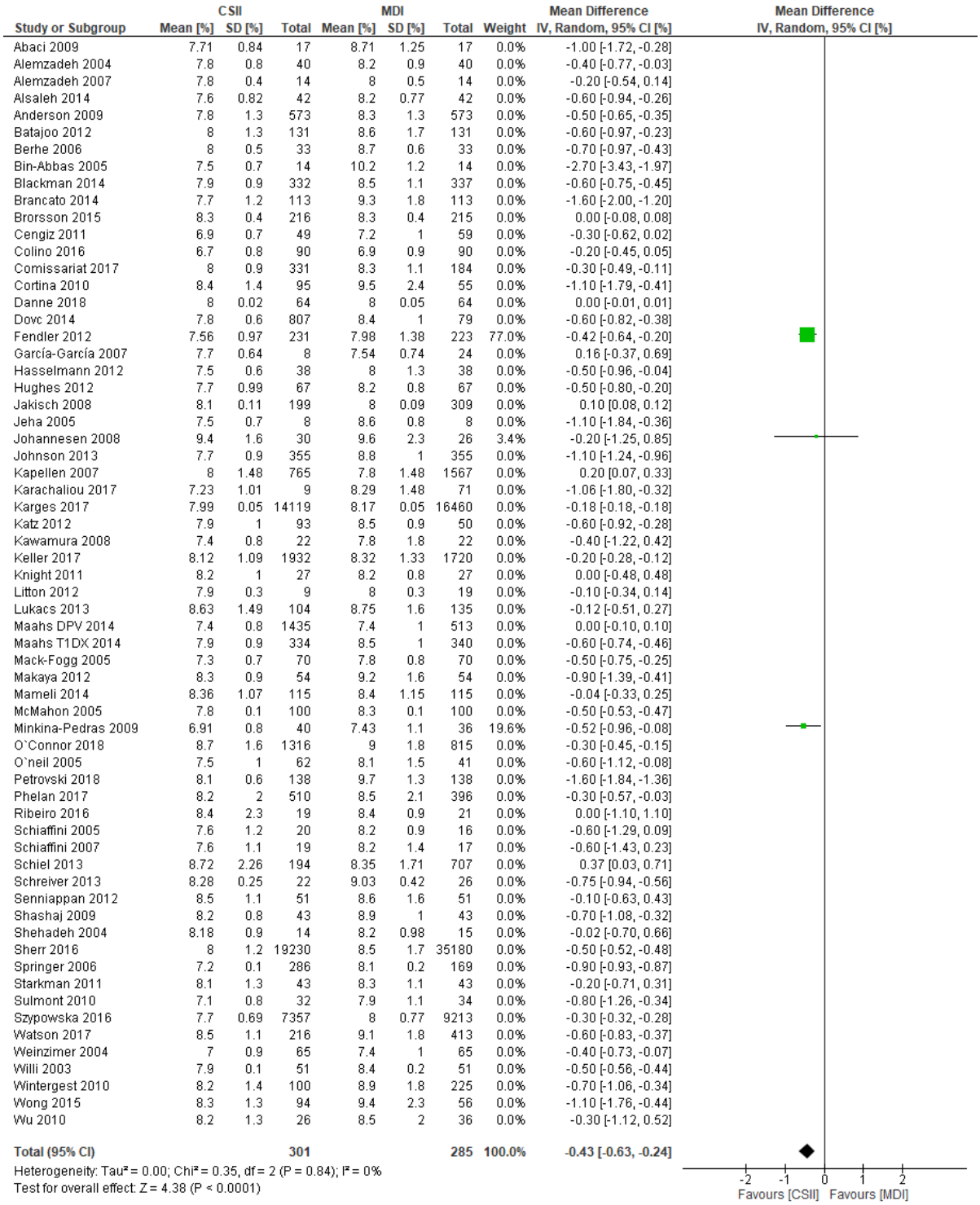
SD: standard deviation; IV: inverse variance; CI: Confidence interval; MD: Mean difference.

Figure S2: Report of sensitivity analyses restricted to the studies with low risk of bias for the mean difference of glycated hemoglobin (HbA1c), the incidence rate ratio of severe hypoglycemia (SH) episodes, and the risk ratio of diabetic ketoacidosis (DKA) in RCT (S2.1, S2.3, S2.5) and NRS (S2.2, S2.4, S2.6)

S2.1: Glycated hemoglobin (RCT)



S2.2: Glycated hemoglobin (NRS)



Study or Subgroup	CSII Mean [%]	CSII SD [%]	CSII Total	MDI Mean [%]	MDI SD [%]	MDI Total	Weight	Mean Difference IV, Random, 95% CI [%]
Abaci 2009	7.71	0.84	17	8.71	1.25	17	0.0%	-1.00 [-1.72, -0.28]
Alemzadeh 2004	7.8	0.8	40	8.2	0.9	40	0.0%	-0.40 [-0.77, -0.03]
Alemzadeh 2007	7.8	0.4	14	8	0.5	14	0.0%	-0.20 [-0.54, 0.14]
Alsaleh 2014	7.6	0.82	42	8.2	0.77	42	0.0%	-0.60 [-0.94, -0.26]
Anderson 2009	7.8	1.3	573	8.3	1.3	573	0.0%	-0.50 [-0.65, -0.35]
Batajoo 2012	8	1.3	131	8.6	1.7	131	0.0%	-0.60 [-0.97, -0.23]
Berhe 2006	8	0.5	33	8.7	0.6	33	0.0%	-0.70 [-0.97, -0.43]
Bin-Abbas 2005	7.5	0.7	14	10.2	1.2	14	0.0%	-2.70 [-3.43, -1.97]
Blackman 2014	7.9	0.9	332	8.5	1.1	337	0.0%	-0.60 [-0.75, -0.45]
Brancato 2014	7.7	1.2	113	9.3	1.8	113	0.0%	-1.60 [-2.00, -1.20]
Brorsson 2015	8.3	0.4	216	8.3	0.4	215	0.0%	0.00 [-0.08, 0.08]
Cengiz 2011	6.9	0.7	49	7.2	1	59	0.0%	-0.30 [-0.62, 0.02]
Colino 2016	6.7	0.8	90	6.9	0.9	90	0.0%	-0.20 [-0.45, 0.05]
Comissariat 2017	8	0.9	331	8.3	1.1	184	0.0%	-0.30 [-0.49, -0.11]
Cortina 2010	8.4	1.4	95	9.5	2.4	55	0.0%	-1.10 [-1.79, -0.41]
Danne 2018	8	0.02	64	8	0.05	64	0.0%	0.00 [-0.01, 0.01]
Dovc 2014	7.8	0.6	807	8.4	1	79	0.0%	-0.60 [-0.82, -0.38]
Fendler 2012	7.56	0.97	231	7.98	1.38	223	77.0%	-0.42 [-0.64, -0.20]
García-García 2007	7.7	0.64	8	7.54	0.74	24	0.0%	0.16 [-0.37, 0.69]
Hasselmann 2012	7.5	0.6	38	8	1.3	38	0.0%	-0.50 [-0.96, -0.04]
Hughes 2012	7.7	0.99	67	8.2	0.8	67	0.0%	-0.50 [-0.80, -0.20]
Jakisch 2008	8.1	0.11	199	8	0.09	309	0.0%	0.10 [0.08, 0.12]
Jeha 2005	7.5	0.7	8	8.6	0.8	8	0.0%	-1.10 [-1.84, -0.36]
Johannesen 2008	9.4	1.6	30	9.6	2.3	26	3.4%	-0.20 [-1.25, 0.85]
Johnson 2013	7.7	0.9	355	8.8	1	355	0.0%	-1.10 [-1.24, -0.96]
Kapellen 2007	8	1.48	765	7.8	1.48	1567	0.0%	0.20 [0.07, 0.33]
Karachaliou 2017	7.23	1.01	9	8.29	1.48	71	0.0%	-1.06 [-1.80, -0.32]
Karges 2017	7.99	0.05	14119	8.17	0.05	16460	0.0%	-0.18 [-0.18, -0.18]
Katz 2012	7.9	1	93	8.5	0.9	50	0.0%	-0.60 [-0.92, -0.28]
Kawamura 2008	7.4	0.8	22	7.8	1.8	22	0.0%	-0.40 [-1.22, 0.42]
Keller 2017	8.12	1.09	1932	8.32	1.33	1720	0.0%	-0.20 [-0.28, -0.12]
Knight 2011	8.2	1	27	8.2	0.8	27	0.0%	0.00 [-0.48, 0.48]
Litton 2012	7.9	0.3	9	8	0.3	19	0.0%	-0.10 [-0.34, 0.14]
Lukacs 2013	8.63	1.49	104	8.75	1.6	135	0.0%	-0.12 [-0.51, 0.27]
Maahs DPV 2014	7.4	0.8	1435	7.4	1	513	0.0%	0.00 [-0.10, 0.10]
Maahs T1DX 2014	7.9	0.9	334	8.5	1	340	0.0%	-0.60 [-0.74, -0.46]
Mack-Fogg 2005	7.3	0.7	70	7.8	0.8	70	0.0%	-0.50 [-0.75, -0.25]
Makaya 2012	8.3	0.9	54	9.2	1.6	54	0.0%	-0.90 [-1.39, -0.41]
Mameli 2014	8.36	1.07	115	8.4	1.15	115	0.0%	-0.04 [-0.33, 0.25]
McMahon 2005	7.8	0.1	100	8.3	0.1	100	0.0%	-0.50 [-0.53, -0.47]
Minkina-Pedras 2009	6.91	0.8	40	7.43	1.1	36	19.6%	-0.52 [-0.96, -0.08]
O`Connor 2018	8.7	1.6	1316	9	1.8	815	0.0%	-0.30 [-0.45, -0.15]
O`neil 2005	7.5	1	62	8.1	1.5	41	0.0%	-0.60 [-1.12, -0.08]
Petrovski 2018	8.1	0.6	138	9.7	1.3	138	0.0%	-1.60 [-1.84, -1.36]
Phelan 2017	8.2	2	510	8.5	2.1	396	0.0%	-0.30 [-0.57, -0.03]
Ribeiro 2016	8.4	2.3	19	8.4	0.9	21	0.0%	0.00 [-1.10, 1.10]
Schiaffini 2005	7.6	1.2	20	8.2	0.9	16	0.0%	-0.60 [-1.29, 0.09]
Schiaffini 2007	7.6	1.1	19	8.2	1.4	17	0.0%	-0.60 [-1.43, 0.23]
Schiel 2013	8.72	2.26	194	8.35	1.71	707	0.0%	0.37 [0.03, 0.71]
Schreiver 2013	8.28	0.25	22	9.03	0.42	26	0.0%	-0.75 [-0.94, -0.56]
Senniappan 2012	8.5	1.1	51	8.6	1.6	51	0.0%	-0.10 [-0.63, 0.43]
Shashaj 2009	8.2	0.8	43	8.9	1	43	0.0%	-0.70 [-1.08, -0.32]
Shehadeh 2004	8.18	0.9	14	8.2	0.98	15	0.0%	-0.02 [-0.70, 0.66]
Sherr 2016	8	1.2	19230	8.5	1.7	35180	0.0%	-0.50 [-0.52, -0.48]
Springer 2006	7.2	0.1	286	8.1	0.2	169	0.0%	-0.90 [-0.93, -0.87]
Starkman 2011	8.1	1.3	43	8.3	1.1	43	0.0%	-0.20 [-0.71, 0.31]
Sulmont 2010	7.1	0.8	32	7.9	1.1	34	0.0%	-0.80 [-1.26, -0.34]
Szypowska 2016	7.7	0.69	7357	8	0.77	9213	0.0%	-0.30 [-0.32, -0.28]
Watson 2017	8.5	1.1	216	9.1	1.8	413	0.0%	-0.60 [-0.83, -0.37]
Weinzimer 2004	7	0.9	65	7.4	1	65	0.0%	-0.40 [-0.73, -0.07]
Willi 2003	7.9	0.1	51	8.4	0.2	51	0.0%	-0.50 [-0.56, -0.44]
Wintergest 2010	8.2	1.4	100	8.9	1.8	225	0.0%	-0.70 [-1.06, -0.34]
Wong 2015	8.3	1.3	94	9.4	2.3	56	0.0%	-1.10 [-1.76, -0.44]
Wu 2010	8.2	1.3	26	8.5	2	36	0.0%	-0.30 [-1.12, 0.52]
Total (95% CI)			**301**			**285**	**100.0%**	**-0.43 [-0.63, -0.24]**

Heterogeneity: Tau² = 0.00; Chi² = 0.35, df = 2 (P = 0.84); I² = 0%
Test for overall effect: Z = 4.38 (P < 0.0001)

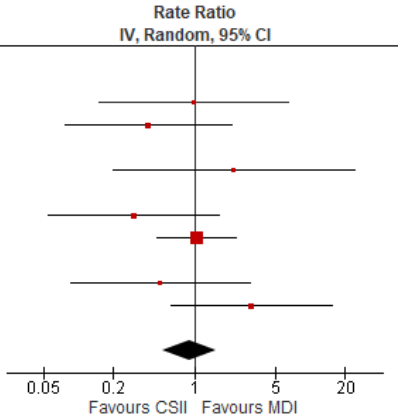
Mean Difference
IV, Random, 95% CI [%]

-2 -1 0 1 2
Favours [CSII] Favours [MDI]

S2.3: Severe hypoglycemia (RCT)

Study or Subgroup	log[Rate Ratio]	SE	CSII Total	MDI Total	Weight	Rate Ratio IV, Random, 95% CI
Cohen 2003	-1.6607	1.12	18	14	0.0%	0.19 [0.02, 1.71]
Weintrob 2003	-1.1087	1.15	23	23	0.0%	0.33 [0.03, 3.14]
DiMeglio 2004	-0.0101	0.96	21	20	8.1%	0.99 [0.15, 6.50]
Doyle 2004	-0.9163	0.84	16	16	10.5%	0.40 [0.08, 2.08]
Weintrob 2004	-1.1087	1.15	22	22	0.0%	0.33 [0.03, 3.14]
Fox 2005	0.7793	1.22	11	12	5.0%	2.18 [0.20, 23.82]
Wilson 2005	0.1044	1.41	9	10	0.0%	1.11 [0.07, 17.60]
Nuboer 2008	-1.204	0.87	19	19	9.8%	0.30 [0.05, 1.65]
Skogsberg 2008	0.0488	0.4	34	33	46.5%	1.05 [0.48, 2.30]
Bergenstal 2010	0.5988	0.63	78	81	0.0%	1.82 [0.53, 6.26]
Mueller-Godeffroy 2018	-0.6733	0.91	113	86	9.0%	0.51 [0.09, 3.04]
Blair 2019	1.1314	0.82	144	149	11.1%	3.10 [0.62, 15.46]
Total (95% CI)			**358**	**335**	**100.0%**	**0.91 [0.54, 1.56]**

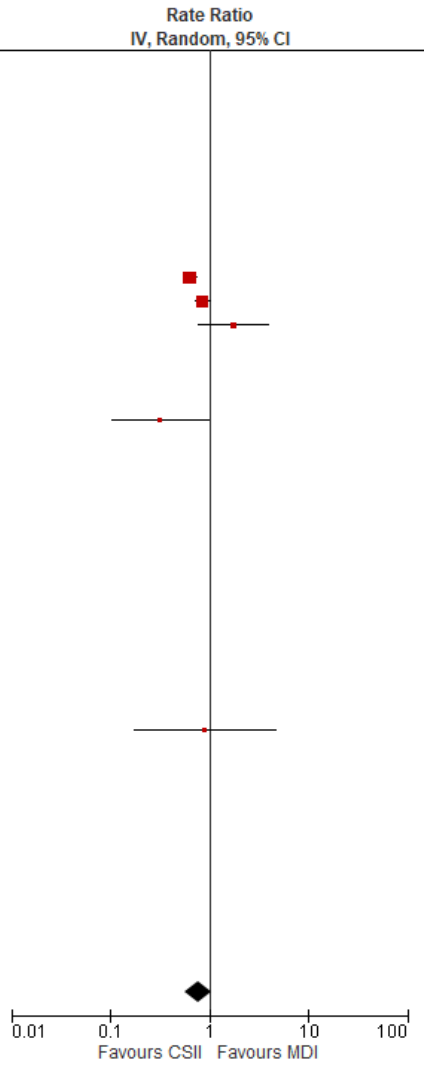
Heterogeneity: Tau² = 0.00; Chi² = 5.87, df = 6 (P = 0.44); I² = 0%
Test for overall effect: Z = 0.33 (P = 0.74)



S2.4: Severe hypoglycemia (NRS)

Study or Subgroup	log[Rate Ratio]	SE	CSII Total	MDI Total	Weight	Rate Ratio IV, Random, 95% CI
Alemzadeh 2004	0.0953	0.8	40	40	0.0%	1.10 [0.23, 5.28]
Alemzadeh 2007	-0.2485	0.85	14	14	0.0%	0.78 [0.15, 4.13]
Berghaeuser 2008	-0.5447	0.2	104	145	0.0%	0.58 [0.39, 0.86]
Blackman 2014	-0.0101	0.45	332	337	0.0%	0.99 [0.41, 2.39]
Brorsson 2015	-0.6931	0.48	216	215	0.0%	0.50 [0.20, 1.28]
Colino 2016	-1.0498	0.47	90	90	0.0%	0.35 [0.14, 0.88]
Comissariat 2017	-0.3011	0.34	331	184	0.0%	0.74 [0.38, 1.44]
Cooper 2013	0.077	0.07	469	1301	0.0%	1.08 [0.94, 1.24]
Hasselmann 2012	-0.462	0.57	38	38	0.0%	0.63 [0.21, 1.93]
Haynes DPV 2016	-0.462	0.08	7702	11085	40.2%	0.63 [0.54, 0.74]
Haynes T1DX 2016	-0.1625	0.09	4190	2912	39.1%	0.85 [0.71, 1.01]
Haynes WACDD 2016	0.5596	0.42	303	562	10.9%	1.75 [0.77, 3.99]
Hughes 2012	-0.2231	0.67	67	67	0.0%	0.80 [0.22, 2.97]
Jakisch 2008	-0.5621	0.21	199	309	0.0%	0.57 [0.38, 0.86]
Jeha 2005	-1.4697	0.76	8	8	0.0%	0.23 [0.05, 1.02]
Johannesen 2008	-1.1394	0.58	30	26	6.5%	0.32 [0.10, 1.00]
Johnson 2013	-0.3711	0.26	355	355	0.0%	0.69 [0.41, 1.15]
Kapellen 2007	-0.5798	0.14	765	1567	0.0%	0.56 [0.43, 0.74]
Karges 2017	-0.2485	0.03	14119	16460	0.0%	0.78 [0.74, 0.83]
Katz 2012	-0.1393	0.23	93	50	0.0%	0.87 [0.55, 1.37]
Kawamura 2008	-0.1278	0.52	22	22	0.0%	0.88 [0.32, 2.44]
Litton 2012	-0.9943	1.04	9	19	0.0%	0.37 [0.05, 2.84]
Maahs DPV 2014	-0.5276	0.34	1435	513	0.0%	0.59 [0.30, 1.15]
Maahs T1DX 2014	-0.0726	0.46	334	340	0.0%	0.93 [0.38, 2.29]
Mack-Fogg 2005	-0.734	0.31	70	70	0.0%	0.48 [0.26, 0.88]
Makaya 2012	0.4055	0.91	54	54	0.0%	1.50 [0.25, 8.93]
Mameli 2014	-0.3567	0.73	115	115	0.0%	0.70 [0.17, 2.93]
McMahon 2005	-1.0498	0.34	100	100	0.0%	0.35 [0.18, 0.68]
Minkina-Pedras 2009	-0.1054	0.84	0	0	3.3%	0.90 [0.17, 4.67]
Petrovski 2018	0	1.2	138	138	0.0%	1.00 [0.10, 10.51]
Ribeiro 2016	-1.1087	0.52	40	40	0.0%	0.33 [0.12, 0.91]
Schiaffini 2005	0	0.75	20	16	0.0%	1.00 [0.23, 4.35]
Schiaffini 2007	0.3436	0.48	19	17	0.0%	1.41 [0.55, 3.61]
Schiel 2013	1.3002	0.41	194	707	0.0%	3.67 [1.64, 8.20]
Schreiver 2013	-0.0943	1.73	22	26	0.0%	0.91 [0.03, 27.02]
Shehadeh 2004	-0.2485	0.65	14	15	0.0%	0.78 [0.22, 2.79]
Sulmont 2010	-0.844	0.67	32	34	0.0%	0.43 [0.12, 1.60]
Weinzimer 2004	-0.755	0.25	65	65	0.0%	0.47 [0.29, 0.77]
Total (95% CI)			**12225**	**14585**	**100.0%**	**0.77 [0.56, 1.05]**

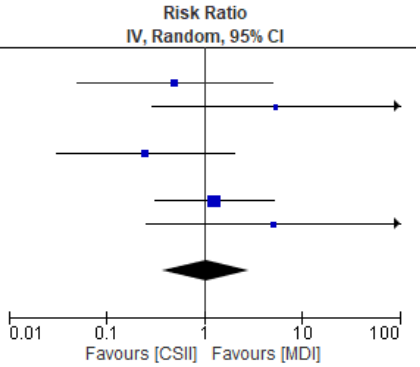
Heterogeneity: Tau² = 0.06; Chi² = 12.66, df = 4 (P = 0.01); I² = 68%
Test for overall effect: Z = 1.67 (P = 0.10)



S2.5: Diabetes ketoacidosis (RCT)

Study or Subgroup	CSII Events	CSII Total	MDI Events	MDI Total	Weight	Risk Ratio IV, Random, 95% CI
Cohen 2003	1	18	0	14	0.0%	2.37 [0.10, 54.08]
Doyle 2004	1	16	2	16	17.6%	0.50 [0.05, 4.98]
Fox 2005	2	11	0	12	11.3%	5.42 [0.29, 101.77]
Opipari-Arrigan 2007	3	6	2	8	0.0%	2.00 [0.47, 8.46]
Nuboer 2008	1	19	4	19	20.7%	0.25 [0.03, 2.04]
Bergenstal 2010	1	78	1	81	0.0%	1.04 [0.07, 16.31]
Mueller-Godeffroy 2018	5	113	3	86	39.8%	1.27 [0.31, 5.16]
Blair 2019	2	144	0	149	10.6%	5.17 [0.25, 106.82]
Total (95% CI)		**303**		**282**	**100.0%**	**1.05 [0.38, 2.92]**
Total events	11		9			

Heterogeneity: Tau² = 0.17; Chi² = 4.54, df = 4 (P = 0.34); I² = 12%
Test for overall effect: Z = 0.10 (P = 0.92)



S2.6: Diabetes ketoacidosis (NRS)

Study or Subgroup	CSII Events	CSII Total	MDI Events	MDI Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Alemzadeh 2004	2	40	0	40	0.0%	5.00 [0.25, 100.97]	2004
Weinzimer 2004	3	65	0	65	0.0%	7.00 [0.37, 132.87]	2004
Bin-Abbas 2005	0	14	12	14	0.0%	0.04 [0.00, 0.62]	2005
Mack-Fogg 2005	2	70	0	70	0.0%	5.00 [0.24, 102.30]	2005
García-García 2007	2	8	2	24	0.0%	3.00 [0.50, 17.95]	2007
Berghaeuser 2008	0	104	2	145	0.0%	0.28 [0.01, 5.73]	2008
Jakisch 2008	2	199	4	309	0.0%	0.78 [0.14, 4.20]	2008
Johannesen 2008	8	30	0	26	43.0%	14.81 [0.90, 244.74]	2008
Kawamura 2008	3	22	0	22	0.0%	7.00 [0.38, 128.02]	2008
Minkina-Pedras 2009	2	40	2	36	57.0%	0.90 [0.13, 6.06]	2009
Abaci 2009	0	17	1	17	0.0%	0.33 [0.01, 7.65]	2009
Sulmont 2010	10	32	9	34	0.0%	1.18 [0.55, 2.52]	2010
Makaya 2012	11	54	4	54	0.0%	2.75 [0.93, 8.10]	2012
Litton 2012	6	9	14	19	0.0%	0.90 [0.53, 1.54]	2012
Hughes 2012	4	67	4	67	0.0%	1.00 [0.26, 3.83]	2012
Hasselmann 2012	8	38	19	38	0.0%	0.42 [0.21, 0.84]	2012
Johnson 2013	8	355	17	355	0.0%	0.47 [0.21, 1.08]	2013
Mameli 2014	1	115	9	115	0.0%	0.11 [0.01, 0.86]	2014
Maahs T1DX 2014	21	334	19	340	0.0%	1.13 [0.62, 2.05]	2014
Maahs DPV 2014	52	1435	7	513	0.0%	2.66 [1.21, 5.81]	2014
Blackman 2014	20	332	16	337	0.0%	1.27 [0.67, 2.41]	2014
Brorsson 2015	6	216	1	215	0.0%	5.97 [0.73, 49.19]	2015
Colino 2016	0	90	2	90	0.0%	0.20 [0.01, 4.11]	2016
Shulman 2017	130	3700	128	3376	0.0%	0.93 [0.73, 1.18]	2017
Comissariat 2017	10	331	15	184	0.0%	0.37 [0.17, 0.81]	2017
Karges 2017	533	14119	886	16460	0.0%	0.70 [0.63, 0.78]	2017
Evans-Cheung 2018	18	161	4	161	0.0%	4.50 [1.56, 13.00]	2018
Petrovski 2018	3	138	8	138	0.0%	0.38 [0.10, 1.38]	2018
Total (95% CI)		**70**		**62**	**100.0%**	**3.00 [0.20, 45.40]**	
Total events	10		2				

Heterogeneity: Tau² = 2.42; Chi² = 2.62, df = 1 (P = 0.11); I² = 62%
Test for overall effect: Z = 0.79 (P = 0.43)

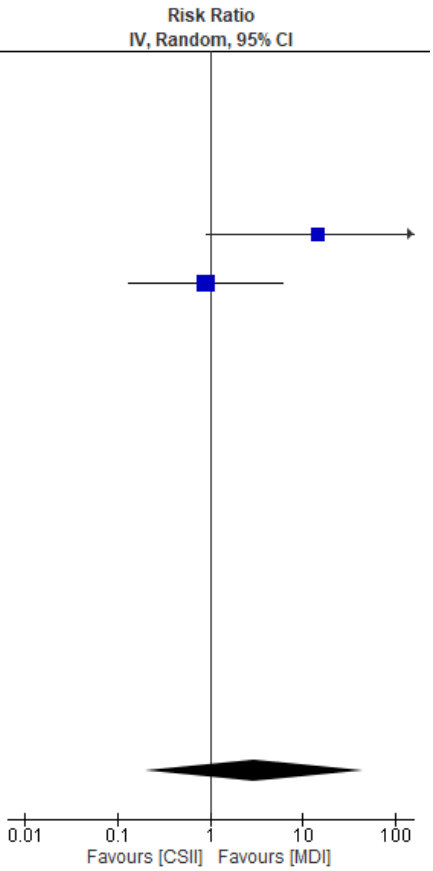
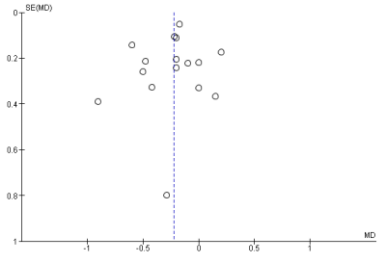


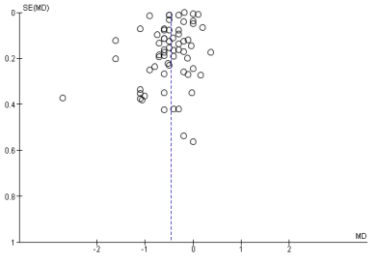
Figure S3: Funnel plots of randomized controlled trials (RCT) and non-randomized studies (NRS). Studies showed no evidence of asymmetry for all the glycemic outcomes, as corresponding with the Egger test (p<0.05 correspond to an asymmetric funnel plot).

Glycated hemoglobin (RCT)



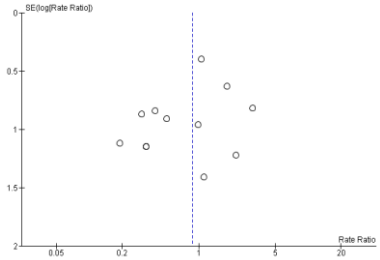
p=0.80

Glycated hemoglobin (NRS)



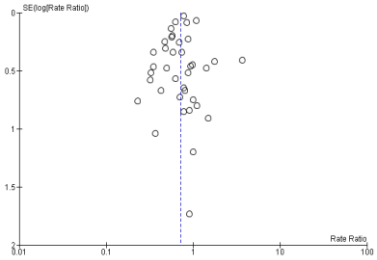
p=0.18

Severe Hypoglycemia (RCT)



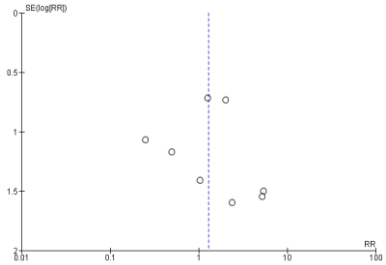
p=0.29

Severe Hypoglycemia (NRS)



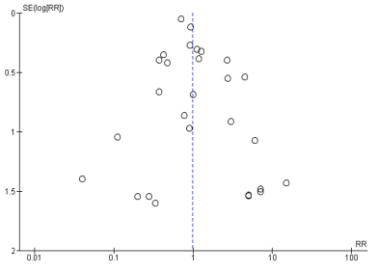
p=0.21

Diabetic ketoacidosis (RCT)



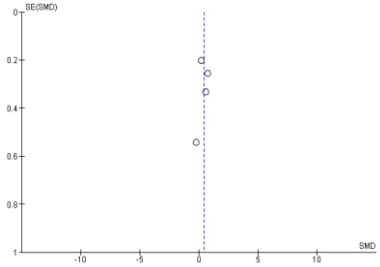
p=0.23

Diabetic ketoacidosis (NRS)



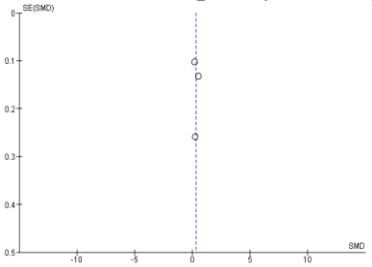
p=0.07

Health-related quality of life (RCT)



p=0.73

Health-related quality of life (NRS)



p=0.92

Checklist of Items for Reporting Equity-Focused Systematic Reviews				
Section	**Item**	**Standard PRISMA Item**	**Extension for Equity-Focused Reviews**	**Pg #**
Title				
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Identify equity as a focus of the review, if relevant, using the term equity	1
Abstract				
Structured summary	2	2. Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	State research question(s) related to health equity.	3-4
	2A		Present results of health equity analyses (e.g. subgroup analyses or meta-regression).	3-4
	2B		Describe extent and limits of applicability to disadvantaged populations of interest.	3-4
Introduction				
Rationale	3	Describe the rationale for the review in the context of what is already known.	Describe assumptions about mechanism(s) by which the intervention is assumed to have an impact on health equity.	7-8
	3A		Provide the logic model/analytical framework, if done, to show the pathways through which the intervention is assumed to affect health equity and how it was developed.	7-8
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Describe how disadvantage was defined if used as criterion in the review (e.g. for selecting studies, conducting analyses or judging applicability).	8
	4A		State the research questions being addressed with reference to health equity	8
Methods				
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.		2; 8
Eligibility criteria	6	6. Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Describe the rationale for including particular study designs related to equity research questions.	9-10
	6A		Describe the rationale for including the outcomes - e.g. how these are relevant to reducing inequity.	10
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Describe information sources (e.g. health, non-health, and grey literature sources) that were searched that are of specific relevance to address the equity questions of the review.	8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Describe the broad search strategy and terms used to address equity questions of the review.	10; 12
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).		9-10
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.		9-10

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	List and define data items related to equity,where such data were sought (e.g. using PROGRESS-Plus or other criteria, context).	10; 12
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.		11
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).		11-12
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Describe methods of synthesizing findings on health inequities (e.g. presenting both relative and absolute differences between groups).	10-12
Risk of bias across studies	15	15. Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).		11
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Describe methods of additional synthesis approaches related to equity questions, if done, indicating which were pre-specified	13
Results				
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.		13-14, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Present the population characteristics that relate to the equity questions across the relevant PROGRESS-Plus or other factors of interest.	13-14, Table 2, Table S1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).		14-15; Tables S3 and S4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.		15-17, Figures 2, S1, S2, S3, S4, S5, S6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Present the results of synthesizing findings on inequities (see 14).	Table 1; Table 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).		Tables S3 and S4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Give the results of additional synthesis approaches related to equity objectives, if done, (see 16).	Figure S2
Discussion				
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).		Table 1, Table 2
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).		20-22
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Present extent and limits of applicability to disadvantaged populations of interest and describe the evidence and logic underlying those judgments.	22
	26A		Provide implications for research, practice or policy related to equity where relevant (e.g. types of research needed to address unanswered questions).	22
Funding				

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.		23

From: Source: Welch V, Petticrew M, Tugwell P, Moher D, O'Neill J, Waters E, White H, and the PRISMA-Equity Bellagio Group. (2012) PRISMA-Equity 2012 Extension: Reporting Guidelines for Systematic Reviews with a Focus on Health Equity. PLoS Med 9(10): e1001333. doi:10.1371/journal.pmed.1001333

MOOSE (Meta-analyses Of Observational Studies in Epidemiology) Checklist

A reporting checklist for Authors, Editors, and Reviewers of Meta-analyses of Observational Studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Reporting Criteria	Reported (Yes/No)	Reported on Page No.
Reporting of Background		
Problem definition	Yes	7
Hypothesis statement	Yes	7
Description of Study Outcome(s)	Yes	7
Type of exposure or intervention used	Yes	7
Type of study design used	Yes	7
Study population	Yes	7
Reporting of Search Strategy		
Qualifications of searchers (eg, librarians and investigators)	Yes	8
Search strategy, including time period included in the synthesis and keywords	Yes	suppl file 1
Effort to include all available studies, including contact with authors	Yes	8
Databases and registries searched	Yes	8
Search software used, name and version, including special features used (eg, explosion)	No	
Use of hand searching (eg, reference lists of obtained articles)	Yes	Suppl file
List of citations located and those excluded, including justification	Yes	13
Method for addressing articles published in languages other than English	Yes	8
Method of handling abstracts and unpublished studies	No	
Description of any contact with authors	No	
Reporting of Methods		
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Yes	8; 9
Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	Yes	9
Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)	Yes	9;10
Assessment of confounding (eg, comparability of cases and controls in studies where appropriate	Yes	11

Reporting Criteria	Reported (Yes/No)	Reported on Page No.
Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Yes	11-13
Assessment of heterogeneity	Yes	12
Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Yes	11;12
Provision of appropriate tables and graphics	Yes	Table S1
Reporting of Results		
Table giving descriptive information for each study included	Yes	Table S1
Results of sensitivity testing (eg, subgroup analysis)	Yes	Figure S2
Indication of statistical uncertainty of findings	No	
Reporting of Discussion		
Quantitative assessment of bias (eg, publication bias)	Yes	Figure S7
Justification for exclusion (eg, exclusion of non–English-language citations)	Yes	Figure 1
Assessment of quality of included studies	Yes	Tables S2 and
Reporting of Conclusions		
Consideration of alternative explanations for observed results	Yes	18-20
Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	Yes	19-21
Guidelines for future research	No	
Disclosure of funding source	Yes	23

Once you have completed this checklist, please save a copy and upload it as part of your submission. DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.

Section 5

Diabetes technologies for children and adolescents with type 1 diabetes are highly dependent on coverage and reimbursement

5.1 Introduction

Use of insulin pumps and continuous glucose monitoring (CGM) systems in the management of type 1 diabetes is gaining ground over conventional treatment with syringes, pens and glucometers (39,199,200). Although use of insulin pumps has been shown to lower HbA_{1c} levels in pediatric age when compared with multiple-daily injections, few differences have been described in other glycemic outcomes (51,52,201–204). On the other hand, the use of integrated CGM systems has shown to improve time in range and decrease frequency and severity of hypoglycemia (205–207). In addition, people wearing these devices have reported increased flexibility and feeling of wellbeing (208).

Despite these benefits, there are considerable differences between countries in healthcare system coverage of diabetes technologies (12,36,209,210), clinicians' role in counselling, and individuals' and families' preferences (36,211,212) that prevent diabetes technologies from being used. In addition, the hassle of wearing devices, dislike of alarms and inadequate counselling may also decrease use (211,213,214).

There is a gap in the literature regarding the opinion of multinational healthcare professionals (HCPs) that are directly involved with recommendation of diabetes technologies (215). In addition, socioeconomic background of people with diabetes and HCP's work profile may indirectly impact the willingness to recommend diabetes technologies(12). Therefore, with this survey, we aimed to

comprehensively evaluate the reasons why providers do or do not recommend diabetes devices for children and adolescents with type 1 diabetes.

5.2 Methods

We used an electronic survey powered by Survey Monkey Inc. (San Mateo, California, USA) containing 33 questions in English language, and data were collected anonymously. The survey was disseminated through an open weblink for a calendar month to members of the *International Society for Pediatric and Adolescent Diabetes* (ISPAD) including past participants of Annual Meetings and training courses which approximately reach 2,300 HCPs. Members were also encouraged to share the survey with colleagues which prevented us from being able to calculate a precise response rate. Responses were included if HCP confirmed their involvement in the decision or recommendation to start diabetes technology. If respondents completed the survey, $1 was donated to Life for a Child.

The survey questions (Appendix) were divided into four topics: (i) baseline profile of HCPs; (ii) HCPs' opinions about recommendation, use, and relevance of indications and contraindications for initiating insulin pumps); (iii) HCP's opinions about recommendation and use of CGM; and (iv) six case vignettes with variation of factors thought to impact decision to recommend diabetes technologies including individuals age, history of severe hypoglycemia, history of diabetic ketoacidosis, glycemic control, household composition, parental occupation, healthcare coverage, income, place of residence, parental literacy, immigration, religious affiliation, language comprehension, and social supports.

We did a post hoc subgroup analyses to compare responses between different subgroups, including: (i) age of HCP below or over 40 years old; (ii) years of clinical practice under or over ten years; (iii) main practice setting - private, public/government or university/academic hospital/outpatient clinic; (iv) size of diabetes clinic - more or less than two hundred patients being followed; (v) HCPs who consider themselves a racial/ethnic minority and those who do not; (vi) provision of universal healthcare insurance/coverage for diabetes technologies; and (viii) coverage/reimbursement from private insurance companies for diabetes technologies.

Categorical data are presented as proportions (%), and comparisons between groups were based on a chi-squared test (χ^2) or Fisher's exact test when appropriate. Qualitative data (content from the comments provided under "Other, please specify") were analyzed using a coding technique, where similar answers are summarized by approximation into similar semantic content (216). The unit of analysis correspond to one single response, so one health center could have contributed more than one survey response. Statistical analyses were performed with Stata 14.0 for Windows (College Station, TX, USA). Statistical significance level was set at $p < 0.05$.

5.3 Results

We received a total of 270 responses, with an average completion rate of 78% and a median time spent by participant of less than ten minutes. Nearly 91% (n=247) of the survey responses were from HCPs involved in the decision or recommendation to start a person with diabetes on insulin pump and/or CGM and were included in the analysis. Seventy percent of the respondents were members of ISPAD.

5.3.1 Participant characteristics

Table 1 summarizes participant characteristics. We highlight that approximately 45% of HCPs cannot count on their healthcare system to provide coverage for insulin pumps and/or CGM systems in their country/region of service, while 55% can fully or partially count on it. Approximately 46% of HCPs agreed that private insurance companies totally or partially cover/reimburse for insulin pumps and/or CGMs, while the other 54% cannot count on their coverage.

5.3.2 Viewpoints on insulin pumps

Insulin pumps are available to more than 95% of HCPs in their practice setting with at least 73% having more than one brand available. We saw significantly more uptake among patients whose HCPs had more years of practice, practiced in public/government or university/academic centers and followed more people with diabetes (Table 2). Age and racial/ethnic minority did not show statistical differences.

There was significantly more use of, and agreement to start, insulin pump therapy in countries or regions that could rely upon universal or partial healthcare insurance/coverage for diabetes technologies and in those that could count on private insurance companies to cover/reimburse diabetes technologies when compared to countries that could not (Table 3).

Reasons to turndown technology also differed depending on the coverage. In countries that could count on universal or partial healthcare insurance/coverage, the main reason for declining diabetes technology was “not wanting to wear something on the body”, while in countries where diabetes technologies are not covered, the main reason was the difficulty to afford or maintain therapy (Table

3). Providers who were older than forty (58 vs. 39%, p=0.03), with more years of practice (64 vs. 35%, p<0.001), and with a greater number of people with diabetes followed (61 vs. 38%, p<0.001) were more likely to endorse their reason to turndown technology as “Patient does not want to wear something on its body”.

More than 80% of HCPs agreed with the statement “All patients, regardless of circumstance, should be offered insulin pump therapy”. And nearly 90% disagreed with the statement “No patient, regardless of circumstance, should be offered insulin pump therapy”. No differences were seen between subgroups.

In order of importance, HCPs considered “history of severe hypoglycemia”, “requirement of small doses of insulin”, “suboptimal glycemic control despite good compliance”, and “patient age” as extremely relevant indications to start insulin pump. “Patient or caregiver´s preference” was considered fairly relevant for most HCPs. No statistical differences were seen between subgroups.

Overall, a “history of infrequent blood glucose monitoring (less than three times per day) or no use of CGM” and “infrequent follow-up” were considered the most relevant absolute contraindications to starting a person with diabetes on insulin pump, regardless of healthcare coverage/insurance reimbursement. However, HCPs that cannot count on coverage for insulin pump were more likely to endorse infrequent blood glucose monitoring as a relative contraindication for starting an insulin pump when compared to HCPs who could count on coverage (Table 3). Other reasons like “age less than three years old”, and “one or more episodes of DKA” were not found to be contraindications, whereas most of HCPs found “inadequate parental/caregiver supervision” as a relative contraindication.

Figure 1 shows that among socioeconomic factors assessed, “parental educational level”, “family/patient first language being different from that of the diabetes team”, “parental affordability to maintain therapy or having it provided by insurance coverage”, and “family income” were mostly considered as relevant factors in the decision-making to start insulin pump. Other socioeconomic factors such as “gender”, “religious affiliation”, “race, ethnicity, or citizenship”, “place of residence (rural versus urban)”, and “family social networking (belonging to social support groups)” were mostly found to be totally irrelevant factors. No statistical differences were seen between subgroups.

5.3.3 Viewpoints on continuous glucose monitoring systems

Almost 95% of the respondents have CGM systems available in their practice; of which, at least 85% have access to more than one brand. Although more than half of people with diabetes agreed to start CGM, only roughly one third of them regularly wear it. Those people whose HCPs were under forty years of age were found to have more access to CGM (57.6 vs. 35.4%, $p=0.019$). A significantly higher percentage of people that use CGM have coverage for it compared with those who do not ($p<0.01$). In the same line, we saw a higher uptake of CGM in those who can count on insurance coverage for CGM when compared with those who do not ($p<0.01$). The percentage of people that agreed/consented to use CGM after it was recommended was affected by coverage for CGM ($p<0.01$), and insurance reimbursement ($p<0.01$).

5.3.4 Case scenarios

i. *“**One-year-old girl**, during her partial remission phase, receiving 2.5 IU/day of basal long-acting analog insulin, and doing corrections with rapid-acting*

analogues when needed, has faced two ***severe hypoglycemia episodes****, one of them with seizures. She has a* ***single mother****,* ***unemployed****, and they live in a country where there is* ***universal coverage*** *for CSII and CGM."*

Nearly 80% of the HCP respondents would recommend both insulin pump and CGM, and 18% would only recommend CGM in this scenario (Figure 2i). HCPs from university or academic hospitals were more likely to recommend both insulin pump and CGM than HCPs from other settings, 90.3% and 73%, respectively, p=0.012.

ii. *"****One-year-old girl****, during her partial remission phase, receiving 2.5 IU/day of basal long-acting analog insulin, and doing corrections with rapid-acting analogues when needed, has faced two* ***severe hypoglycemia episodes****, one of them with seizures. She* ***lives with her parents in a wealthy village four-hour away from nearest diabetes center****, and family has* ***full insurance coverage*** *for CSII and CGM."*

About 84% of the HCP respondents would recommend both insulin pump and CGM, and 12% would only recommend CGM in this scenario (Figure 2ii). HCPs from university or academic hospitals were more likely to recommend both insulin pump and CGM than HCPs from private or public/governmental setting, 93%, 76% and 80%, respectively, p=0.009).

iii. *"A* ***6-year-old girl*** *has been suffering blood sugar fluctuations which include one episode of* ***diabetic ketoacidosis*** *last month. Her parents are facing a* ***difficult economic situation*** *because both are unemployed and* ***do not have insurance coverage*** *for diabetes suppliers. The* ***young parents have not***

***completed their secondary studies**, and family lives in a **deprived area** of a big city."*

Around 15% of the HCP respondents would recommend both insulin pump and CGM, and 39% would only recommend CGM in this scenario; however, 45% of the respondents would not recommend insulin pump nor CGM (Figure 2iii). While 52% of HCPs from university or academic hospital settings would recommend CGM, 33% and 24% of the HCPs from private and public/government hospitals, respectively, would recommend it (p=0.02). Moreover, 46% of the HCPs who follow more than 200 patients would recommend CGM, while 27% of the HCPs who follow less than 200 patients would recommend it (p=0.008).

iv. *"A **6-year-old girl** has been suffering blood sugar fluctuations which include one episode of **diabetic ketoacidosis** last month. The family recently moved to a **new country** where there is **universal healthcare and coverage** for CSII and CGM. The family belongs to a **minority religion** and has **low language comprehension** in their new country."*

Close to 48% of HCPs would recommend both insulin pump and CGM, and 41% would recommend only CGM in this scenario (Figure 2iv). No significant differences were seen between subgroups.

v. *"An **adolescent boy**, from a **racial/ethnic minority group**, diagnosed eight years ago, lives with his grandmother who works as a nurse and is his **only guardian**. Their **health insurance** recently approved him the provision of an intermittent CGM (Libre flash). He has suffered **uncontrolled blood glucose**, despite been on MDI with intensive basal-bolus requiring 1.8 IU/kg/day. Every year he **participates in a regional diabetes camp.**"*

Approximately 55% of the respondents would recommend both insulin pump and CGM in this scenario, and 33% would recommend only CGM (Figure 2v). Nearly 68% of the HCPs who follow more than 200 patients would recommend both therapies, while 47% of the HCP who follow less than 200 patients would recommend them (p=0.04).

vi. *"A **Caucasian adolescent girl**, belonging to a **major racial/ethnic group**, diagnosed eight years ago, lives with her **grandparents who are retired**. Their **health insurance** recently approved her the provision of an intermittent CGM (Libre flash). She has been suffering **uncontrolled blood glucose**, despite been on MDI with intensive basal-bolus requiring 1.8 IU/kg/day. In the village where they live, there are **lacking of social support and counselling**."*

Approximately 38% of the respondents would recommend both insulin pump and CGM in this scenario, and 48% of the respondents would recommend only CGM (Figure 2vi). Nearly 48% of the HCPs who count on diabetes technology coverage would recommend both therapies, while 33% who cannot count on coverage would recommend them (p=0.03).

HCP responses to vignettes i and ii demonstrate that HCPs have similar recommendations about insulin pump and CGM for children and adolescents with diabetes with healthcare coverage/insurance despite family differences in household composition and employment, although HCPs from university or academic hospitals seem to be more likely to recommend both therapies. HCPs recommendations in vignettes iii and iv may have differed because of the absence of insurance coverage in addition to other difficult social circumstances in vignette iii, unlike what was presented in vignette iv where universal healthcare and coverage were present even though the child was from a minority group and

had low language comprehension. Although both adolescents in vignettes v and vi had healthcare insurance/coverage, the girl in vignette vi without social support and counselling was less likely to have an insulin pump recommended by HCPs, especially in those that cannot rely upon healthcare coverage for diabetes technologies.

5.4 Discussion

We performed an electronic, worldwide, survey with responses from 249 HCPs from 49 different countries to assess their viewpoints on recommending insulin pumps and CGM systems for children and adolescents with type 1 diabetes. Although most HCPs were working at university/academic centers with a considerable number of people with type 1 diabetes, approximately 45% cannot count on their national/regional healthcare system to cover diabetes technologies, and 56% cannot count on insurance companies' reimbursement to cover the cost of diabetes technologies. Even so, our findings suggest that most HCPs are very flexible in recommending insulin pumps and CGMs, but different impressions depended on age, years of practice, clinical setting, number of patients, and availability of coverage for diabetes technology.

Our main finding is significantly more adoption of insulin pumps and CGM systems in those having healthcare or insurance coverage for diabetes devices. Although 95% of HCPs have insulin pumps and CGM systems available at their practice setting, the lack of coverage for them is an immediate explanation for the weak uptake. Countries with universal healthcare and wider availability of diabetes technologies, along with insurance-based countries with coverage for diabetes technologies are more likely to have a higher proportion of people with diabetes using technology, whereas most developing countries, despite holding

universal healthcare, do not finance the newest diabetes delivery devices and make access to diabetes technology more limited (30,36,209,217). However, after cost and economic concerns, the most commonly reason to turndown technology has been pointed out to be wear-related issues, in line with what was found in our survey (214).

Three large international registries of type 1 diabetes in developed countries demonstrated that less than 50% of youth assessed were receiving pump therapy, and the rate of insulin pump usage was dependent on age group, ethnicity, and gender (30). In the same line, an international network of pediatric diabetes centers stated that coverage and reimbursement policies for diabetes technologies are very heterogeneous in Europe, which may cause inequality in diabetes management (218,219). However, the uptake of diabetes technologies may be higher when insurance coverage is approved even when used in people with lower SES(36,220).

Our post hoc analysis evaluated a few variables found to be important in decision-making about insulin pumps and CGM systems. HCPs with more years of experience who are working at centers with larger number of patients and larger multidisciplinary teams may provide different quality of care (218). In our study, this group of HCPs were more likely to extend flexibility to their patients to start on pumps or turndown this technology, especially when they can count on healthcare/insurance coverage for them. We believe that coverage for diabetes technologies could influence not only the access to these devices, but also HCP's personal impressions on recommending it, as innovative therapies may facilitate the motivation to improve outcomes (39). For instance, some HCPs were keener to recommend and prescribe them when family income was not an issue.

We assessed HCP's recommendation of insulin pump and CGM systems with two strategies. First, we asked providers to rate the relevance of various socioeconomic factors in their decision to recommend insulin pumps. Second, we used six case scenarios to explore the same socioeconomic factors. In the first strategy, HCP's viewpoints about the relevance of socioeconomic factors did not seem to vary by presence or absence of healthcare/insurance coverage for diabetes devices. However, with the second strategy, we saw some different viewpoints, especially when diabetes technology coverage was absent. When the coverage for diabetes technology exists, younger age along with severe hypoglycemic episodes seemed to be a factor for greater adoption of pumps and CGMs. School age children with similar social circumstances are more likely to be advised to start on pumps and CGMs if they are covered by healthcare system. For the adolescent group with similar suboptimal glycemic control and coverage for diabetes technologies, the lack of social support and counselling seemed to be associated with less recommendation for starting an insulin pump. Indeed, it is important to highlight that the six case-vignettes were created by the authors, based on their expertise, and supported by the ISPAD, to assess main clinical conditions and different socioeconomic factors that might impact on recommendation of diabetes technologies. However, as the vignettes are not validated in the literature, the results should be read with cautious before being extrapolated into clinical decision-making.

The results of our survey are in line with previous studies that showed that universal coverage for diabetes technology may be as relevant as individuals' metabolic control when HCPs recommend diabetes technologies(30,32,33). Additionally, some modifiable socioeconomic factors, such as language

comprehension, educational level and income would also influence HCPs to recommend technology. However, while unmodifiable socioeconomic factors such as gender, religious affiliation and race/citizenship seemed to be less important in their decision, background HbA_{1c} level does not appear to influence the initiation of insulin pumps(32).

Given the results of our study, guidelines and educational programs for starting insulin pumps and/or CGMs should address some of the perceived barriers to starting diabetes technologies including language comprehension, parental educational level, and social supports. Video interpretation services and educational material in different languages, for example, should be used during education for families who do not speak the same language as the diabetes team. Educational material should also be adapted so that parents of different educational levels can all be successful.

Our study has some limitations. First, individual responses of HCPs might not be representative of their whole country/region but represent an effort to acknowledge the viewpoints from members of an international medical society. Second, our survey was targeted to HCPs who were ISPAD members, comprising 70% of the respondents; however, the other 30% of respondents were mostly pediatric endocrinologists with more than ten years of practice, who follow less than 100 people with diabetes at their clinic, working in a country/region that lacks coverage/reimbursement for insulin pump and CGM systems. We believe that the dissemination through an open weblink reduced a sampling bias, by surveying HCPs either belonging to ISPAD community or not, and balanced a response (acquiescence) bias that happens when respondents subconsciously or consciously express in less-than-truthful responses, most of them in

agreement with the society view, since they belong to the same medical society (221,222).

We conclude that most HCPs are aware of the advantages of using diabetes technologies and are permissive to recommend them to benefit their patients. Although personal's clinical circumstances, language comprehension, educational level, and income affect the recommendation to initiate these technologies, the availability of insurance/coverage for diabetes technology seems to be the biggest factor when HCPs are deciding to recommend them. Therefore, it should be a policy priority to ensure coverage for diabetes technologies, especially in young age groups. Moreover, educational programs, resources, and strategies should be developed so that parental education level and language comprehension are no longer barriers to accessing diabetes technology.

Table 1: Participant's characteristics

Characteristics (n of respondents)	Respondents (%)
Age, years (n=247)	
Under 30	11 (4.5)
30 to 40	104 (42.1)
41 to 50	64 (25.9)
51 to 60	50 (20.2)
Over 60	18 (7.3)
Gender (n=246)	
Female	158 (64.2)
Male	88 (35.8)
Country¥ (n=245)	
India	30 (12.2)
Brazil	26 (10.6)
United States of America	23 (9.4)
Canada	20 (8.2)
Mexico	14 (5.7)
Australia	13 (5.3)
United Kingdom	12 (4.9)
Chile	11 (4.5)
Italy	8 (3.3)
Portugal	7 (2.9)
Belgium	7 (2.9)
Others§	74 (30.2)
Consider themselves to be from minority racial/ethnic group (n=245)	
Yes	30 (12.2)
No	215 (87.8)
Current clinical role (n=245)	
Resident	6 (2.4)
Primary care practitioner, paediatrician, family doctor, or internal medicine doctor	11 (4.5)
Paediatric endocrinology fellow	18 (7.3)
Paediatric endocrinologist/diabetologist	154 (62.9)
Adult endocrinology fellow	1 (0.4)
Adult endocrinologist/diabetologist	24 (9.8)
Nurse practitioner/registered nurse	24 (9.8)
Other (registered nutritionist, dietitian, nutritionist, diabetes educator, mental health professional)	13 (5.3)
Years of practice (n=246)	
Less than 3	42 (17.1)
3 to 5	37 (15)
5 to 10	46 (18.7)
More than 10	121 (49.2)
Main practice setting (n=245)	
Private hospital/outpatient clinic	56 (22.9)
Public or government hospital/outpatient clinic	73 (29.8)
University or academic hospital/outpatient clinic	104 (42.5)
Primary care centre	4 (1.6)
General practitioner office	2 (0.8)
Other (Diabetes association)	6 (2.5)
Access to an endocrinologist/diabetologist as a consultant (n=247)	
Yes	56 (22.7)
No	3 (1.2)
She/he is an endocrinologist/diabetologist	188 (76.1)
Number of patients with T1D followed (n=247)	
Less than 100	71 (29.1)
100 to 200	42 (16.9)

201 to 500	59 (23.8)
More than 500	75 (30.2)
Provision of universal health care insurance/coverage for the use of insulin pump and/or CGM systems in your country (n=247)	
Yes	65 (26.3)
No	112 (45.3)
Partially	70 (28.3)
Coverage/reimbursement of private insurance companies for insulin pump and/or CGM systems in your country (n=246)	
Yes	57 (23.2)
No	132 (53.7)
Partially	59 (24)
Member of the International Society for Pediatric and Adolescent Diabetes (ISPAD) (n=247)	
Yes	173 (70)
No	74 (30)

¥ Top 11 country. § Countries with response: Argentina, Bangladesh, Bulgaria, Denmark, Ecuador, Egypt, Finland, Germany, Greece, Haiti, Indonesia, Ireland, Israel, Japan, Liberia, Luxembourg, Malaysia, Malta, Mauritius, Morocco, Myanmar, Netherlands, Norway, Pakistan, Paraguay, Peru, Poland, Republic of Korea, Romania, Saudi Arabia, Serbia, Slovenia, South Africa, Spain, Sweden, Thailand, Turkey, and Uruguay.

Table 2: Percentages of patients counselled by HCP that agreed or consented to start insulin pump therapy.

	Percentage of patients				P value
n of responses by HCP subgroups, (%)	**< 25%**	**25-50%**	**50-75%**	**>75%**	
Age					**NS**
≤ 40 years-old: 85 (44.7)	20 (23.5)	21 (24.7)	21 (24.7)	23 (27.1)	
> 40 years-old: 105 (55.3)	24 (22.9)	17 (16.2)	33 (31.4)	31 (29.5)	
Years of practice					**0.001**
≤ 10 years: 97 (48.0)	36 (37.1)	19 (19.6)	20 (20.6)	22 (22.7)	
> 10 years: 105 (52.0)	14 (13.3)	20 (19.1)	36 (34.3)	35 (35.3)	
Practice setting					**0.008**
Private Hospital: 48 (24.2)	20 (41.7)	13 (27.1)	7 (14.6)	8 (16.7)	
Public/Governmental: 59 (29.8)	14 (23.7)	9 (15.2)	16 (27.1)	20 (33.9)	
University/Academic: 91 (46.0)	15 (16.5)	17 (18.7)	30 (33.0)	29 (31.9)	
Clinic size					**0.020**
≤ 200 patients with T1D: 93 (46.0)	31 (33.3)	19 (20.4)	18 (19.3)	25 (26.9)	
> 200 patients with T1D: 110 (54.0)	19 (17.3)	20 (18.2)	38 (34.5)	33 (30.0)	
Health care coverage					**<0.001**
Universal or partially: 84 (41.4)	40 (47.6)	13 (15.5)	19 (22.6)	12 (14.3)	
No coverage: 119 (58.6)	10 (8.4)	26 (21.8)	37 (31.1)	46 (38.7)	
Insurance reimbursement					**<0.001**
Yes, or partially: 96 (48)	9 (9.4)	22 (22.9)	33 (34.4)	32 (33.3)	
No: 106 (52)	41 (38.7)	17 (16.0)	22 (20.7)	26 (24.5)	
Racial/ethnic minority HCP					**NS**
Yes: 21 (10.4)	6 (28.6)	3 (14.3)	9 (42.9)	3 (14.3)	
No: 181 (89.6)	44 (24.3)	36 (19.9)	47 (26.0)	54 (29.8)	

HCP: healthcare professionals; T1D: type 1 diabetes: NS: non-significant

Table 3: Overview of insulin pumps and continuous glucose monitoring (CGM) systems uptake depending on healthcare coverage or insurance reimbursement.

	Universal or partial healthcare insurance/coverage for diabetes technologies	No healthcare insurance/coverage for diabetes technologies	P value	Private insurance companies cover/reimburse for diabetes technologies	Private insurance companies do not cover/reimburse for diabetes technologies	P value
Use of insulin pump			< 0.0001			< 0.0001
• **Less than 10%**	11.8%	70.6%		20.6%	50.9%	
• **10-30%**	27.7%	4.7%		15.5%	20.8%	
• **30-50%**	33.6%	12.9%		32.0%	17.9%	
• **More than 50%**	26.9%	11.8%		32.0%	10.3%	
Agreement to start on insulin pump			<0.0001			< 0.0001
• **Less than 25%**	8.4%	47.6%		9.4%	38.7%	
• **25-50%**	21.8%	15.4%		22.9%	16.0%	
• **50-75%**	31.1%	22.6%		34.4%	20.7%	
• **More than 75%**	38.9%	14.3%		33.3%	24.5%	
Use of CGM systems			<0.01			<0.01
• **Less than 10%**	11.1%	47.7%		15.4%	43.9%	
• **10-30%**	14.8%	23.9%		13.5%	28.0%	
• **30-50%**	16.7%	14.8%		19.2%	11.2%	
• **More than 50%**	57.4%	14.8%		51.9%	16.8%	
Agreement to start on CGM system			<0.01			<0.01
• **Less than 25%**	3.7%	32.6%		9.8%	28.3%	
• **25-50%**	16.7%	20.9%		11.8%	20.7%	
• **50-75%**	20.4%	26.7%		31.4%	27.4%	
• **More than 75%**	59.3%	19.8%		47.1%	23.6%	
Reason why patients turndown technology:			<0.0001			0.03
• **Family preference for keeping on injections and fingersticks**	7.5%	4.7%		8.2%	4.7%	
• **Fear**	4.2%	3.5%		3.1%	4.7%	
• **Parents cannot afford or maintain therapy**	17.5%	57.6%		26.5%	41.5%	

• **Patient does not want to wear something on its body**	65.8%	28.2%		58.2%	42.4%	
• **Unawareness of technology**	3.3%	3.5%		1.0%	5.7%	
• **Reduced diabetes literacy**	0.8%	1.2%		2.0%	0	
• **No available**	0.8%	1.2%		1.0%	0.9%	
Agreement with the statement "All patients, regardless of circumstance, should be offered insulin pump therapy"	85.2%	78.9%	0.12	85.0%	79.6%	0.13
Disagreement with the sentence "No patient, regardless of circumstance, should be offered insulin pump therapy"	87.3%	86.6%	0.70	86.2%	87.7%	0.88
Relevant factors when starting a patient on insulin pump [a]						
• **Extremely relevant:**						
○ **Age**	35.6%	31.9%	0.75	28.2%	39.4%	0.20
○ **History of severe hypoglycemia**	58.9%	55.1%	0.79	50.6%	62.8%	0.32
○ **Suboptimal glycemic control**	44.1%	35.6%	0.07	34.5%	44.8%	0.15
○ **Requirement of small dosage of insulin**	48.4%	51.1%	0.72	50.6%	49.0%	0.87
• **Fairly relevant:**						
○ **Patient or caregiver preference**	31.9%	38.9%	0.27	32.0%	39.1%	0.09
Contraindications to starting a patient on insulin pump [b]						
• **No contraindication:**						
○ **Age less than 3 years old**	86.3%	87.5%	0.62	87.2%	86.7%	0.08
○ **One or more episodes of diabetic ketoacidosis**	50.0%	48.0%	0.96	50.0%	48.1%	0.96
• **Relative contraindication**						

○ **History of infrequent glucose monitoring/no use of CGM**	46.1%	72.0%	0.007	55.4%	65.1%	0.07
○ **Inadequate parental/caregiver supervision**	45.9%	56.0%	0.47	53.4%	48.7%	0.41
• **Absolute contraindication:**						
○ **Infrequent follow-up**	48.7%	49.4%	0.13	41.6%	56.2%	0.17

a. On a scale from not at all relevant to extremely relevant, data were assessed for the most indicated option.
b. On a scale from not at all a contra-indication to an absolute contra-indication, data were assessed for the most indicated option.

Figure 1: Relevance of socioeconomic factors when insulin pumps are prescribed or recommended.

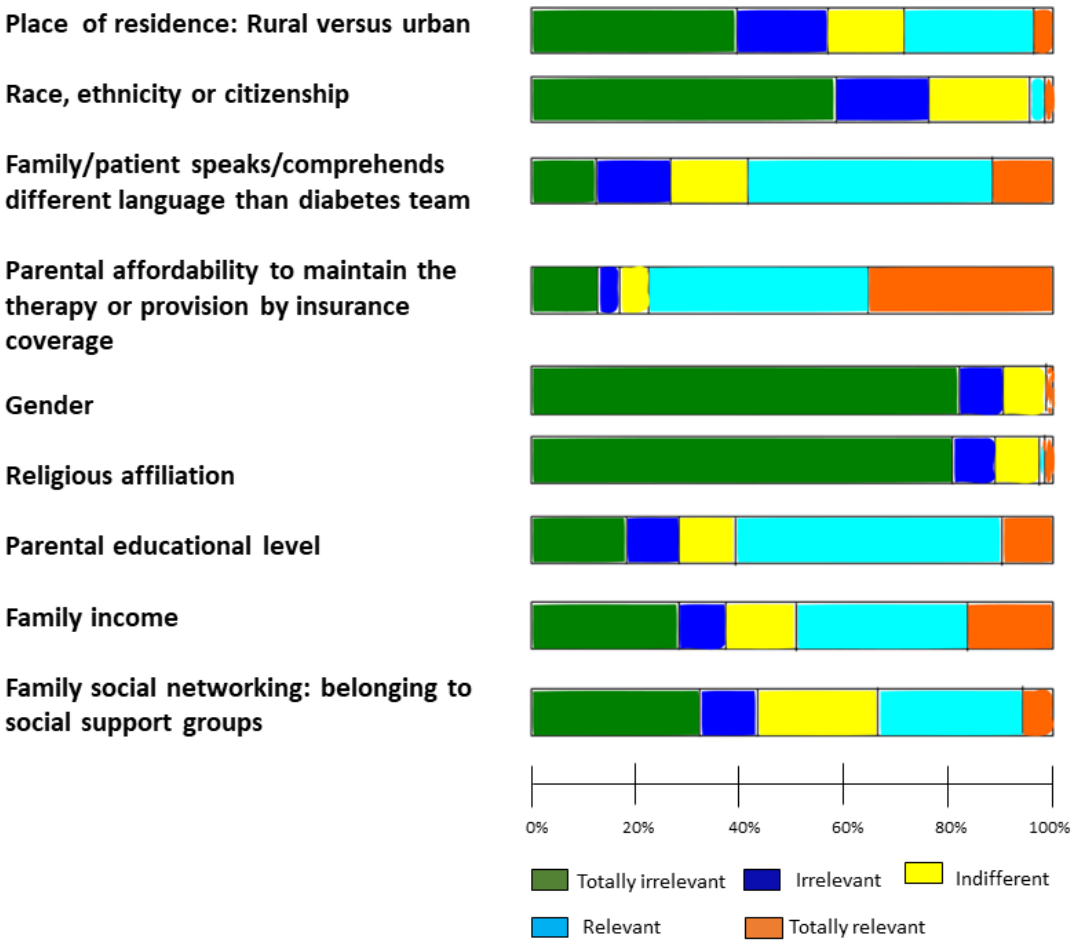
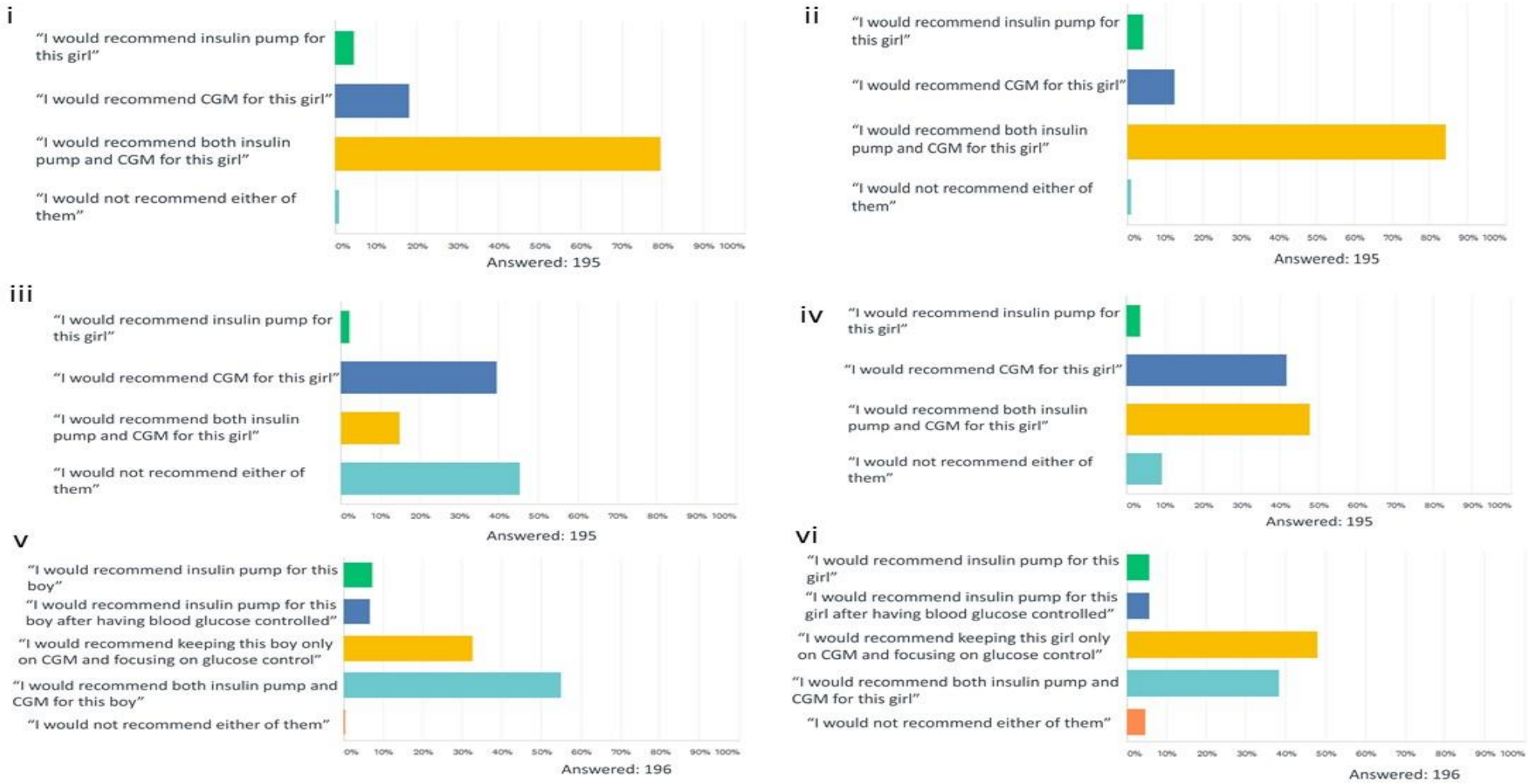


Figure 2: Global results on the six different case vignettes assessing factors thought to impact decision to recommend diabetes technologies for paediatric type 1 diabetes. (i) first case scenario; (ii) second case scenario; (iii) third case scenario; (iv) forth case scenario; (v) fifth case scenario; (vi) sixth case scenario.



5.5 Appendix:

Questions through the SurveyMonkey weblink:

1. **Baseline profile of healthcare professionals (13 questions):** this section aims to assess providers' personal demographics and work profile.

Q1. Are you a prescribing practitioner?

a) Yes
b) No

Q2. What is your age?

a) Under 30
b) 30 to 40
c) 41 to 50
d) 51 to 60
e) Over 60

Q3. What is your gender?

a) Female
b) Male
c) Other, please specify: _____

Q4. In what country do you work? (LIST OF OPTIONS)

Q5. Do you belong to a minority racial/ethnic group in your country of service?

a) Yes
b) No

Q6. What is your main clinical role?

a) Resident
b) Primary care practitioner, pediatrician, family doctor, or an internal medicine doctor
c) Pediatric endocrinology fellow
d) Pediatric endocrinologist/diabetologist
e) Adult Endocrinology fellow
f) Adult endocrinologist/diabetologist
g) Nurse practitioner or a registered nurse
h) Other (please, specify): ____

Q7. How long have you been in practice since completing your training?

a) Less than 3 years
b) 3 to 5 years
c) 5 to 10 years
d) More than 10 years

Q8. Where is your main practice setting? (You can choose more than one option)

a) Private hospital/outpatient clinic
b) Public or governmental hospital/outpatient clinic
c) University or academic hospital/outpatient clinic
d) Primary care center
e) General practitioner office
f) Other, please specify: _____

Q9. If you are not an endocrinologist/diabetologist, do you have access to one as a consultant?

a) Yes
b) No
c) I am an endocrinologist/diabetologist

Q10. How many patients with type 1 diabetes are followed in your clinic?

a) Less than 100
b) 100 to 200
c) 201 to 500
d) More than 500

Q11. Does your country/region have universal health care insurance/coverage for the use of insulin pump and/or the CGM systems?

a) Yes
b) No
c) Partially

Q12. In your country/region, do private insurance companies cover/reimburse for insulin pump and/or CGM systems?

a) Yes
b) No
c) Partially

Q13. Are you an International Society for Pediatric and Adolescent Diabetes (ISPAD) member?

a) Yes
b) No

2. **Regarding the use of insulin pumps (10 questions):** this section aims to assess personal thoughts when providers prescribe or refuse insulin pump.

Q14. Are insulin pumps available in your practice setting?

a) Yes
b) No

Q15. Is there more than one insulin pump brand available in your practice setting?

a) Yes
b) No

Q16. What is the percentage of patients on insulin pump in your center?

a) Less than 10%
b) Between 10 to 30%
c) Between 30 to 50%
d) More than 50%

Q17. What percentages of patients counselled by you agree/consent to start on insulin pump therapy?

a) Less than 25%
b) Between 25 to 50%
c) Between 50 to 75%
d) More than 75%

Q18. What is your opinion on the reasons why patients and caregivers turn down technology after being offered it? (multiple choice)

a) Unawareness
b) Fear
c) Shame
d) Patient does not want to wear something on its body
e) Parents cannot afford and/or maintain therapy
f) Reduced diabetes literacy
g) Family preference for keeping on injections and fingerstick
h) Other, please specify: _____

Q19. Do you agree with the statement **"All patients, regardless of circumstance, should be offered insulin pump therapy"**?

a) Totally agree
b) Agree
c) Partially agree
d) Disagree
e) Totally disagree

Q20. Do you agree with the statement **"No patient, regardless of circumstance, should be offered insulin pump therapy"**?

a) Totally agree
b) Agree
c) Partially agree
d) Disagree
e) Totally disagree

Q21. On a scale from 1 (not all relevant) to 5 (extremely relevant), what is the importance you give for the following indications to start a patient on insulin pump therapy? (MATRIX/RATING SCALE: 1 – not all relevant; 2- slightly relevant; 3 – relevant; 4 – fairly relevant; 5 – extremely relevant)

a) Patient age
b) History of severe hypoglycemia (values of glycemia <54 mg/dL (<3.0 mmoL/L), or severe cognitive impairment, including coma and convulsions, requiring external assistance by another person to actively administer carbohydrates, glucagon, or take other corrective actions) or hypoglycemia unawareness
c) Suboptimal glycemic control despite good compliance
d) Patient or caregiver´s preference
e) Requirement of small doses of insulin

Q22. On a scale from 1 (not at all a contraindication) to 3 (an absolute contraindication), what is the importance you give when decide to start a patient on insulin pump therapy? (MATRIX/RATING SCALE: 1-not all a contraindication; 1- relative contraindication; 2- absolute contraindication).

a) Age less than three years old
b) History of infrequent blood glucose monitoring (less than three a day) or not on CGM
c) One or more episodes of diabetic ketoacidosis
d) Inadequate parental/caregiver supervision
e) Infrequent follow-up

Q23. Do you consider relevant the following socioeconomic factors when you prescribe insulin pumps? (MATRIX/RATING SCALE: 1 – totally irrelevant; 2 – irrelevant; 3 – indifferent; 4 – relevant; 4 – totally relevant)

Factors of socio-economic health determinants	1	2	3	4	5
i. Place of residence: Rural versus urban					
ii. Race, ethnicity or citizenship					
iii. Family/patient speaks/comprehend different language than diabetes team					

iv. Parental affordability to maintain the therapy or provision by insurance coverage					
v. Gender					
vi. Religious affiliation					
vii. Parental educational level					
viii. Family income					
ix. Family social networking: belonging to social support groups					

3. **Regarding the use of continuous glucose monitoring (CGM) systems (4 questions):** this section aims to assess personal thoughts when providers prescribe or refuse CGM.

Q24. Are there any CGM systems available in your practice setting?

a) Yes
b) No

Q25. Is there more than one CGM system brand available in your practice setting?

a) Yes
b) No

Q26. What is the percentage of patients on CGM in your unit?

a) Less than 10%
b) Between 10 to 30%
c) Between 30 to 50%
d) More than 50%

Q27. What percentages of patients counselled by you agree/consent to start on CGM?

a) Less than 25%
b) Between 25 to 50%
c) Between 50 to 75%
d) More than 75%

4. According to the following vignettes would you recommend insulin pump, CGM, both or neither of them? In all the scenarios, patients have type 1 diabetes and have been already introduced to diabetes education regarding the use of technological devices. (6 questions)

Infant and toddlers:

Q28. One-year-old girl, during her partial remission phase, receiving 2.5 IU/day of basal long-acting analog insulin, and doing corrections with rapid-acting analogs when needed, has faced two **severe hypoglycemia episodes**, one of them with seizures. She has a **single mother**, **unemployed**, and they live in a country where there is **universal coverage** for CSII and CGM.

i. I would recommend insulin pump for this girl
ii. I would recommend CGM for this girl
iii. I would recommend both insulin pump and CGM for this girl
iv. I would not recommend either of them

Q29. One-year-old girl, during her partial remission phase, receiving 2.5 IU/day of basal long-acting analog insulin, and doing corrections with rapid-acting analogs when needed, has faced two **severe hypoglycemia episodes**, one of them with seizures. She **lives with her parents in a wealthy village four-hour away from nearest diabetes center**, and **family has full insurance coverage** for CSII and CGM.

i. I would recommend insulin pump for this girl
ii. I would recommend CGM for this girl
iii. I would recommend both insulin pump and CGM for this girl
iv. I would not recommend either of them

School Age:

Q30. A 6-year-old girl has been suffering **blood sugar fluctuations** which include one episode of **diabetic ketoacidosis** last month. Her parents are facing a **difficult economic situation** because both are **unemployed and do not have insurance coverage for diabetes suppliers**. The **young parents have not completed their secondary studies**, and **family lives in a deprived area of a big city**.

i. I would recommend insulin pump for this girl
ii. I would recommend CGM for this girl
iii. I would recommend both insulin pump and CGM for this girl
iv. I would not recommend either of them

Q31. A 6-year-old girl has been suffering **blood sugar fluctuations** which include one episode of **diabetic ketoacidosis** last month. The family recently moved to a **new country** where there is **universal healthcare and coverage for CSII and CGM**. The **family belongs to a minority religion** and has **low language comprehension** in their new country.

i. I would recommend insulin pump for this girl
ii. I would recommend CGM for this girl
iii. I would recommend both insulin pump and CGM for this girl
iv. I would not recommend either of them

Adolescent

Q32. An adolescent **boy,** from a **racial/ethnic minority group**, diagnosed eight years ago, lives with his grandmother who **works as a nurse** and is his **only guardian**. Their health insurance recently approved him the provision of an intermittent CGM (Libre flash). He has suffered **uncontrolled blood glucose**, despite been on MDI with intensive basal-bolus requiring 1.8 IU/kg/day. Every year he **participates in a regional diabetes camp**.

i. I would recommend insulin pump for this boy
ii. I would recommend insulin pump for this boy after having blood glucose controlled
iii. I would recommend keeping this boy only on CGM and focusing on glucose control
iv. I would recommend both insulin pump and CGM for this boy
v. I would not recommend either of them

Q33. A Caucasian adolescent **girl**, belonging to a major racial/ethnic group, diagnosed eight years ago, lives with **her grandparents who are retired**. Their health insurance recently approved her the provision of an intermittent CGM (Libre flash). She has been suffering **uncontrolled blood glucose**, despite been on MDI with intensive basal-bolus requiring 1.8 IU/kg/day. In the village where they live, there are **lacking of social support and counselling**.

i. I would recommend insulin pump for this girl
ii. I would recommend insulin pump for this girl after having blood glucose controlled
iii. I would recommend keeping this girl only on CGM and focusing on glucose control
iv. I would recommend both insulin pump and CGM for this girl
v. I would not recommend either of them

Conclusions

Conclusions

1. In children and adolescents, the type 1 diabetes treatment with continuous subcutaneous insulin infusions (CSII) without integration of continuous glucose monitoring (CGM) systems, has moderate-level evidence of modestly lowering HbA1c when compared with multiple-daily injections of insulin (MDI). More evidence is needed on the effect of the CSII vs MDI on other important glycemic outcomes and health-related quality of life.

2. Studies on the effectiveness of CSII versus MDI have reported very little data on health inequalities regarding use and outcomes of these technologies. Most of the existing literature corresponded to high-income countries; however, data available on socially disadvantaged groups suggests that they would benefit from CSII. Prescription of CSII seems to be mostly based on patients' or family's preference. Future research on diabetes technology assessment should include individual and area-level socioeconomic information to enable a full equity-oriented analysis of the effectiveness of the CSII in children and adolescents.

3. Healthcare professionals seem to be markedly supportive to start treatment of children and adolescents with new diabetes technologies. However, coverage/insurance for CSII and other recent devices holds the biggest impact on the extent of their recommendations.

Conclusiones

Conclusiones

1. En niños y adolescentes, el tratamiento de la diabetes tipo 1 con las infusiones subcutánea continuas de insulina (ISCI), sin integrarlas con los sistemas de monitorización continua de glucosa (CGM), presenta con una evidencia de nivel moderado una disminución moderada de la HbA1c en comparación con la terapia de múltiples dosis de insulina (MDI). Se necesitan más evidencias sobre el efecto de las ISCI frente a las MDI sobre otros resultados glucémicos y la calidad de vida relacionada con la salud.
2. Los estudios sobre la efectividad de la ISCI versus MDI han reportado muy pocos datos sobre las desigualdades en salud con respecto al uso y los resultados glucémicos con el uso de estas tecnologías. La mayor parte de la literatura existente correspondía a países de ingresos altos; sin embargo, los datos disponibles sobre grupos socialmente desfavorecidos sugieren que estos se beneficiarían de la ISCI. El empleo de la ISCI parece basarse principalmente en las preferencias del paciente o de la familia. Futuros estudios sobre la evaluación de esta tecnología deben incluir información socioeconómica individual y comunitaria para permitir un análisis completo orientado a la equidad de la efectividad de la ISCI en niños y adolescentes.
3. Los profesionales de la salud parecen respaldar el inicio del tratamiento con el uso de los nuevos dispositivos en niños y adolescentes con diabetes tipo 1. Sin embargo, la cobertura / seguro para la ISCI y para los otros dispositivos tiene un mayor impacto en la toma de decisión.

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Appendix

Activities during the training period

2017/18

Meetings:

- Jornada en Avances en Pubertad de la Sociedad Española de Endocrinología, Madrid, Spain.
- XXIV Congreso de la Sociedad Española de Medicina de la Adolescencia, Sevilla, Spain.
- 57th European Society for Pediatric Endocrinology Meeting, Athens, Greece
- European Society for Pediatric Endocrinology Diabetes, Obesity, and Metabolism Postgraduation School, Delphi, Greece

Cross-border mobility:

- Campamento de Diabetes de la Federación de Diabetes Juvenil de Ecuador

Communications:

- 57th European Society for Paediatric Endocrinology: Clinical management of childhood hyperthyroidism: A longitudinal study at a single center

Index-linked publication:

- Ybarra M, **Dos Santos TJ**, Pinheiro CTC, Dichtchekenian V, Damiani D. Rectal Levothyroxine for the Treatment of Hypothyroidism: A Case Study. Pediatrics. 2018 Aug;142(2):e20173317. doi: 10.1542/peds.2017-3317. Epub 2018
- **Dos Santos TJ**, Martos-Moreno GÁ, Muñoz-Calvo MT, Pozo J, Rodríguez-Artalejo F, Argente J. Clinical management of childhood hyperthyroidism with and without Down syndrome: a longitudinal study at a single center. J Pediatr Endocrinol Metab. 2018 Jul 26;31(7):743-750. doi: 10.1515/jpem-2018-0132.

2018/19

Meetings:

- Curso de postgrado en diabetes tipo 1, Sociedad Española de Endocrinología Pediátrica, Madrid, Spain.
- Jornada de actualización en diabetes tipo 1, Hospital Universitario La Paz, Madrid, Spain.
- Curso de Revisión Sistemática Cochrane, Hospital Ramón y Cajal, Madrid, Spain.
- Reunión Anual de la Sociedad Española de Endocrinología Pediátrica, Madrid, Spain.
- Jornada de Casos clínicos en Endocrinología, Hospital Universitario Infantil Niño Jesús, Madrid, Spain.
- Joint EASD/ISPAD/ESPE Posgraduation Course on Type 1 diabetes in children, adolescents and young adults, Prague, Czech Republic.

Cross-border mobility:

- Campamento de Diabetes de la Federación de Diabetes Juvenil de Ecuador

Communications:

- Reunión Anual de la Sociedad Española de Endocrinología Pediátrica: "Nuevas formas de administración de insulina y resultados glucémicos en pacientes pediátricos con diabetes tipo 1: un protocolo de estudio bajo una óptica de equidad en salud."

Index-linked publication:

- **Dos Santos TJ,** Passone CGB, Ybarra M, Ito SS, Teles MG, Manna TD, Damiani D. Pitfalls in the diagnosis of insulin autoimmune syndrome (Hirata's disease) in a hypoglycemic child: a case report and review of the literature. J Pediatr Endocrinol Metab. 2019 Apr 24;32(4):421-428. doi: 10.1515/jpem-2018-0441.

2019/20

Meetings:

- XXXVII Reunión Anual de la Sociedad Española de Epidemiología (SEE), XIV Congresso da Associação Portuguesa de Epidemiologia (APE), Oviedo, Spain.

- 45th ISPAD Annual Conference, Boston, USA

Cross-border mobility:

- Allan Drash ISPAD Clinical Fellowship, UH Rainbow Babies and Children's Hospital, Cleveland, Ohio, USA

- Mentorship Program at the ISPAD Science School for Physicians, Rotterdam, The Netherlands

Communications:

- 45th ISPAD Annual Conference:

  "Continuous subcutaneous insulin infusions (CSII) versus multiple-daily injections (MDI) in youths with type 1 diabetes mellitus: a systematic review and meta-analysis of the literature with an equity lens"

  "Acquired lipodystrophy among children and adolescents attending a diabetes camp"

Index-linked publication:

- Ybarra M, **Santos TJD**, Queiroz ES, Rachid L, Franco RR, Cominato L, Moura FC, Velhote MC, Damiani D. BARIATRIC SURGERY AS A TREATMENT FOR IDIOPATHIC INTRACRANIAL HYPERTENSION IN A MALE ADOLESCENT: CASE REPORT. Rev Paul Pediatr. 2020 Jan 13;38:e2018239. doi: 10.1590/1984-0462/2020/38/2018239.

- Vukovic R, **Dos Santos TJ**, Ybarra M, Atar M. Children With Metabolically Healthy Obesity: A Review. Front Endocrinol (Lausanne). 2019 Dec 10;10:865. doi: 10.3389/fendo.2019.00865.

- **Dos Santos TJ**, Donado Campos JM, Fraga Medin CA, Argente J, Rodríguez-Artalejo F. New insulin delivery devices and glycemic outcomes in young patients with type 1 diabetes: a protocol for a systematic review and meta-analysis. Syst Rev. 2019 Nov 4;8(1):259. doi: 10.1186/s13643-019-1171-9.

2020/21

Meetings:

- 46th ISPAD Annual Conference (Virtual)
- Reunión Anual de la Sociedad Española de Endocrinología Pediátrica (Virtual)
- Encuentro Anual de la Asociación Española de Pediatría (Virtual)

Communications:

- 46th ISPAD Annual Conference (Virtual):

  "Viewpoints of health-care professionals on recommending type-1 diabetes technologies in children and adolescents: a worldwide survey."

Index-linked publication:

- Elbarbary NS, **Dos Santos TJ**, de Beaufort C, Agwu JC, Calliari LE, Scaramuzza AE. COVID-19 outbreak and pediatric diabetes: Perceptions of health care professionals worldwide. Pediatr Diabetes. 2020 Nov;21(7):1083-1092. doi: 10.1111/pedi.13084. Epub 2020 Aug 17.

- **Dos Santos TJ**, Donado Campos JM, Argente J, Rodríguez-Artalejo F. Effectiveness and equity of continuous subcutaneous insulin infusions in pediatric type 1 diabetes: A systematic review and meta-analysis of the literature. Diabetes Res Clin Pract. 2021 Feb;172:108643. doi: 10.1016/j.diabres.2020.108643.

Biosketch

The author of this thesis, Tiago Jeronimo dos Santos, was born on January 2nd, 1985, in Gravataí, State of Rio Grande do Sul, in Southern Brazil. He attended his primary studies at *Dr Martinho Lutero, Governador Roberto Silveira and Carlos Antonio Wilkens Elementary* Schools, and his secondary studies at the *Instituto Estadual Marechal Mascarenhas de Moraes*, in Cachoeirinha, Brazil. He obtained his Medical Degree from the *Universidade Federal de Ciências da Saúde de Porto Alegre*, in Porto Alegre, Brazil, in 2010. He obtained his Pediatric specialty from the *Hospital de Clínicas de Porto Alegre/Universidade Federal do Rio Grande do Sul*, Porto Alegre in 2013, and his Pediatric Endocrinology specialty from the *Instituto da Criança/Faculdade de Medicina da Universidade de São Paulo*, São Paulo, Brazil in 2015. In 2016 he moved to Madrid, Spain, to boost his career as a pediatric endocrinologist after being awarded with a grant from the European Society for Pediatric Endocrinology to work as a clinical fellow at the *Hospital Infantil Universitario Niño Jesús*, mentored by Prof. Dr. Jesús Argente. In 2017 he received his master's degree in Quantitative Methods for Epidemiological Research at the *School of Medicine, Universidad Autónoma de Madrid*, Spain, and at the same year he started his doctorate studies on type 1 diabetes-related technology and health inequalities at the *Universidad Autónoma de Madrid* & the *Hospital Infantil Niño Jesús*, Madrid, mentored by Prof. Dr Fernando Rodríguez Artalejo and Prof. Dr. Jesús Argente. In 2019 he completed a research stay in Cleveland, Ohio, USA at the *UH Rainbow Babies and Children's Hospital*, mentored by Dr. Jamie Wood, with the Allan-Drash Fellowship grant from the International Society for Pediatric and Adolescent Diabetes.

Today he works as a pediatric endocrinologist at the *Hospital Vithas Almería-Instituto Hispalense de Pediatría*, Almería, Spain, and is member of the European Society for Pediatric Endocrinology (ESPE) and the International Society for Pediatric and Adolescent Diabetes (ISPAD), where he also acts as a vocal for the ISPAD young community.

Citation

Tiago Jeronimo dos Santos, Juan de Mata Donado Campos, Cristina Alexandra Fraga Medin, Jesús Argente Oliver, Fernando Rodríguez-Artalejo. New insulin delivery devices and glycemic outcomes in young patients with type 1 diabetes: a protocol for a systematic review and meta-analysis. PROSPERO 2018 CRD42018116474 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42018116474

Review question

Which are the effects of using continuous subcutaneous insulin infusion (CSII) versus multiple daily insulin injections (MDI) on glycemic outcomes (glycated hemoglobin, severe hypoglycemia and diabetic ketoacidosis episodes, glycemic variability and health/diabetes-related quality of life) among young patients with type 1 diabetes, assessed with an equity-lens.

Searches

The bibliographic search will be conducted from 2000 to 2019 in MEDLINE (via PubMed), EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Database of Systematic Reviews and the Health technology Assessment (HTA) Database. Previous reviews and handsearch from the original articles will also be scanned for additional references. Searched terms will be combined using standardized subject terms assigned by indexers, designed and conducted by a librarian with the input from the principal investigators, using Boolean operators for MEDLINE, EMBASE, CENTRAL and HTA databases. The final search strategy will be documented, and will have no restrictions based on language or publication status.

Types of study to be included

We will include randomized clinical trials, diabetes registries and other types of longitudinal studies (cohort), and before/after studies in which patients were switched from MDI to CSIII, that assessed each of the therapies between January 2000 and September 2019.

Condition or domain being studied

Type 1 diabetes mellitus. Diabetes-related technology. Health inequity.

Participants/population

We will select studies that compared the use of CSII with MDI and evaluated, as glycemic endpoints, the glycated hemoglobin (HbA1c) value, hypoglycemia episodes [e.g., severe, minor or nocturnal] and diabetic ketoacidosis (DKA) events, glycemic variability [the percentage of the time glucose values were in range (70-180 mg/dl), in hypo (<70 mg/dL) and in hyperglycemia (>180 mg/dL). Patient-reported outcomes will be assessed with health-related quality of life (HRQoL) questionnaires. Specifically, the studies must meet the following selection criteria: (i) to be conducted with children and adolescents (under 20 years of age); (ii) exclusively on patients with T1D; (iii) designed as randomized controlled trials (RCT) or non-randomized studies (NRS) - longitudinal registries and cohorts; and (iv) to have reported any of the outcomes of interest: HbA1c, hypoglycemia, DKA, % of TIR and in hypo-hyperglycemia, and HRQoL.

Intervention(s), exposure(s)

Continuous subcutaneous insulin infusion (CSII) is an external pump device that is currently the best way to imitate the physiological insulin profile. Insulin is infused subcutaneously at a preprogrammed basal rate and boluses are added to counterbalance the intake of carbohydrates. Usually, the insulin pump is an alternative to the treatment with conventional care - with the multiple daily insulin injections (MDI) with syringe or pen - when glycated hemoglobin (HbA1c) is persistently above the individual target, hypoglycemia is a major problem, or if quality of life needs to be improved.

Comparator(s)/control

Multiple daily injections (MDI) of insulin consist of the accomplishment of the total daily insulin requirements by syringe and/or pen. Approximately 30% to 45% (sometimes ~50% when insulin analogs are used) should be basal insulin, with the remaining dosage being adjusted for preprandial rapid-acting or regular insulin. Injections of prandial insulin before each meal (breakfast, lunch, and main evening meal), should be given as

rapid-acting insulin immediately before (or in exceptional cases after) and adjusted to glycemia, meal content and daily activity. In any case, MDI will be considered as an intensive insulin injection regimen.

Context
Clinical and/or community based research.

Main outcome(s)
Glycemic endpoints:

1. The pooled mean difference for HbA1c in CSII vs. MDI, [mean % (SD)];
2. The pooled rate ratio for severe hypoglycemia in CSII vs. MDI, (event/100 patient/year);

3. The pooled risk ratio for DKA in CSII vs. MDI, (number of patients with a frequency of ? 1);

4. The pooled mean difference for %TIR, in hypo and in hyperglycemia in CSII vs MDI, [mean % (SD)];

5. The pooled mean difference for HRQoL scores in CSII vs. MDI, [mean % (SD)].

Measures of effect
The effect size of the SMD will be classified as small (0.1-0.3), medium (0.3-0.6) or large (?0.6).

Additional outcome(s)
Determinants of health inequity will be assessed using variables with an equity lens, according to the acronym PROGRESS, which is a framework to guide data extraction by social determinants factors:

a) Place of residence: will be summarized as if patients reside in a high- or low-to-middle-income country, as per the World Bank database.

b) Race, Ethnicity, Culture and Language: if patients belong to a context of disadvantage, as being member of minority group (including nationality status) or having low language comprehension (as a second language).

c) Occupation: if parental occupancy affect the affordability to access and adopt technological devices or the recipient of them from medical insurance.

d) Sex: if there were any unequal distribution of therapies between sex.

e) Religion: if insulin delivery system was restricted because of a certain religious affiliation or lack of it.

f) Education: if parental educational level (or health literacy and numeracy) affected the access/use of either therapies.

g) Socioeconomic status: if estimated household income entailed better access to resources and privilege.

h) Social capital: if ascertained civic participation and networking (e.g. participating in a diabetes camp, membership in diabetes associations) resulted in benefits.

Measures of effect
We will specify different hypothesis for each factor of inequality and its influence on the glycemic outcomes, as:

(1) a positive social gradient in effectiveness, when better outcomes are expected for more advantaged groups;

(2) a negative social gradient in effectiveness, when better outcomes are expected for less advantaged groups; and (3) a neutral social gradient in effectiveness, when no significant differences are found between groups.
Also, depending on how each variable PROGRESS were displayed across the studies, we will classify the information as retrieved from:

(a) baseline demographics;

(b) subgroup analysis;

and (c) interaction analysis.

Data extraction (selection and coding)

Two reviewers will work independently to check eligibility of studies (title and abstract and, if needed, full-text) and extract the appropriate information in full-text articles. Disagreements will be resolved by consensus. Search of studies, assessment of eligibility and its inclusion will be conducted according to the indications of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. Data to be extracted from articles include year of publication, country, study design and period of data collection, baseline characteristics of participants, interventions and comparators, factors of inequalities at baseline, and outcomes. We will collect data on factors that may contribute for inequalities by means of the guidance of the PROGRESS framework.

Risk of bias (quality) assessment

Two reviewers will independently assess risk of bias of each study using two different tools: the Cochrane Risk of Bias form for randomized controlled trials (RCT) and the RTI Item Bank for observational studies.

A review of only RCT may provide insufficient information on vulnerable subpopulations. Still, the inclusion of observational studies may increase the challenges in establishing causal inference because they are at greater risk of bias than RCT, resulting from confounding by indication and selection bias. In contrast, threats to validity from performance and detection bias, and to precision from inadequate sample size, should not differ markedly between RCT and observational studies (although some features such as blinding of assessors that protect against detection bias are more likely in experimental designs than in observational studies).

By including observational studies (mainly registries), we may capture valuable information on the intended population for whom CSII is preferred, because registries are larger, studied over a longer time, and may better reflect all subgroups of patients and routine clinical practice.

Strategy for data synthesis

We will summarize the main characteristics of selected studies, including the study´s objectives and design, characteristics of study participants, type of intervention and comparator, PROGRESS factors, outcomes and follow-up.

We will retrieve standardized mean HbA1c (%) endpoint for both children treated with CSII and MDI. Results on hypoglycemia will be presented as incidence rate ratios, the number of patients with ? 1 DKA event as risk ratio, the % of TIR and in hypo-hyperglycemia in mean (±SD), and the HRQoL scores in mean difference (±SD).

Meta-analyses will be performed when data are available for at least two studies with comparable results, with their 95% confidence interval, calculated with a random-effects model. Heterogeneity among studies will

be assessed with the I^2 statistic, whose values will be classified as follows: no relevant heterogeneity (0-25%), moderate heterogeneity (25-50%) and substantial heterogeneity (>50%). When it is not possible to perform a meta-analysis, we will elaborate a narrative synthesis.

Publication bias will be evaluated graphically using a funnel plot and also with the method of Egger et al.

The strength of the body of evidence will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool.

Analysis of subgroups or subsets
Subgroup analyses will be executed based on length of duration (less or more than one year), and the use of adjunctive glucose sensor that might directly improve glycemic outcomes.

Sensitivity analysis will be repeated after exclusion of studies with high risk of bias.

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Professor Jesús Argente Oliver. Universidad Autónoma de Madrid
Professor Fernando Rodríguez-Artalejo. Universidad Autónoma de Madrid

Type and method of review
Intervention, Meta-analysis, Narrative synthesis, Systematic review

Anticipated or actual start date
01 October 2018

Anticipated completion date
01 October 2019

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None

Conflicts of interest

Language
English

Country
Spain

Published protocol
https://www.crd.york.ac.uk/PROSPEROFILES/116474_PROTOCOL_20210517.pdf

Stage of review
Review Completed published

Details of final report/publication(s) or preprints if available

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Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Blood Glucose; Diabetes Mellitus, Type 1; Humans; Insulin

Date of registration in PROSPERO
04 December 2018

Date of first submission
13 November 2018

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Revision note
The protocol has been accepted for a publication in a peer-review journal which lead us to make arrangements in the original protocol.

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.
The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

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Systematic Reviews

PROTOCOL Open Access

New insulin delivery devices and glycemic outcomes in young patients with type 1 diabetes: a protocol for a systematic review and meta-analysis

Tiago Jeronimo Dos Santos[1,2*], Juan de Mata Donado Campos[1,3], Cristina Alexandra Fraga Medin[4], Jesús Argente[2,5,6,7] and Fernando Rodríguez-Artalejo[1,3,7]

Abstract

Background: Optimal type 1 diabetes mellitus (T1D) care requires lifelong appropriate insulin treatment, which can be provided either by multiple daily injections (MDI) of insulin or by continuous subcutaneous insulin infusion (CSII). An increasing number of trials and previous systematic reviews and meta-analyses (SRMA) have compared both CSII and MDI but have provided limited information on equity and fairness regarding access to, and the effect of, those insulin devices. This study protocol proposes a clear and transparent methodology for conducting a SRMA of the literature (1) to assess the effect of CSII versus MDI on glycemic and patient-reported outcomes (PROs) among young patients with T1D and (2) to identify health inequalities in the use of CSII.

Methods: This protocol was developed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P), the PRISMA-E (PRISMA-Equity 2012 Guidelines), and the Cochrane Collaboration Handbook. We will include randomized clinical trials and non-randomized studies published between January 2000 and June 2019 to assess the effectiveness of CSII versus MDI on glycemic and PROs in young patients with T1D. To assess health inequality among those who received CSII, we will use the PROGRESS framework. To gather relevant studies, a search will be conducted in MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Database of Systematic Reviews, and the Health Technology Assessment (HTA) database. We will select studies that compared glycemic outcomes (the glycosylated hemoglobin values, severe hypoglycemia episodes, diabetic ketoacidosis events, and/or time spent in range or in hyper-hypoglycemia), and health-related quality of life, as a PRO, between therapies. Screening and selection of studies will be conducted independently by two researchers. Subgroup analyses will be performed according to age group, length of follow-up, and the use of adjunctive technological therapies that might influence glycemic outcomes.

Discussion: Studies of the average effects of CSII versus MDI may have not assessed their impact on health equity, as some intended populations have been excluded. Therefore, this study will address health equity issues when assessing effects of CSII. The results will be published in a peer-review journal. *Ethics* approval will not be needed.

Systematic review registration: PROSPERO CRD42018116474

Keywords: Insulin pump, Continuous subcutaneous insulin infusion, Multiple daily injections, Health inequity, Type 1 diabetes

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Background

Optimal type 1 diabetes mellitus (T1D) care requires lifelong appropriate insulin treatment that can be provided by either multiple daily injections (MDI) of insulin or by a continuous subcutaneous insulin infusion (CSII) pump [1]. Over the last years, the use of CSII has increased substantially among pediatric patients [1]. However, the selection of CSII versus MDI might have not been based only on clinical indications (e.g., elevated glycosylated hemoglobin and higher hypoglycemia rate), but also could have been influenced by social factors, such as the place of residence and socioeconomic status, which may have led to health inequalities [1–3].

Meeting glycemic targets is a challenging task in young patients with T1D; thus, new insulin delivery systems represent an opportunity to improve glycemic control, to promote patient-centered decisions, and to reduce the burden of diabetes care [4, 5]. Although an increasing number of trials has assessed whether the CSII is more effective than the intensive insulin therapy with syringe and/or pen [6–13], previous systematic reviews and meta-analyses (SRMA) of trials have not reported adequate information concerning equity and fairness in treatment selection [14–17].

Given the greater difficulty for good glycemic control in patients/families with lower health literacy and poor access to some healthcare resources, it is possible that the absolute benefit of CSII would be greater in those with lower socioeconomic status [18]. However, we do not know if they have the chance to participate and benefit from this intervention. In addition, there might exist several barriers for patient access and/or maintenance using CSII, and only a few studies (e.g., diabetes registries) have investigated the role of unequal health care access and social disparities on glycemic outcomes [2, 19, 20]. In consequence, SRMAs with an equity lens could assess whether unequal benefits across sociodemographic population groups could contribute to worsening health inequalities in T1D management [21–23].

Therefore, this paper aims to report a standardized and transparent methodology for conducting a SRMA of the literature (1) to assess the effectiveness of using CSII versus MDI on glycemic (glycosylated hemoglobin, severe hypoglycemia, diabetes ketoacidosis and glycemic variability) and patient-related outcomes among young patients with T1D and (2) to identify health inequalities for those who use CSII.

Methods

Review design

This protocol was developed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) [24] and was registered and published on PROSPERO international prospective register of systematic reviews (registration number CRD42018116474). The Cochrane Collaboration Handbook [25] will also be used to guide the review methods, and PRISMA-E (PRISMA-Equity 2012) Guidelines [26] to elaborate the final report. To perform the SRMA, we will include randomized clinical trials (RCT) and non-randomized studies (NRS)—which cover diabetes registries and longitudinal studies—that compared the clinical effectiveness of CSII versus MDI in youths with T1D.

Data sources and search strategy

The bibliographic search will be conducted from January 2000 to June 2019 in MEDLINE (via PubMed), EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Database of Systematic Reviews, and the Health Technology Assessment (HTA) Database. We will also carry out a handsearch of the previous reviews and the bibliography from the original articles for additional references, as well as of the gray literature focusing on abstracts from diabetes associations and conference proceedings, and from technical reports (research and governmental agencies). Search will use standardized subject terms and will be conducted by a librarian with the input from the principal investigator, using Boolean operators for MEDLINE, EMBASE, CENTRAL, and HTA database. The final search strategy will have no restrictions based on language or publication status (see Additional file 1).

Eligibility criteria

We will select studies that compared the use of CSII with MDI and evaluated any of the following glycemic outcomes: glycosylated hemoglobin (HbA_{1c}, percentage), the incidence of hypoglycemia episodes [e.g., severe, serious and/or nocturnal], diabetic ketoacidosis (DKA) events, and/or time spent in range or in hyper-hypoglycemia. Studies that mentioned health-related quality of life (HRQoL) as a PRO will also be selected. Specifically, the studies must meet the following selection criteria: (1) to be conducted with children and adolescents (under 20 years of age), (2) exclusively on patients with T1D, (3) designed as RCT or NRS, and (4) to have reported any of the outcomes of interest: HbA_{1c}, hypoglycemia, DKA, time in range or in hyper-hypoglycemia, and HRQoL. Bihormonal or dual-hormone closed-loop systems that deliver glucagon in addition to insulin will not be included.

Equity analysis

To explore equity in CSII, we will use indicators of social disadvantages defined by PROGRESS [27]. The acronym PROGRESS is a framework to guide data extraction to relate the outcomes with equity of access to an intervention, according to "*place of residence*" (residing in a high- or low-to-middle-income country, as per the

World Bank database), "*race, ethnicity, culture and language*" (racial, ethnical, and cultural background, when the majority of the groups include belonging to a distinctive group who shares origin, culture, traditions, and language through generations), "*occupation*" (parental patterns of work that favor proper maintenance of a therapy or not), "*gender/sex*" (sex refers to identify sex distribution when recommended each therapy), "*religion*" (religious affiliation, spiritual beliefs, or values that promote better access to health services), "*education*" (assumes that high parental educational level, or health literacy and numeracy, is an advantage), "*socioeconomic status*" (access to resources and privilege with greater household wealth, as an advantage), and "*social capital*" (benefits obtained by individuals due to their social relationships, as an advantage).

For each factor of inequality, we hypothesized different social gradients: (1) a positive gradient, when better glycemic outcomes are found in more socially advantaged groups; (2) a negative gradient, when better outcomes are found in less advantaged groups; and (3) a neutral gradient, when no significant differences exist between groups. The results will be summarized with the aid of a harvest plot, which is a graphical technique that helps to illustrate a narrative synthesis [28].

Study selection and data extraction

Two reviewers will work independently to check eligibility of studies (title and abstract and, if needed, full-text) and extract the appropriate information in full-text articles. Disagreements will be resolved by consensus. Assessment of eligibility and its inclusion will be conducted according to the indications of the PRISMA statement. Data to be extracted from articles include the year of publication, country, study design and period of data collection, baseline characteristics of participants, interventions and comparators, factors of inequalities at baseline, and outcomes (Tables 1 and 2).

The glycemic endpoints include (1) the mean value of HbA_{1c} (percentage), assessed preferably at the end of the study, (2) the number of serious, severe and/or nocturnal hypoglycemia episodes [≤ 3.0 mmol/L (54 mg/dL) or an event associated with severe cognitive impairment (including coma and convulsions) requiring assistance], (3) the number of patients with ≥ 1 DKA event, and (4) the percentage of time spent in range [percentage of readings in the glycemic range of 3.9–10.0 mmol/L (70–180 mg/dL) per unit of time] or in hypo [< 3.9 mmol/L (< 70 mg/dL)] and hyperglycemia [> 10 mmol/L (> 180 mg/dL)] [23, 29–32]. PRO will be captured with the HRQoL questionnaires. When necessary, authors of eligible studies will be contacted to provide additional information.

Assessment of risk of bias

Two reviewers will independently assess the risk of bias of each study using two different tools: the Cochrane Risk of Bias form RCT and the RTI Item Bank for NRS [33, 34]. A review of only RCT may provide insufficient information on vulnerable subpopulations. Still, the inclusion of NRS may increase the challenges in establishing causal inference because they are at greater risk of bias than RCT, resulting from confounding by indication and selection bias. In contrast, threats to validity from performance and detection bias, and to precision from the inadequate sample size, should not differ markedly between RCT and NRS (although some features such as blinding of assessors that protect against detection bias are more likely in experimental designs than in observational studies). By including NRS (mainly registries), we may capture valuable information on the intended population for whom CSII is preferred, because registries are larger, studied over a longer time, and may better reflect all subgroups of patients and routine clinical practice [3].

Statistical analysis

We will summarize the main characteristics of selected studies, including the study's objectives and design, characteristics of study participants, intervention and comparator, inclusion of PROGRESS categories, and outcomes (Tables 1 and 2). Effects across the studies will be summarized with (1) the pooled mean difference for HbA_{1c}; (2) the pooled rate ratio for hypoglycemia; (3) the pooled risk ratio for DKA; (4) the mean difference in percentage of time that blood glucose concentration remained in target range, in hypo- or in hyperglycemia; and (5) the pooled standardized mean difference (SMD) for quality of life outcomes, with their 95% confidence interval (CI), calculated with inverse variance random effects models to incorporate the level of heterogeneity found across studies [25, 35]. The effect size of the SMD will be classified as small (0.1–0.3), medium (0.3–0.6) or large (≥ 0.6) [36]. Heterogeneity among studies will be assessed with the I^2 statistic, whose values will be classified as follows: no relevant heterogeneity (0–25%), moderate heterogeneity (25–50%), and substantial heterogeneity (> 50%) [37]. Meta-analyses will be performed separately for RCTs and NRS when data are available for at least two studies with comparable results. For equity outcomes, results will be summarized as a narrative synthesis [28]. Publication bias will be evaluated graphically using a funnel plot and also with the method of Egger et al. [37]. The strength of the

Table 1 Table of evidence with main characteristics of the included studies

Reference	Design and registration details; founding	Country	Year of baseline data collection	N and clinical characteristics	Setting	Type of diabetes-related technology	Type of conventional treatment comparator	Inequality assessed from baseline characteristics	Outcomes	Length of follow-up
Authors, year of publication, name of the study	Study design/ registration number/ founding	Country or region	Year	Number of patients assigned and that received each treatment (CSII:MDI); Sex (M:F); Age; Baseline characteristics of participants (including duration of the disease, baseline HbA_{1c} [mean % (SD)] and HRQoL assessment tool); Other definition or comment	Community/ clinical based research	Continuous subcutaneous insulin infusion (CSII), including the use of adjunctive glucose monitors: model of devices and insulin	Multiple daily injections (MDI): injections and insulins	A. Place of residence B. Race, ethnicity, culture and language C. Occupation D. Sex E. Religion F. Education G. Socioeconomic status H. Social capital	1. HbA_{1c} at the end of the study: CSII versus MDI [mean % (SD)], sig 2. Total number of hypoglycemic episodes: CSII versus MDI, sig 3. Number of patients with a frequency of ≥ 1 Ketoacidosis episode: CSII versus MDI, sig 4. Glycemic variability: % of time in range, hypo and/or hyperglycemia: CSII versus MDI, sig 5. HRQoL score (±SD) at the end of the study: CSII vs. MDI, sig	Duration of follow

CSII continuous subcutaneous insulin infusion, *MDI* multiple daily injection, *M* male, *F* female, *HbA_{1c}* glycosylated hemoglobin, *SD* standard deviation, *sig* significance, *HRQoL* health-related quality of life

Table 2 PROGRESS framework to guide health equity data extraction on type 1 diabetes

PROGRESS framework	Social gradient		
	Positive	**Negative**	**Neutral**
Place of residence: Country where individuals reside (as per the World Bank database).	To reside in a high income country	To reside in a low-to-middle income country	No matter the place of residence, outcomes are non-significant
Race, ethnicity, culture and language: Self-identification racial or ethnic group, or different culture and language, including nationality status.	To be a based-country language comprehension inhabitant or to be part of an ethnic majority	To be part of minority groups or to be a foreign with low language comprehension	No matter the race or ethnic group, outcomes are non-significant
Occupation: Patterns of work that provide proper maintenance of a treatment.	Affordability to have access and maintain technological devices	No affordability to have access and maintain technological devices	No matter the parental occupancy status, outcomes are non-significant
Gender/Sex: Boys and girls were identified between groups.	Characterization of sex distribution between therapies; girls are related to belonging to an advantaged group	No characterization of sex distribution between therapies; boys are related to belonging to a disadvantaged group	No matter the sex distribution, outcomes are non-significant
Religion: Religious affiliation of spiritual beliefs or values.	Access to health services is favored for a subgroup because of its religious affiliation or beliefs	Access to health services is limited because of its religious affiliation or beliefs or due to the lack of religion	No matter the religion or beliefs, outcomes are non-significant
Education: Assessed by the informed educational level or approximated by health literacy and numeracy.	High educational level or health literacy and numeracy are considered advantaged group	Low educational level or health literacy and numeracy are considered disadvantaged group	No matter the education, outcomes are non-significant
Socioeconomic status (SES): To obtain information considering access to resources and privilege.	A higher household wealth is considered advantaged group	A lower familial income is considered disadvantaged group	No matter the SES, outcomes are non-significant
Social capital: Benefits obtained by individuals due to their social relationships, e.g.: to be member of a diabetes foundation, to participate in diabetes camp.	To have network involvement	Not to have network involvement	No matter the network involvement, outcomes are non-significant

body of evidence will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool [38].

Subgroup analysis

Subgroup analyses will be performed based on age group, length of follow-up, and the use of adjunctive

technological therapies that might directly improve glycemic outcomes.

Sensitivity analysis

The analyses will be repeated after exclusion of studies with a high risk of bias, and separately for RCT and NRS.

Discussion

Given the increase of worldwide incidence of T1D, the wider use of the CSII pump among some specific socioeconomic and demographic groups, and the lack of evidence of its superiority when compared with the conventional therapy using MDI, there is a need to critically assess the rise of inequalities in treatment selection [39]. Furthermore, the inclusion of PRO captured by health-related quality of life questionnaires will contribute to a complete diabetes measures portfolio [40]. Hence, the assessment of the effects of CSII versus MDI on glycemic outcomes, across social factors defined by PROGRESS, may contribute better to understand their impact on health equity [12, 16, 41, 42].

A major issue will probably be the limited data reported in the reviewed studies on the PROGRESS factors. For this reason, supplementary information will also be gathered from authors of the included studies. We are aware that the lack of important published information on equity may be a limitation of our review.

The results of an equity-oriented SRMA may yield an opportunity to discuss not only the effects of such interventions on glycemic endpoints, but also the existing gap of information in the included studies regarding social inequities; it will pave the way to use those results to orient clinical practice, equity-based research, and health policy formulation.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s13643-019-1171-9.

Additional file 1. Search Strategies.

Abbreviations

CSII: Continuous subcutaneous insulin infusion; DKA: Diabetes ketoacidosis; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HbA_{1c}: Glycosylated hemoglobin; HRQoL: Health-related quality of life; HTA: Health Technology Assessment; MDI: Multiple daily injections; NRS: Non-randomized studies; PRISMA-E: Preferred Reporting Items for Systematic Reviews and Meta-Analysis – Equity Report; PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols; PRO: Patient-related outcome; PROGRESS: Place of residence, race/ethnicity/culture/language, occupation, gender/sex, religion, education, socioeconomic status, and social capital; RCT: Pandomized clinical trials; SMD: Standardized mean difference; SRMA: Systematic review and meta-analysis; T1D: Type 1 diabetes mellitus

Authors' contributions

TJ was responsible for the conception and design of the study. FRA and JA were the principal investigators and guarantors. CAFM prepared the search strategy. TJ and JDC selected the articles, extracted the data, and conducted the statistical analyses. TJ drafted the manuscript with the support of JA and FRA. All authors revised this work for important intellectual content, and approved the final manuscript.

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TJ is a member of the International Society for Pediatric and Adolescent Diabetes (ISPAD) and the European Society for Paediatric Endocrinology (ESPE). JA is a member of the European Society for Paediatric Endocrinology (ESPE) and the Endocrine Society.

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Review

Effectiveness and equity of continuous subcutaneous insulin infusions in pediatric type 1 diabetes: A systematic review and meta-analysis of the literature

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ABSTRACT

Aims: We conducted a systematic review and meta-analysis of randomized controlled trials (RCT) and non-randomized studies (NRS) to assess the effectiveness and equity of continuous subcutaneous insulin infusions (CSII) versus multiple-daily injections (MDI) on glycemic outcomes.

Methods: Searches were conducted between 2000 and 2019 in MEDLINE, CENTRAL, EMBASE and HTA. Included studies compared the CSII vs MDI in children and young people (CYP) $\leq$ 20 years with type 1 diabetes. Two independent reviewers screened the articles, extracted the data, assessed the risk of bias, evaluated the quality of evidence, and identified equity data. Results were pooled with a random-effects model.

Results: Of the 578 articles screened, 16 RCT (545 CYP on CSII) and 70 NRS (73253 on CSII) were included in the meta-analysis. There was moderate-level evidence that the CSII lower HbA_{1c} in RCT (pooled mean difference [MD]: −0.22%; 95% confidence interval [CI]: −0.33, −0.11%; I^2:34%) and insufficient in NRS (pooled MD: −0.45%; 95%CI: −0.52, −0.38%; I^2:99%). The pooled incidence rate ratio of severe hypoglycemia on CSII vs MDI in RCT was 0.87 (95%CI: 0.55, 1.37; I^2:0%; low-level evidence), and 0.71 (95%CI: 0.63, 0.81; I^2:57%,

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insufficient evidence) in NRS. Health-related quality of life presented insufficient evidence. Equity data were scarcely reported.

Conclusions: CSII modestly lower HbA_{1c} when compared with MDI. Current literature does not provide adequate data on other glycemic outcomes. Future assessment on diabetes technology should include individual and area-level socioeconomic data.

The study protocol was pre-registered in PROSPERO (CRD42018116474).

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1. Introduction

Continuous subcutaneous insulin infusions (CSII) are gaining ground over multiple-daily injections (MDI) as a standard therapy for pediatric type 1 diabetes [1]. A number of clinical trials have highlighted that the CSII improve glycemic outcomes, promote patient-centered decisions, and reduce the burden of diabetes care in children and adolescents with type 1 diabetes [2–9]. However, most of the trials in this field lacked data on clinical effectiveness, the extent to which clinical efficacy of CSII translates into better glycemic outcomes in a real-world setting [10,11]. This information is usually provided by large clinical practice registries [12–17] and, to our knowledge, no previous systematic review of the literature on the CSII has included pediatric diabetes registry databases.

Moreover, the prescription of the CSII vs MDI may not have been based only on clinical indications (e.g., elevated glycated hemoglobin and frequent hypoglycemic events), but also on favorable social factors, which may have led to health inequalities in this field [18–20]. In addition, because meeting glycemic targets is more difficult in young people and families with low health literacy and poor access to healthcare resources, it is possible that the absolute benefit of the CSII varies according to socioeconomic status (SES) [11,19,20]. Nevertheless, while there might still exist barriers to access and maintain this therapy, previous systematic reviews of clinical trials have not assessed equity and fairness in treatment selection [21–26], and only a few studies have investigated the role of unequal healthcare access and social disparities on glycemic outcomes [17,18,27]. A systematic review of the literature using an equity lens could assist in bridging the gap between the clinical indications of CSII and the unmet needs of the socially disadvantaged young individuals and their families [28–31].

Therefore, we conducted a systematic review and meta-analysis of RCTs and non-randomized studies (NRS) to (i) assess the effectiveness of CSII vs MDI on glycemic outcomes, and (ii) identify health equity data among children and adolescents with type 1 diabetes.

2. Methods

This review was developed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [32], the PRISMA-Equity extension [33], the Meta-analyses of Observational Studies in Epidemiology (MOOSE) checklist [34], and the Cochrane Collaboration Handbook [35]. A protocol for this review was registered in PROSPERO (Registration Number: CRD42018116474) and published elsewhere [36].

2.1. Data sources and search strategy

The bibliographic search was conducted from January 2000 to September 2019 in MEDLINE (via PubMed), EMBASE (via Elsevier), Cochrane Central Register of Controlled Trials (CENTRAL), and the Health Technology Assessment (HTA) Database. We also hand-searched for additional references in previous reviews, and in abstracts from conference proceedings. Our search strategy used standardized subject terms and no language restrictions were set (supplementary content).

2.2. Eligibility criteria

We selected studies that compared CSII against MDI, and evaluated, as glycemic endpoints, any of the following: glycated hemoglobin (HbA_{1c}), severe hypoglycemia (SH) episodes, diabetic ketoacidosis (DKA) events, and the percentage of time that the glucose level was in the target (TIR), below (TBR) and above the range (TAR) of 70 to 180 mg/dL (3.9 to 10.0 mmol/L), assessed with continuous glucose monitoring (CGM) systems [37]. As a secondary endpoint, we also selected studies that measured health/diabetes-related quality of life (HRQoL). We included all the studies that met the following criteria: (i) were conducted with children and adolescents $\leq$20 years; (ii) exclusively with type 1 diabetes; (iii) designed as RCT or NRS - such as diabetes registries, cohort and other types of observational studies; and (iv) reported any of the outcomes of interest: HbA_{1c}, SH, DKA, percentage in TIR, TBR and TAR, or HRQoL. We did not include studies that compared the use of single-hormonal or dual-hormonal closed-loop systems.

2.3. Study selection and data extraction

Two reviewers (TJ, JD) worked independently to check eligibility of studies (title and abstract and, if needed, full-text) and extracted the appropriate information in full-text articles [35]. Differences in opinion were resolved through consensus between the two reviewers. Data extracted from articles included year of publication, study design and period of data collection, country, baseline characteristics of participants (number of subjects by treatment including dropouts, sex, age, duration of type 1 diabetes, mean baseline HbA_{1c}, and HRQoL assessment tool), research setting, type of intervention (CSII device, including the use of adjunctive glucose sensor, and type of insulin), comparator (number of injections per day and type of insulin), factors of inequality, glycemic outcomes, and duration of follow-up (Supplemental Table S1).

We analyzed the following glycemic outcomes: (i) HbA_{1c} (%/mmol/mol), preferably at the end of the study, (ii) the number of severe hypoglycemia episodes [$\leq$54 mg/dL (3.0 mmol/L) or an event associated with severe cognitive impairment (including coma and convulsions) requiring external assistance], (iii) the number of CYP with $\geq$1 DKA event, and (iv) the mean (±SD) percentage of TIR [percentage of readings in the glycemic range of 70–180 mg/dl (3.9–10.0 mmol/L) per unit of time], TAR and TBR assessed with any continuous glucose monitor systems [30,37-40]. We collected information on questionnaires that assessed the overall mean (±SD) HRQoL score for each group at the end of the study.

2.4. Equity analysis

To explore health inequalities, we focused on indicators of social disadvantages defined by PROGRESS [19,41]. Most of social factors were identified in the baseline patient characteristics. We still examined whether the existing studies reported each of the social determinants of health according to the given therapy and the benefits with such therapy, and if CYP and caregivers belonged to advantaged or disadvantaged groups. Advantaged groups were considered those who reside in high-income countries, belong to major racial/ethnic/religious aspects, attain higher socioeconomic status and educational level, whose caregivers have better occupation and are recipients of governmental assistance, and that families are included in greater social network involvement; the disadvantaged groups comprised the rest of CYP/families. For gender/sex, we considered that a disadvantaged existed when there was an unequal prescription of CSII between boys and girls.

2.5. Assessment of risk of bias

Two reviewers (TJ, JD) independently assessed the risk of bias of each study using two instruments: the Cochrane Risk of Bias tool for RCT [42], and the RTI Item Bank for NRS [43]. We assigned an "overall assessment" with three categories: a) Low risk of bias (low risk in each of the six domains of the Cochrane tool; or unclear risk in one domain); b) Intermediate risk of bias (high risk in one domain; or unclear risk in two domains, and the judgment that this was unlikely to bias the results); and c) High risk of bias (high risk in one or more domains; or unclear risk in two domains, and the judgment that this was likely to bias the results).

For RCT, lack of "Allocation concealment" was judged as the domain that is most likely to bias the study results, because an inadequate technique of concealment might lead to greater benefit in those with better clinical baseline parameters [42]. Also, in line with well-established epidemiological knowledge, we considered that, for NRS, "Confounding" was most likely to bias the results [42]. We also registered the

sponsorship of studies by the pharmaceutical industry, though we did not equate such sponsorship with higher risk of bias [44].

2.6. Statistical analyses

We retrieved the standardized mean (±SD) HbA_{1c} (%/mmol/-mol) among therapies. Results on hypoglycemia were extracted as incidence rates (event/100 patients-year), and those on DKA as the number of subjects with ≥1 DKA event. For TIR, TAR and TBR, we retrieved the mean (±SD) %. Finally, HRQoL data corresponded to the overall final score in each scale, presented as the standardized mean difference (±SMD). The effect size of the SMD was classified as small (0.1–0.3), medium (0.3–0.6) or large (≥0.6) [45].

The effect of CSII vs MDI was summarized with the pooled (i) mean difference for HbA_{1c}, (ii) rate ratio for hypoglycemia, (iii) risk ratio for DKA, (iv) mean difference in the percentage of time that blood glucose remained in target, above and below the range, and (v) standardized mean difference for HRQoL. Pooling was performed with inverse variance random-effects models, to incorporate the level of heterogeneity found across studies [46]. Heterogeneity was assessed with the I^2 statistic, classified as follows: no relevant heterogeneity (0–25%), moderate heterogeneity (25–50%) and substantial heterogeneity (>50%) [47]. Meta-analyses were performed separately for RCT and NRS. We conducted subgroup analyses for HbA_{1c} according to the length of follow-up (≤or more than one year) and to different groups of age (under 6, 6 to 11, and over 11 years), when appropriate. Lastly,

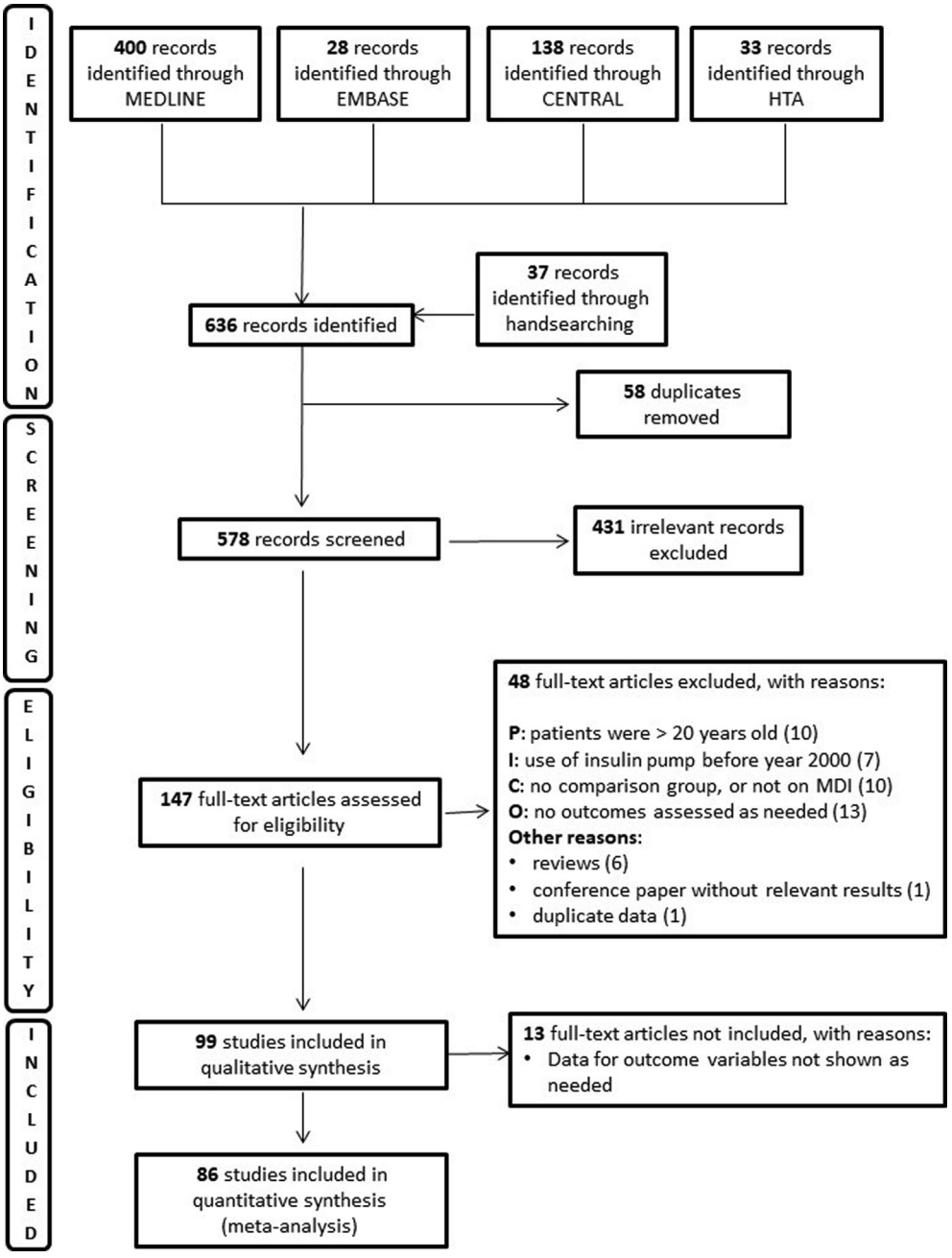


Fig. 1 – Flow of studies across the review.

the main analyses were repeated for each type of NRS, and after exclusion of studies with high risk of bias. The STATA (v14.0; StataCorp, USA) and Review Manager Software (v5.3; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011) were used for all analyses.

For equity data, we elaborated a narrative synthesis aiming to identify the number and frequency of studies reporting the PROGRESS social determinants [48], to classify study participants as belonging to more or less advantaged groups, and to examine the potential benefit of each therapy according to PROGRESS variables.

2.7. *Quality of the evidence*

The quality of the body of evidence was assessed by the two independent reviewers (TJ, JD) using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool [49]; the rating of quality reflects the extent of our confidence that the estimates of the effect of CSII vs MDI on the outcomes are correct. Four levels of quality of evidence were used: high, moderate, low, and insufficient. For RCT, we downgraded the evidence from high-level by one level for five domains: *high risk of bias* (serious study limitations); serious *inconsistency* of results across studies (effect size are not in the same direction); *indirectness* of evidence (results may not directly apply to young people with type 1 diabetes); *imprecision* of effect estimates (wide confidence intervals); or *publication bias* - by means of funnel plots, which represents the effect estimates against their precision (standard error), and the Egger's test for funnel plot asymmetry [50]. For NRS, level of evidence started at moderate quality, and was downgraded as for RCT.

The reviewers (TJ, JD) achieved a degree of agreement that, before consensus, ranged from 80 to 95% for screening and selection of studies, data extraction, and assessment of risk of bias.

3. Results

A total of 636 records were identified, and their abstracts were screened for eligibility. After removing duplicates and those articles that did not meet the inclusion criteria, we assessed the full text of 147 studies; of them, 48 were excluded with detailed reasons (Fig. 1). A total of 99 studies (214162 CYP) were included in the qualitative review, and 86 (16 RCT) in the meta-analysis.

The characteristics of the articles reviewed are summarized in Supplemental Table S1. In total, there were 19 RCT, involving 765 CYP on CSII and 793 on MDI; of them, three RCT did not report outcome data as needed, and we could not obtain the information after contacting the authors, so they were excluded from the meta-analysis. Three RCT were cross-over trials. The participants' age ranged from 1 to

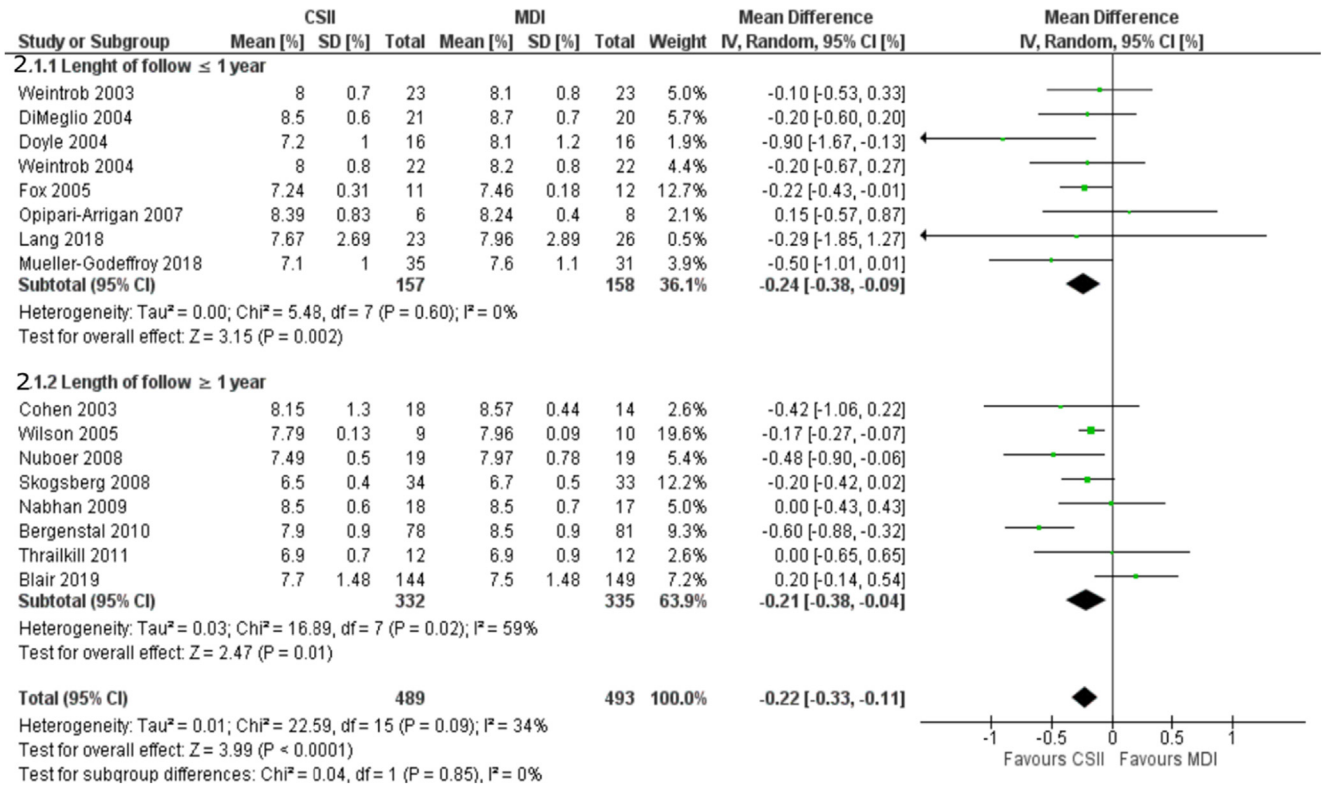


Fig. 2 – Forest plot comparing the effect of continuous subcutaneous insulin infusion (CSII) versus multiple-daily injections of insulin (MDI) on glycated hemoglobin (HbA1c) in randomized clinical trials (RCT) (2.1) and in non-randomized studies (NRS) (2.2). Results are broken down by length of follow-up (2.1 and 2.2), and by type of NRS (2.3).

2.2: Non-randomized studies. Mean difference of HbA1c (%)

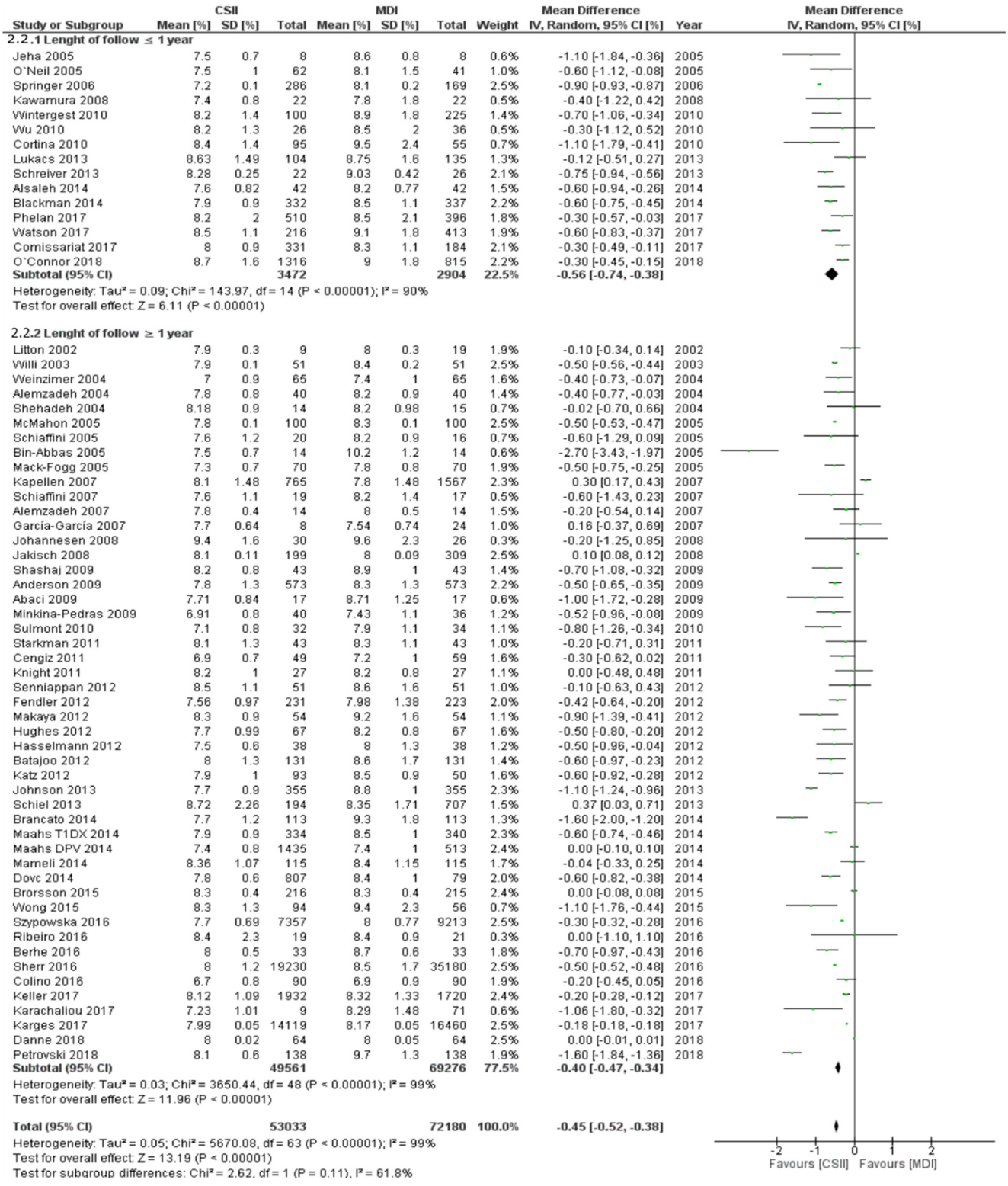
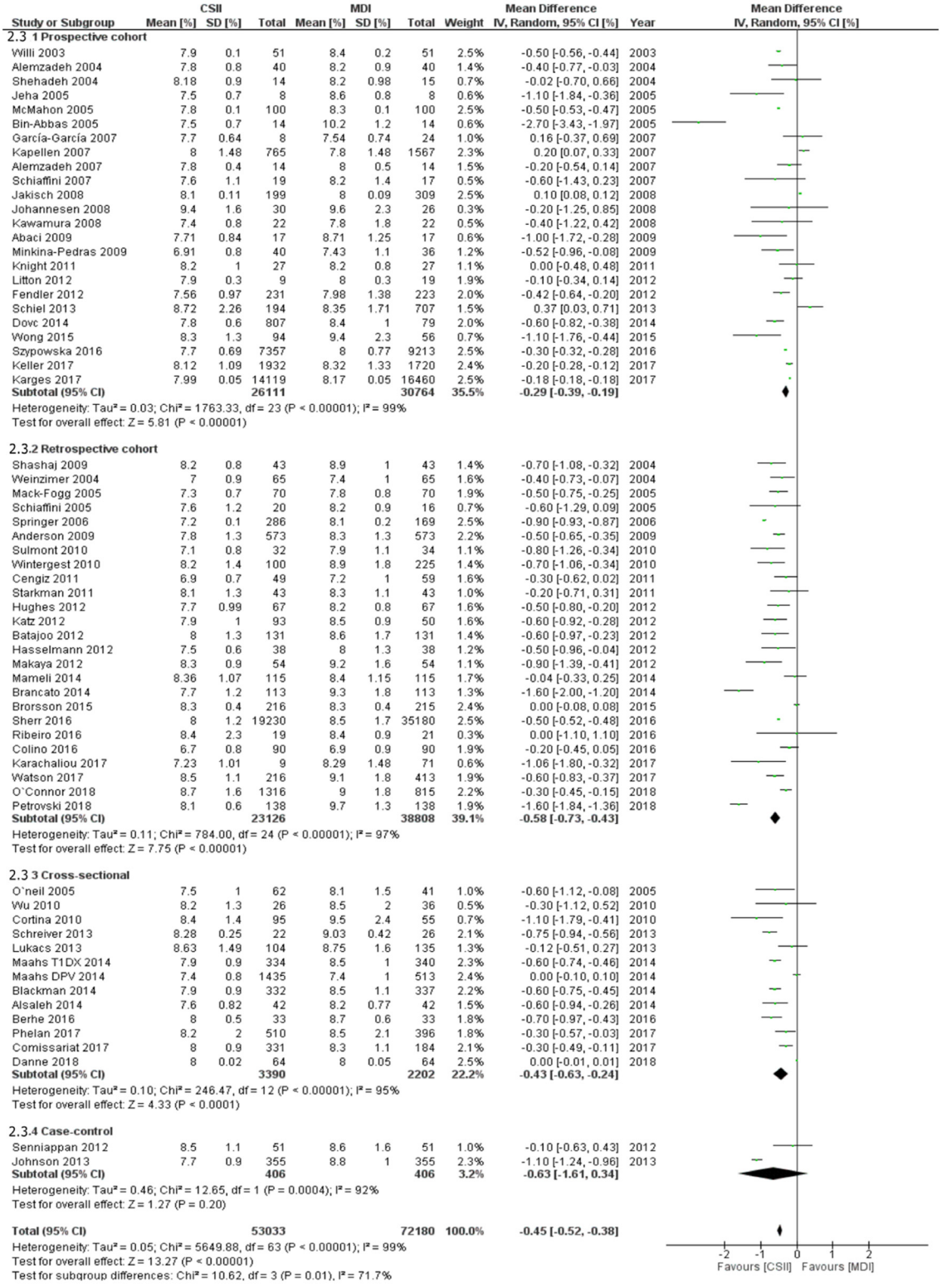


Fig 2. *(continued)*

2.3: Non-randomized studies. Mean difference of HbA1c (%)



SD: standard deviation; IV: inverse variance; CI: Confidence interval; MD: Mean difference.

Fig 2. *(continued)*

Table 1 – Quality of evidence (GRADE approach) on the effect of the continuous subcutaneous insulin infusion (CSII) vs multiple-daily injections (MDI) of insulin on glycemic outcomes and health-related quality of life, in randomized controlled trials and non-randomized studies.

Quality of evidence							Number of patients		Effect		Overall level of evidence
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	CSII	MDI	Relative (95% CI)	Absolute (95% CI)	
Glycated hemoglobin											
16	randomized trials	serious [a]	not serious [b] (I^2: 34%)	not serious	not serious	no evidence	489	493	–	MD **0.22%** (0.33 to 0.11) **lower**	⊕⊕⊕◯ MODERATE
64	non-randomized studies	very serious [c]	not serious [b] (I^2:99%)	not serious	not serious	no evidence	53,033	72,180	–	MD **0.45%** (0.52 to 0.38) **lower**	⊕◯◯◯ INSUFFICIENT [†]
Severe hypoglycemia											
12	randomized trials	serious [a]	not serious (I^2: 0%)	not serious	serious [d]	no evidence	508	485	Rate ratio **0.87** (0.55 to 1.37)	–	⊕⊕◯◯ LOW
38	non-randomized studies	very serious [c]	not serious [e] (I^2:57%)	not serious	not serious	no evidence	32,148	38,056	Rate ratio **0.71** (0.63 to 0.81)	–	⊕◯◯◯ INSUFFICIENT [†]
Diabetic ketoacidosis											
8	randomized trials	not serious	not serious (I^2: 0%)	not serious	serious [d]	no evidence	405	385	Risk Ratio **1.29** (0.62 to 2.69)	–	⊕⊕⊕◯ MODERATE
28	non-randomized studies	very serious [c]	serious [f] (I^2: 63%)	not serious	serious [d]	no evidence	22,135	23,264	Risk Ratio **0.98** (0.75 to 1.29)	–	⊕◯◯◯ INSUFFICIENT [†]
% of Time in target (TIR), below (TBR) and above (TAR) the glucose range											
2	randomized trials	very serious [a]	not serious (I^2:0%)	not serious	serious [d]	no evidence	34	14	-	**TIR:** MD **5.21%** (−2.04 to 12.46) **higher** **TBR:** MD − **1.81%** (−6.33 to 2.72) **higher** **TAR:** MD − **3.88** (−13.92 to 6.16) **higher**	⊕◯◯◯ INSUFFICIENT
Health-related quality of life											
4	randomized trials	serious [g]	serious (I^2:29%) [h]	not serious	not serious	no evidence	106	111	–	SMD **0.42** (0.07 to 0.76) **higher**	⊕◯◯◯ INSUFFICIENT
3	non-randomized studies	very serious [c]	serious (I^2:33%)	not serious	not serious	no evidence	290	409	–	SMD **0.35** (0.15 to 0.55) **higher**	⊕◯◯◯ INSUFFICIENT [†]

CI: Confidence interval; MD: Mean difference; SMD: Standardized mean difference; TIR: Time in range; TBR: Time below range; TAR: Time above range.

[†] In NRS, evidence started as low quality.

[a] Lack of transparency of randomization, and selection bias.

[b] There is statistically significant heterogeneity in effect size, but most effect estimates suggest lower or similar glycated hemoglobin on CSII vs MDI.

[c] Due to potential residual confounding bias.

[d] The confidence interval is wide.

[e] There is statistically significant heterogeneity in effect size, but most effect estimates suggest fewer or similar severe hypoglycemia episodes on CSII vs MDI.

[f] Effect estimates do not have the same direction.

[g] Detection bias found in health-related quality of life outcome.

[h] There is moderate statistically significant heterogeneity in effect size and effects are not clinically relevant.

18 years, and the duration of intervention varied from 4 to 24 months. The model of insulin pump was reported in 15 studies, and the types of insulin were similar (analogues) in both CSII and MDI in 8 studies.

We screened 80 NRS, involving 93,416 CYP on CSII and 120,131 on MDI; of them, 58 were diabetes registries/cohorts, 20 were cross-sectional studies and 2 were case-control studies. We excluded 10 of them from the meta-analysis because they did not report the outcome data as needed. Participants' age ranged from 1 to 19.3 years. The model of insulin pump was mentioned in 15 studies and the types of insulin were similar between therapies in 8 studies.

3.1. *Risk of bias summary assessment*

Supplemental Tables S2 and S3 show the risk of bias assessment in RCT and NRS, respectively. In RCT, 8 (42%) of them had an overall low risk of bias, 5 (26%) an intermediate risk, and 6 (32%) a high risk of bias based on the separate assessment of the glycemic outcomes; about half of the studies presented HRQoL data, whose assessment entailed a high risk of bias. Most of the domains were judged to have a low risk of bias, although we observed selection bias especially in the cross-over trials that, eventually, affected the overall assessment. Blinding of participants and personnel was impractical to intervention group, so we judged this domain as being unclear without affecting the overall risk of bias assessment.

In NRS, 8 (10%) of them were judged to have an overall low risk of bias, 30 (37.5%) intermediate risk, and 42 (52.5%) high risk for all the outcomes (both glycemic variables and HRQoL). Potential residual confounding was the domain that most contributed to bias risk, because approximately half of the studies did not attempt to balance the baseline characteristics of participants by using statistical adjustments.

3.2. *Glycated hemoglobin*

The use of CSII was associated with lower values of HbA_{1c} when compared with MDI in both RCT (16 studies; mean difference: −0.22%; 95% CI: −0.33 to −0.11%; 982 CYP, I^2 34%) and NRS (64 studies; mean difference: −0.45%; 95% CI: −0.52 to −0.38%; 125,213 CYP, I^2 99%). Results did not substantially differ according to the length of follow-up and type of NRS (Fig. 2) or age group (Supplemental Fig. S1) and were not materially modified after removing studies with high and intermediate risk of bias (Supplemental Fig. S2).

In RCT, the quality of evidence was moderate because many RCT presented intermediate risk of bias; however, heterogeneity of results was moderate (I^2 34%), the results directly applied to young people with type 1 diabetes, and the pooled effect estimate had a relatively narrow confidence interval (Table 1). Moreover, we found no obvious indication of publication bias in funnel plots and Egger's test (Supplemental Fig. S3).

By contrast, in NRS the quality of evidence was insufficient because most of them presented a high risk of bias due to uncontrolled confounders (Table 1). The heterogeneity of the results was quantitatively high (I^2: 99%), but we interpreted it as being qualitatively acceptable because HbA_{1c} in those using CSII was similar or lower than in those with MDI, with results presenting effect size with the same direction.

3.3. *Severe hypoglycemia*

In RCT, the pooled incidence rate ratio of severe hypoglycemia episodes on CSII versus MDI was 0.87 (95%CI: 0.55 to 1.37; 993 CYP; I^2:0%); corresponding values in NRS were 0.71 (95%CI: 0.63 to 0.81; 70,204 CYP; I^2:57%) and did not differ according to the type of study (Fig. 3). However, in NRS, the reduction

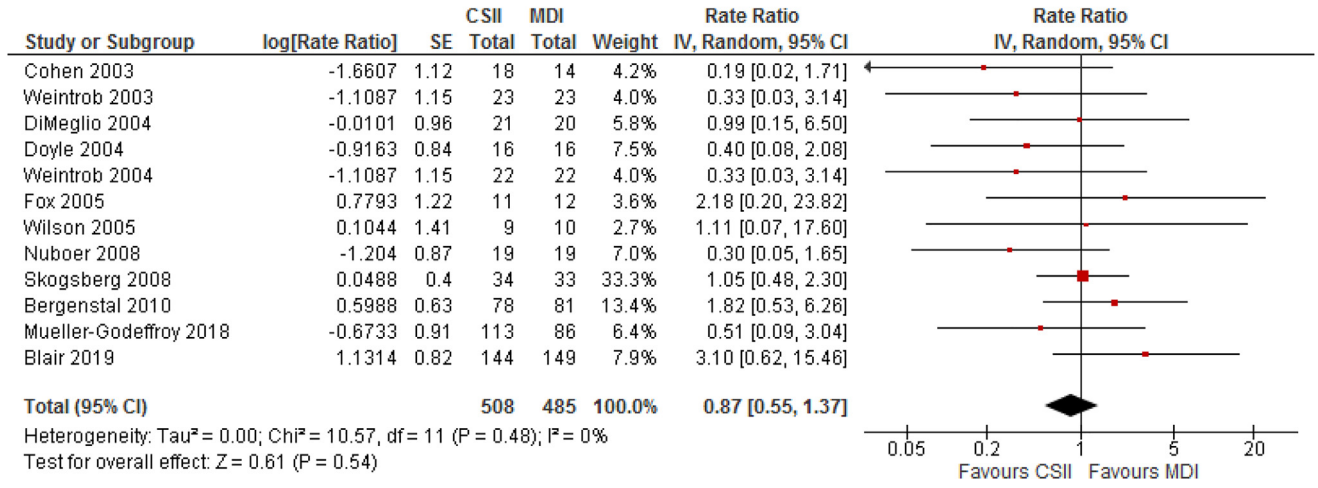
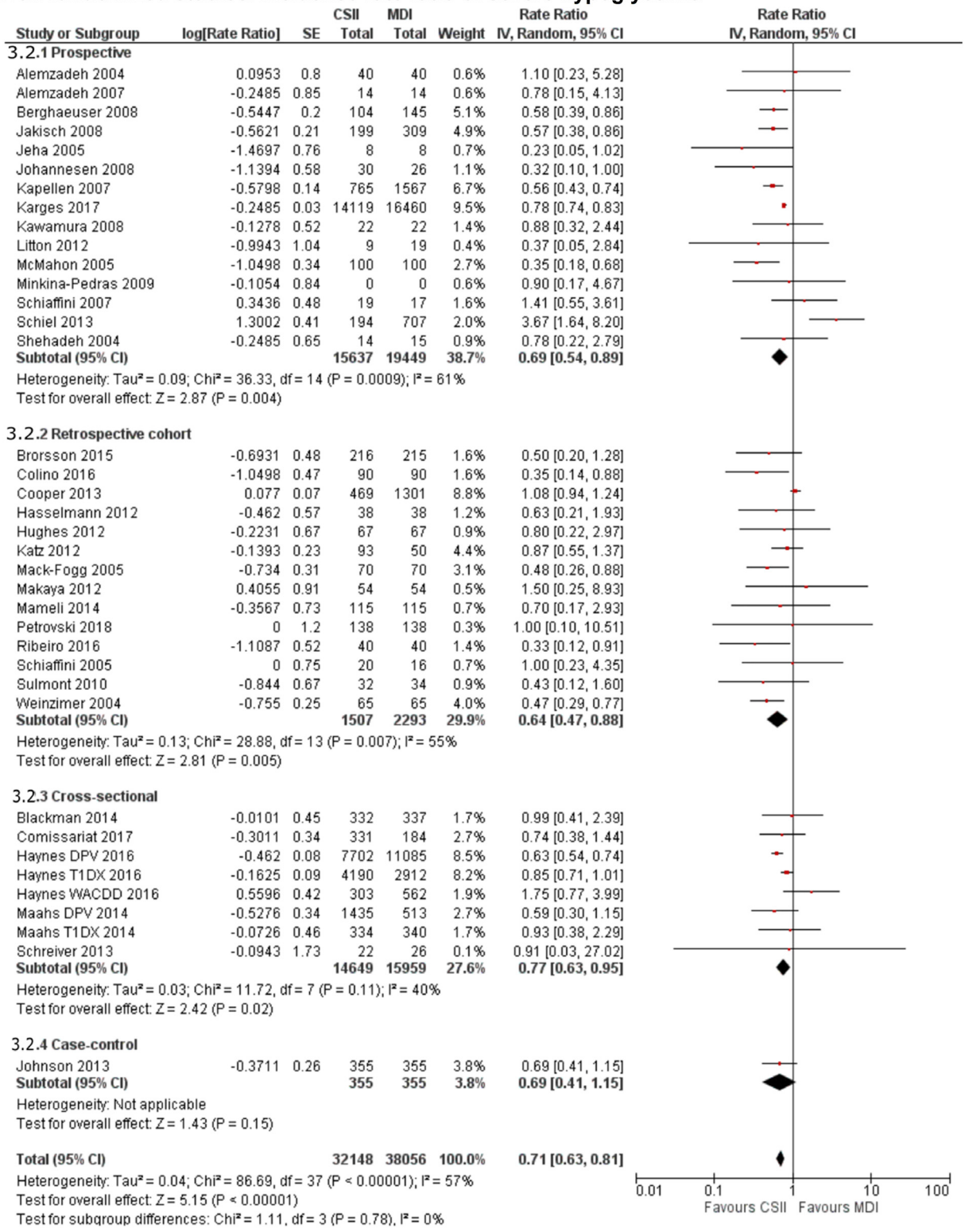


Fig. 3 – Forest plot comparing the effect of continuous subcutaneous insulin infusion (CSII) versus multiple-daily injections of insulin (MDI) on severe hypoglycemia (SH) in randomized controlled trials (RCT) (3.1) and in non-randomized studies (NRS) (3.2). Results in NRS are broken down by type of study.

3.2: Non-randomized studies. Incidence rate ratio of severe hypoglycemia



IV: inverse variance; CI: Confidence interval

Fig 3. *(continued)*

of SH associated with CSII lost statistical significance in analyses restricted to studies with low risk of bias (Supplemental Fig. S2).

The quality of evidence in RCT was low due to the wide confidence interval in the pooled incidence rate ratio (Table 1). Results from NRS had the same direction that those from RCT, but quality of evidence was much lower; according to the GRADE approach, evidence from NRS was insufficient because of very serious risk of bias resulting from important residual confounding (Table 1). Although in NRS the I^2 was 57%, we believe that there is no serious qualitative heterogeneity because most effect estimates across studies were null or favored CSII (Fig. 3).

3.4. *Diabetic ketoacidosis*

The frequency of DKA episodes did not differ between CSII and MDI in both RCT (8 studies; risk ratio: 1.29; 95% CI: 0.62 to 2.69; 790 CYP, I^2 0%) and NRS (28 studies; risk ratio: 0.98; 95% CI: 0.75 to 1.29; 45,399 CYP, I^2 63%) (Fig. 4). Results did not change substantially after removing studies with high and intermediate risk of bias (Supplemental Fig. S2), or across different types of NRS (Fig. 4). The strength of evidence was downgraded in both RCT (moderate-level of evidence) and NRS (insufficient evidence) because of heterogeneity and imprecision of results (Table 1).

3.5. *Time in target, below and above glycemic range*

Two RCT reported data on the percentage of the TIR, TBR and TAR with no significant differences between CSII and MDI. Main pooled results were as follows: percentage of TIR (mean difference: 5.21; 95% CI: −2.04 to 12.46; 68 CYP, I^2 0%), percentage of TBR (mean difference: −1.81; 95% CI: −6.33 to 2.72; 68 CYP, I^2 0%), and percentage of TAR (mean difference: −3.88; 95% CI: −13.92 to 6.16; 68 CYP, I^2 0%) (Fig. 5). Quality of evidence was insufficient because of very serious risk of bias and imprecision of effect estimates (Table 1).

3.6. *Health-Related quality of life*

The included studies used heterogeneous tools to assess HRQoL (Supplemental Table S4). Some studies measured HRQoL with validated and age-appropriated diabetes-related quality of life questionnaires, whereas others measured overall quality of life and focused on parental rather than children's quality of life. Because of the substantial heterogeneity of studies, we performed a meta-analysis with those that presented overall HRQoL mean (±SD) scores at the end of the follow-up. For RCT, SMD was 0.42 (95%CI: 0.07–0.76; 217 CYP; I^2:29%); corresponding values for NRS were 0.35 (95% CI: 0.15–0.55; 699 CYP; I^2:33%) (Fig. 6). In both RCT and NRS, strength of evidence was insufficient due to high risk of bias, inconsistent results across studies, and small number of studies.

3.7. *Equity analysis*

While 100% of the studies reported country/place of residence of CYP/families and 97% the individual's sex, only 38% reported their race/ethnicity, 26% the socioeconomic status, 20% parental occupation, 12% parental education/diabetes literacy, 4% social capital and 1% religion (Table 2). Most socioeconomic data correspond to baseline socio-demographic characteristics of CYP/families and very few studies included subgroup analyses aimed to establish if potential benefits of CSII vary according to the PROGRESS variables into a context of type 1 diabetes care in pediatric age.

Most of the existing literature corresponds to studies conducted in high-income countries that also included data on socially disadvantaged groups of CYP/families. However, some studies also included individuals belonging to racial minorities and immigration groups, with under/unemployed parents, lower educational level, and lower SES. We summarized the information available in both advantaged and disadvantaged groups about the effects of CSII on each significant glycemic outcome (Table 3). There was a suggestion of

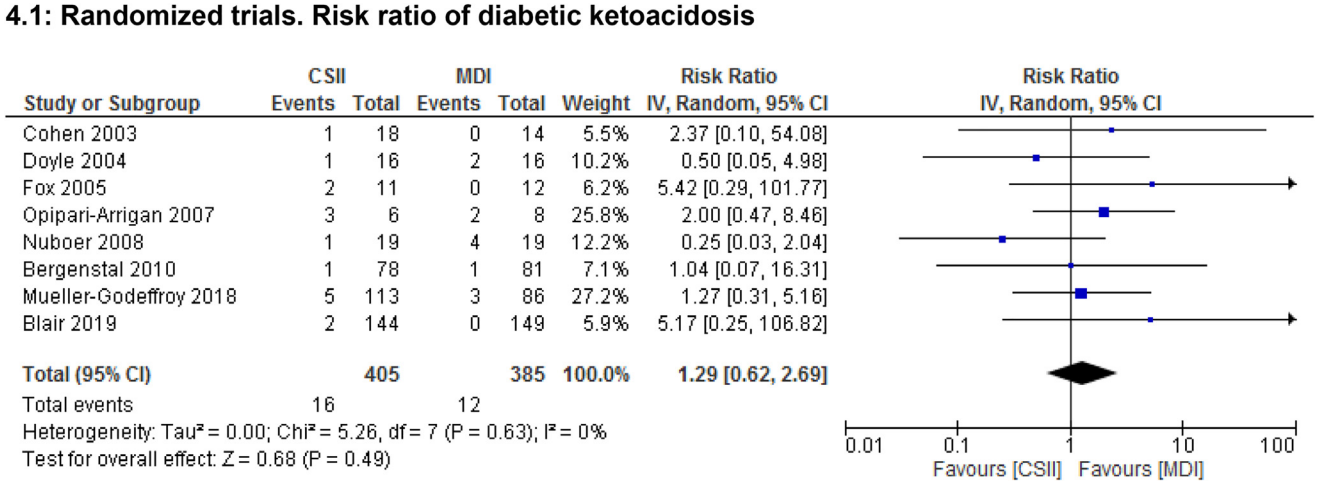
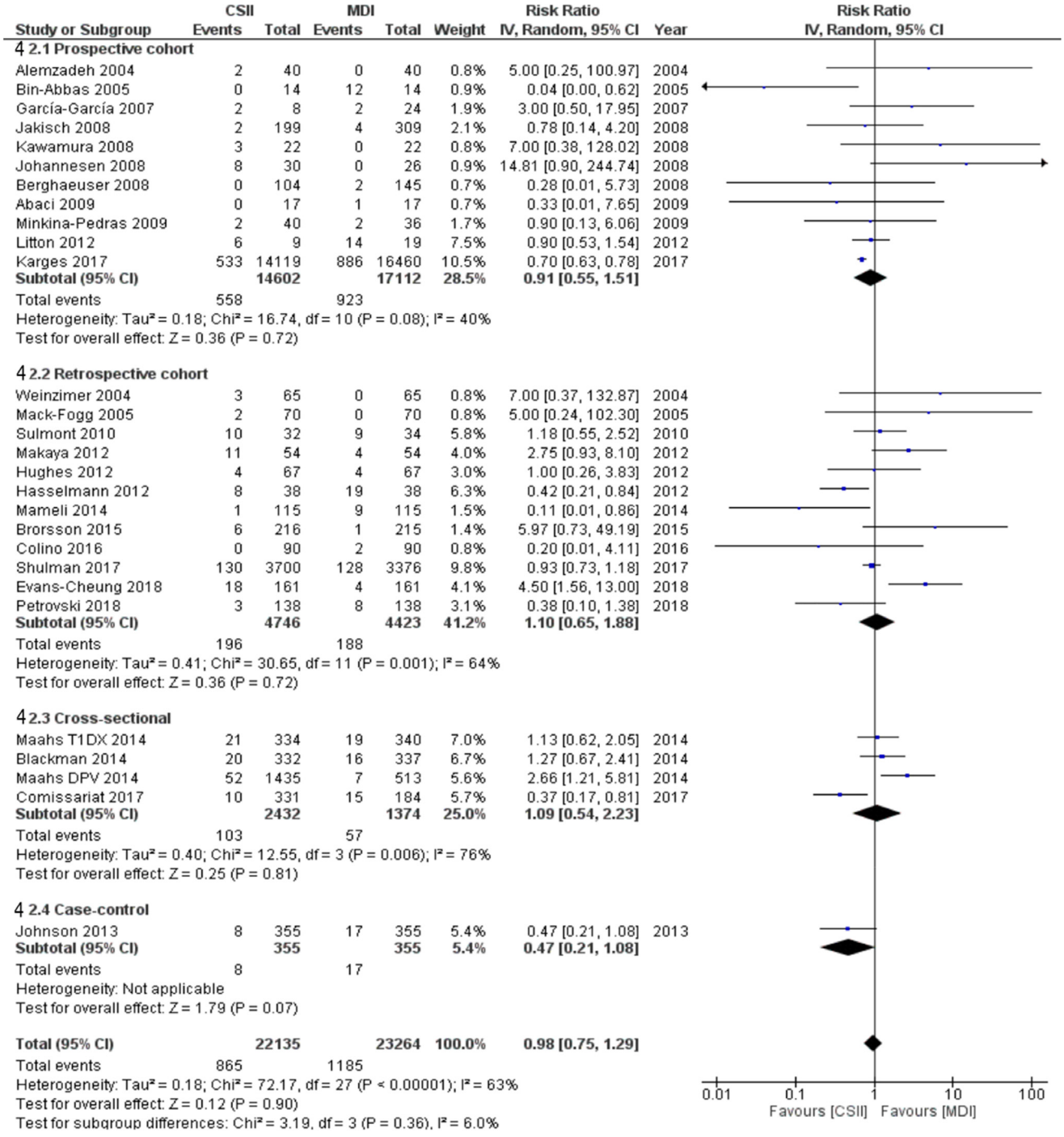


Fig. 4 – Forest plot comparing the effect of continuous subcutaneous insulin infusion (CSII) versus multiple-daily injections of insulin (MDI) on diabetic ketoacidosis (DKA) in randomized controlled trials (RCT) (4.1) and in non-randomized studies (NRS) (4.2). Results in NRS are broken down by type of study.

4.2: Non-randomized studies. Risk ratio of diabetic ketoacidosis



IV: inverse variance; CI: Confidence interval

Fig 4. *(continued)*

improvement of the glycemic outcomes globally, which was also observed across the disadvantaged groups, defined from race/ethnicity, parental occupation and educational level, and SES.

4. Discussion

In this systematic review and meta-analysis of the literature, we found moderate-level evidence from RCT that the CSII

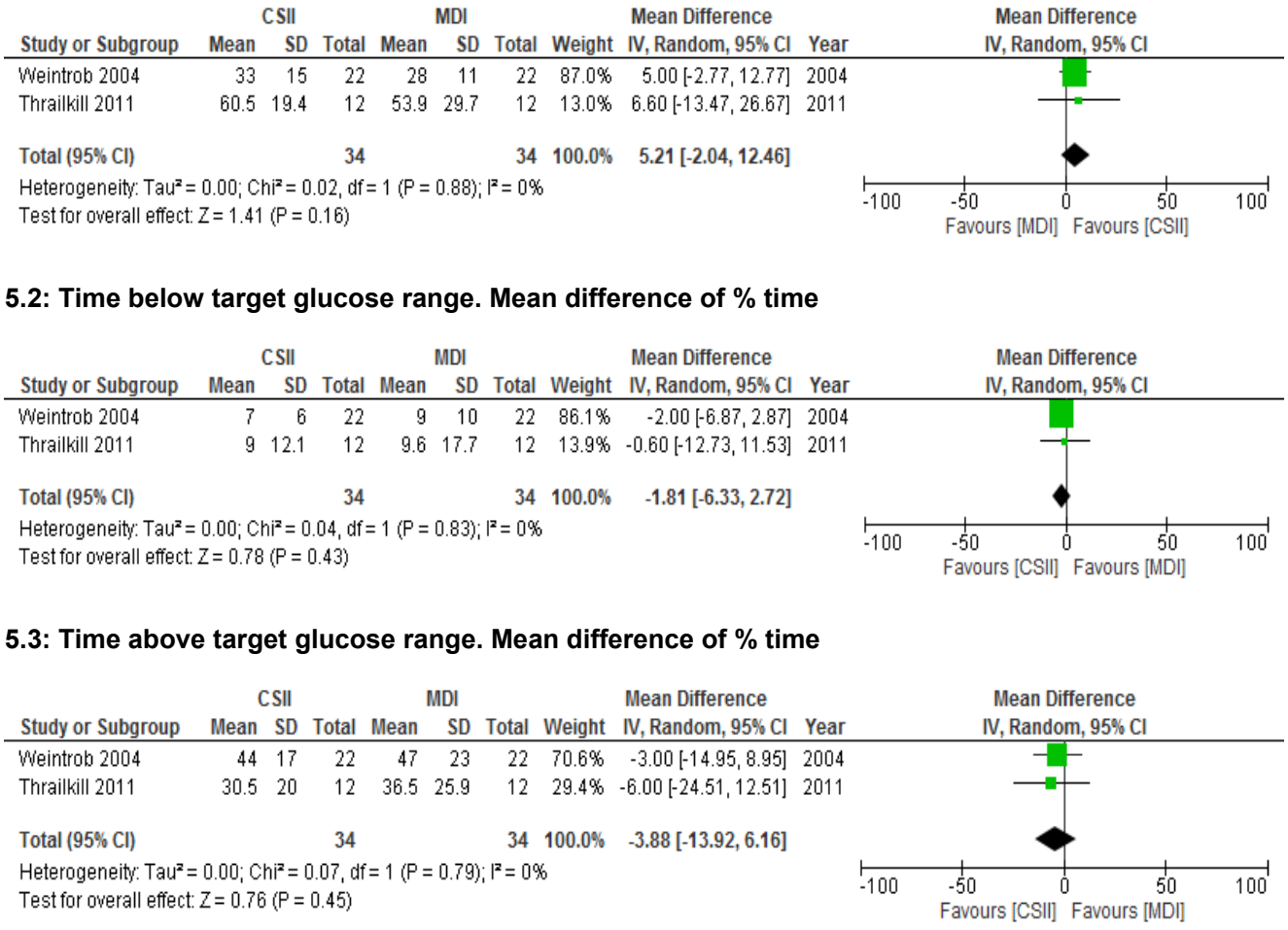


Fig. 5 – Forest plot comparing the effect of continuous subcutaneous insulin infusion (CSII) versus multiple-daily injections of insulin (MDI) on the time spent in target glucose range (5.1), below range (5.2) and above range (5.3) in randomized clinical trials (RCT).

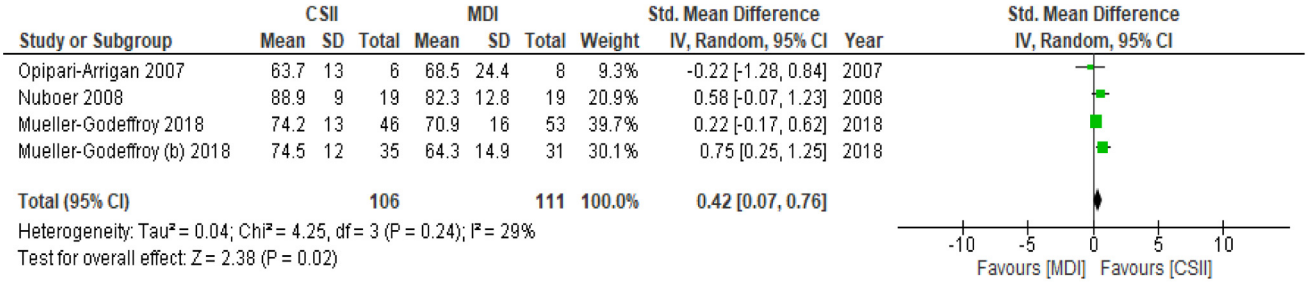
modestly lower HbA_{1c} compared with MDI among children and adolescents with type 1 diabetes. Results were in the same direction in NRS, although the level of evidence was lower. However, in both RCT and NRS, CSII did not show to improve other glycemic outcomes or HRQoL compared with MDI nor presented adequate strength of evidence. Equity data, when reported, suggest that individuals from disadvantaged groups can also benefit from CSII.

Our findings agree with those from recent meta-analyses of RCT [21–26,51], where children and adolescents using CSII vs MDI had lower mean HbA_{1c}, a tendency to fewer severe hypoglycemia episodes, and an improvement of quality of life. Our results did not substantially differ by patient's age. In addition, like RCT, most of the NRS showed a similar increase of HbA_{1c} values after the first year on CSII, which is probably associated with the early motivation for the use of a novel technology [52,53].

Although the pooled reduction of severe hypoglycemia episodes found in NRS was substantial (rate ratio: 0.71), it did not reach statistical significance when we analyzed only the few studies with low risk of bias. As regards the RCT, the failure of the CSII to show a reduction in hypoglycemia episodes could be due to the fact that the selection of most of participants in RCT was based on patient's preferences to wear rather than on pump's indication to "reduce hypoglycemia" [23]. Obtaining favorable results reducing SH may need the use of low glucose suspend systems, which requires the adoption of CGM systems, which were not assessed in this meta-analysis.

HRQoL seemed to be slightly better in CYP on CSII, but the effect estimates were of small size and based on few studies, so they provided an insufficient level of evidence. A recently published meta-analysis reported results similar to ours, though based on a reduced number of studies [51]. We meta-analyzed only those studies with data on overall or diabetes-specific HRQoL at the end of the follow-up, measured with similar scales (PedsQL, KINDL-R and DQoL). Consequently, the pooled results on HRQoL should be

6.1: Randomized trials. HRQoL standardized mean difference (%)



6.2: Non-randomized studies. HRQoL standardized mean difference (%)

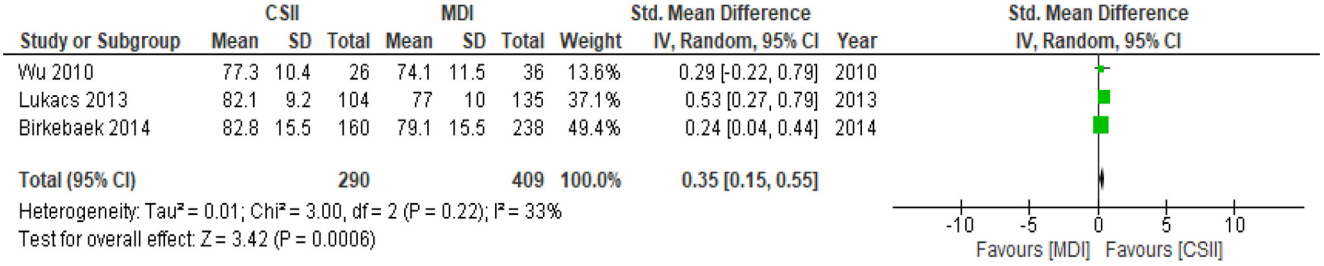


Fig. 6 – Forest plot comparing the effect of continuous subcutaneous insulin infusion (CSII) versus multiple-daily injections of insulin (MDI) on health-related quality of life (HRQoL) in randomized clinical trials (RCT) (6.1) and in non-randomized studies (NRS) (6.2).

interpreted with caution because they were obtained in a selected subsample of studies and HRQoL was measured with heterogeneous tools.

For equity data in the existing literature, most information is derived from high-income countries, despite the evidence of a greater increase in the incidence of type 1 diabetes in countries with low-to-middle income levels [54,55]. However, a few results from these studies correspond to young people belonging to disadvantaged groups and living in high-income countries - such as immigrants, ethnic minority groups, non-recipients of state assistance, whose parents have lower education level. Although current data reveal overall insufficient glycemic control, it seems that the socially disadvantaged groups achieved some improvement in the glycemic outcomes when on CSII therapy [18,56–58].

Unfortunately, we could only partially assess whether the effect of the CSII vs MDI varies across the socioeconomic status and, in particular, if the potential benefits of using CSII would accrue in most socially disadvantaged persons. The lack of standardized terminology and straightforward assessment of equity-relevant information in the literature restrained our ability to fully capture differences between social groups in the access to and effectiveness of the CSII. Thus, our data should be interpreted with caution, as most of the studies are not conducted for this purpose [59–62].

Unlike previous systematic reviews, we also included NRS for three reasons. First, in observational studies with long follow-up, it is more likely that the effects of an enthusiastic environment for a new therapy (CSII) can be mitigated, especially because most CYP and caregivers are willing to receive more diabetes education when starting on CSII [63]. Second, NRS may be more realistic as the clinical profile of the participants is intended to be broader and more representative of the potential candidates for CSII in the general young population [10]. Third, by studying large registries, it is possible to capture the influence of inequality factors on the effectiveness of CSII [64]. The drawback of using NRS is their higher risk of bias; notwithstanding this, the direction of the results has been very consistent in both RCT and NRS.

Current clinical guidelines consider CSII as an appropriate therapy for all CYP with type 1 diabetes [29,31]. Of note, however, is that guidelines particularly consider this therapy for individuals with recurrent severe or nocturnal hypoglycemia, wide glycemic variability regardless of HbA_{1c}, suboptimal diabetes control, and early microvascular complications or elevated cardiovascular risk factors. Moreover, CYP with optimal metabolic control that aim to improve quality of life and/or treatment satisfaction are also considered candidates for CSII [9]. It is worthy to point that most CYP with type 1 diabetes in the T1D Exchange Clinic Registry did not meet the targets for HbA1c suggested by diabetes medical societies clinical guidelines [11]. Additionally, the International Society for Pediatric and Adolescent Diabetes on its latest guidelines was flexible to distinguish individual's glycemic target according to the access or not to advanced insulin delivery technology [65]. Our results, however, show that there is still insufficient evidence to recommend using the CSII without CGM integrated system based on a clinically relevant improvement in glycemic outcomes or HRQoL. Thus, in principle, recommendation for using CSII without the integration of CGM systems seems to be mostly based on patients' or family's preference.

Table 2 – Studies reporting PROGRESS (equity) factors and examples of terminologies used across studies. Values are presented as % and (number of studies).

PROGRESS Framework	PROGRESS factors				
	Report data	Advantaged groups	Examples of terminologies	Disadvantaged groups	Examples of terminologies
Place of Residence [a]	100% (99)	High-income countries96% (95)	USA and Canada EU countries United Kingdom Israel Australia Japan Saudi Arabia Qatar	Low-to-middle-income countries4% (4)	China Brazil Turkey
Race, ethnicity, culture, and language [b]	38% (38)	Majorities6% (6)	Only majority group (100% sharing the same origin and background). Only Caucasians. Only White. Only families that fully speak/ read the national language.	Minorities32% (32)	Immigrants. Different social aspects including Black, African-American, Hispanic, Latino, Asian-British, Indian, Pakistani, Mixed population.
Occupation [c]	20% (20)	Better parental occupation and/ or higher state assistance 17% (17)	Universal health insurance. State assistance. Donation or non-profit organization. Employee-funded insurance system. Fully costed by families. Fully private insurance	Worst parental occupation and/or unprivileged state assistance 3% (3)	Area deprivation score without health assistance. Number of caregivers
Sex [d]	97% (96)	More than 10% of difference between sexes53% (53)	Unbalanced prescription between sexes	Less than 10% of difference between sexes 43% (43)	Balanced prescription between sexes
Religion [e]	1% (1)	Majority religious groups (0)	Not available	Minority religious group 1% (1)	Religion affiliation was accounted: Jewish and Bedouin
Education [f]	12% (12)	Higher educational level 1% (1)	Only higher education level	Lower educational level 11% (11)	Less than High School. Lower education level. Different levels of parental education. Lower deprivation score area with lower education

Table 2 – (continued)

Socioeconomic Status (SES) [g]	26% (26)	Higher SES1% (1)	Families that fully provide treatment	Lower SES25% (25)	Lower SES accounted/inferred. Deprivation score/index/ quintiles including lower SES groups. Annual household income including lower SES group. Hollingshead Four-factor Index of Social Status
Social Capital [h]	4% (4)	Wider set of relationships3% (3)	Individuals that participated in a diabetes camp	No social relationships1% (1)	Individuals without a systematic diabetes education program

[a] Country where individuals reside (as per the World Bank database) [12].
[b] Self-identification racial or ethnic group, or different culture and language, including nationality status [18,58].
[c] Patterns of work that provide proper maintenance of treatment or attain better state assistance [12,58].
[d] Biological identification of boys and girls between groups [66,67].
[e] Mention of religious affiliation of spiritual beliefs or values [68].
[f] Assessment of informed educational level or approximation by health literacy and numeracy [56,69].
[g] Acquisition of information considering access to resources and privilege [18,56,57,69,70].
[h] Information from benefits obtained by individuals due to their social relationships, e.g.: to be member of a diabetes foundation, to participate in diabetes camp [67].

Table 3 – Significant glycemic outcomes and their effects (improvement vs worsening) when using the continuous subcutaneous insulin infusion across studies assessed with the PROGRESS framework (number of studies).[a]

	HbA_{1c}	SH	DKA	TIR, TAR, TBR	HRQoL
Place of Residence	(91)	(60)	(50)	(4)	(26)
Advantaged group	55 vs 1	19 vs 3	9 vs 2	1 vs 0	15 vs 1
Disadvantaged group	1 vs 0	1 vs 0	0	No observations	No observations
Race, ethnicity, culture, and language	(33)	(18)	(17)	(2)	(10)
Advantaged group Advantaged group	4 vs 0	2 vs 1	0	No observations	3 vs 0
Disadvantaged group	22 vs 0	3 vs 1	4 vs 0	0	3 vs 0
Occupation	(19)	(7)	(7)		(2)
Advantaged group	2 vs 0	0	0	No observations	No observations
Disadvantaged group	15 vs 0	5 vs 0	2 vs 0	No observations	2 vs 0
Sex	(90)	(60)	(50)	(4)	(26)
Advantaged group	32 vs 0	8 vs 1	5 vs 1	1 vs 0	7 vs 0
Disadvantaged group	22 vs 1	11 vs 2	4 vs 1	0	8 vs 1
Religion					
Advantaged group	No observations	No observations	No observations	No observations	No observations
Disadvantaged group	No observations	No observations	No observations	No observations	No observations
Education	(11)	(5)	(5)		(3)
Advantaged group	No observations	0	0	No observations	0
Disadvantaged group	10 vs 0	1 vs 0	2 vs 0	No observations	2 vs 0
SES	(26)	(11)	(11)		(3)
Advantaged group	1 vs 0	No observations	No observations	No observations	No observations
Disadvantaged group	17 vs 0	1 vs 0	2 vs 0	No observations	1 vs 0
Social Capital	(3)	(1)	(1)		(3)
Advantaged group	2 vs 0	No observations	No observations	No observations	1 vs 1
Disadvantaged group	1 vs 0	1 vs 0	1 vs 0	No observations	No observations

HbA_{1c}: glycated hemoglobin; SH: severe hypoglycemia; DKA: diabetic ketoacidosis; TIR: time in range: TAR: time above range; TBR: time below range; HRQoL: health-related quality of life; SES: Socioeconomic status.

[a] Represent the total number of studies that assessed any of the glycemic outcomes according to different PROGRESS variables.

Our study has two main limitations. First, information on glycemic outcomes beyond HbA_{1c} could not be retrieved; this is important because newest devices with automated insulin delivery add more information on glycemic variability by measuring TIR, which is considered the best predictor of short- and long-term clinical complications for people living with type 1 diabetes [37]. However, TIR is preferably measured with CGM systems, which was not widely used in the studies reviewed, and makes it a promising outcome to be assessed in future reviews. Second, newest CSII with closed-loop systems have also been used very recently, and they have been shown to be safe for pediatric use [9,31]; however, we did not include them in our review because studies on the close-loop pumps compare them against CSII only, without considering MDI therapy, and our main focus was the form of insulin delivery.

5. Conclusion

As conclusion, we found moderate-level evidence that the CSII, without integration of CGM systems, modestly lower HbA_{1c} when compared with MDI. More evidence is needed on the effect of the CSII vs MDI on other important glycemic outcomes and HRQoL. Future research on diabetes technology assessment should include individual and area-level socioeconomic information to enable a full equity-oriented analysis of the effectiveness of the CSII in CYP.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author Contributions

TJ was responsible for the conception and design of the study. TJ and JD selected the articles, extracted the data, and conducted the statistical analyses. FRA and JA were the principal investigators and guarantors. TJ drafted the whole manuscript with the support of JA and FRA. All authors revised this work for important intellectual content and approved the final manuscript.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2020.108643.

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Title Page

Title: Diabetes technologies for children and adolescents with type 1 diabetes are highly dependent on coverage and reimbursement

Running title: Pediatric diabetes technology: a survey

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Novelty Statements:

- Opinion of multinational healthcare professionals (HCPs) that are directly involved with recommendation of diabetes technologies along with their patients' socioeconomic background may impact the willingness to recommend insulin pumps and continuous glucose monitoring (CGM) systems.
- Our findings suggest that most HCPs are very flexible in recommending insulin pumps and CGMs; however, the adoption of these devices is significantly greater when technologies are available from insurance/coverage.
- While patient's clinical circumstances, language comprehension, educational level, and income affect the recommendation to initiate these technologies, the availability for diabetes technologies seems to be the biggest factor when HCPs decide to recommend them.

Abstract

Aim: To study healthcare professionals (HCP)'s perceptions on decision-making to start insulin pumps and continuous glucose monitoring (CGM) systems in pediatric type 1 diabetes.

Methods: An electronic survey supported by the International Society for Pediatric and Adolescent Diabetes (ISPAD) was disseminated through a weblink structured as follows: (i) HCP's sociodemographic and work profile; (ii) perceptions about indications and contraindications for insulin pumps and (iii) for CGM systems; and (iv) decision-making on six case scenarios.

Results: 247 responses from 49 countries were analyzed. Seventy percent of respondents were members of ISPAD. Most of participants were women over forty years-old, who practice as pediatric endocrinologists for more than ten years at university/academic centers and follow more than 500 people with type 1 diabetes. Although insulin pumps and CGMs are widely available and highly recommended among respondents, their uptake is influenced by access to healthcare coverage/insurance. Personal preference and cost of therapy were identified as the main reasons for turning down diabetes technologies. Parental educational level, language comprehension and income were the most relevant socioeconomic factors that would influence HCPs to recommend diabetes technologies, while gender, religious affiliation and race/ethnicity or citizenship the least.

Conclusions: HCPs seem to be markedly supportive of starting people on diabetes technologies. However, coverage/insurance for devices holds the biggest impact on the extent of their recommendations.

Keywords: type 1 diabetes; insulin pump; continuous glucose monitors; survey; health inequality

1. Introduction

Use of insulin pumps and continuous glucose monitoring (CGM) systems in the management of type 1 diabetes is gaining ground over conventional treatment with syringes, pens and glucometers [1–3]. Although use of insulin pumps has been shown to lower HbA_{1c} levels in pediatric age when compared with multiple-daily injections, few differences have been described in other glycemic outcomes [4–9]. On the other hand, the use of integrated CGM systems has shown to improve time in range and decrease frequency and severity of hypoglycemia [10–12]. In addition, people wearing these devices have reported increased flexibility and feeling of wellbeing [13].

Despite these benefits, there are considerable differences between countries in healthcare system coverage of diabetes technologies [14–17], clinicians' role in counselling, and individuals' and families' preferences [14,18,19] that prevent diabetes technologies from being used. In addition, the hassle of wearing devices, dislike of alarms and inadequate counselling may also decrease use [18,20,21].

There is a gap in the literature regarding the opinion of multinational healthcare professionals (HCPs) that are directly involved with recommendation of diabetes technologies [22]. In addition, socioeconomic background of people with diabetes and HCP's work profile may indirectly impact the willingness to recommend diabetes technologies[16]. Therefore, with this survey, we aimed to comprehensively evaluate the reasons why providers do or do not recommend diabetes devices for children and adolescents with type 1 diabetes.

2. **Methods**

We used an electronic survey powered by Survey Monkey Inc. (San Mateo, California, USA) containing 33 questions in English language, and data were collected anonymously. The survey was disseminated through an open weblink for a calendar month to members of the *International Society for Pediatric and Adolescent Diabetes* (ISPAD) including past participants of Annual Meetings and training courses which approximately reach 2,300 HCPs. Members were also encouraged to share the survey with colleagues which prevented us from being able to calculate a precise response rate. Responses were included if HCP confirmed their involvement in the decision or recommendation to start diabetes technology. If respondents completed the survey, $1 was donated to Life for a Child.

The survey questions (Appendix) were divided into four topics: (i) baseline profile of HCPs; (ii) HCPs' opinions about recommendation, use, and relevance of indications and contraindications for initiating insulin pumps); (iii) HCP's opinions about recommendation and use of CGM; and (iv) six case vignettes with variation of factors thought to impact decision to recommend diabetes technologies including individuals age, history of severe hypoglycemia, history of diabetic ketoacidosis, glycemic control, household composition, parental occupation, healthcare coverage, income, place of residence, parental literacy, immigration, religious affiliation, language comprehension, and social supports.

We did a post hoc subgroup analyses to compare responses between different subgroups, including: (i) age of HCP below or over 40 years old; (ii) years of clinical practice under or over ten years; (iii) main practice setting - private,

public/government or university/academic hospital/outpatient clinic; (iv) size of diabetes clinic - more or less than two hundred patients being followed; (v) HCPs who consider themselves a racial/ethnic minority and those who do not; (vi) provision of universal healthcare insurance/coverage for diabetes technologies; and (viii) coverage/reimbursement from private insurance companies for diabetes technologies.

Categorical data are presented as proportions (%), and comparisons between groups were based on a chi-squared test (χ^2) or Fisher's exact test when appropriate. Qualitative data (content from the comments provided under "Other, please specify") were analyzed using a coding technique, where similar answers are summarized by approximation into similar semantic content [23]. The unit of analysis correspond to one single response, so one health center could have contributed more than one survey response. Statistical analyses were performed with Stata 14.0 for Windows (College Station, TX, USA). Statistical significance level was set at $p < 0.05$.

3. **Results**

We received a total of 270 responses, with an average completion rate of 78% and a median time spent by participant of less than ten minutes. Nearly 91% (n=247) of the survey responses were from HCPs involved in the decision or recommendation to start a person with diabetes on insulin pump and/or CGM and were included in the analysis. Seventy percent of the respondents were members of ISPAD.

3.1. Participant characteristics

Table 1 summarizes participant characteristics. We highlight that approximately 45% of HCPs cannot count on their healthcare system to provide coverage for insulin pumps and/or CGM systems in their country/region of service, while 55% can fully or partially count on it. Approximately 46% of HCPs agreed that private insurance companies totally or partially cover/reimburse for insulin pumps and/or CGMs, while the other 54% cannot count on their coverage.

3.2. Viewpoints on insulin pumps

Insulin pumps are available to more than 95% of HCPs in their practice setting with at least 73% having more than one brand available. We saw significantly more uptake among patients whose HCPs had more years of practice, practiced in public/government or university/academic centers and followed more people with diabetes (Table 2). Age and racial/ethnic minority did not show statistical differences.

There was significantly more use of, and agreement to start, insulin pump therapy in countries or regions that could rely upon universal or partial healthcare insurance/coverage for diabetes technologies and in those that could count on private insurance companies to cover/reimburse diabetes technologies when compared to countries that could not (Table 3).

Reasons to turndown technology also differed depending on the coverage. In countries that could count on universal or partial healthcare insurance/coverage, the main reason for declining diabetes technology was “not wanting to wear something on the body”, while in countries where diabetes technologies are not covered, the main reason was the difficulty to afford or maintain therapy (Table 3). Providers who were older than forty (58 vs. 39%, p=0.03), with more years of

practice (64 vs. 35%, p<0.001), and with a greater number of people with diabetes followed (61 vs. 38%, p<0.001) were more likely to endorse their reason to turndown technology as “Patient does not want to wear something on its body”.

More than 80% of HCPs agreed with the statement “All patients, regardless of circumstance, should be offered insulin pump therapy”. And nearly 90% disagreed with the statement “No patient, regardless of circumstance, should be offered insulin pump therapy”. No differences were seen between subgroups.

In order of importance, HCPs considered “history of severe hypoglycemia”, “requirement of small doses of insulin”, “suboptimal glycemic control despite good compliance”, and “patient age” as extremely relevant indications to start insulin pump. “Patient or caregiver´s preference” was considered fairly relevant for most HCPs. No statistical differences were seen between subgroups.

Overall, a “history of infrequent blood glucose monitoring (less than three times per day) or no use of CGM” and “infrequent follow-up” were considered the most relevant absolute contraindications to starting a person with diabetes on insulin pump, regardless of healthcare coverage/insurance reimbursement. However, HCPs that cannot count on coverage for insulin pump were more likely to endorse infrequent blood glucose monitoring as a relative contraindication for starting an insulin pump when compared to HCPs who could count on coverage (Table 3). Other reasons like “age less than three years old”, and “one or more episodes of DKA” were not found to be contraindications, whereas most of HCPs found “inadequate parental/caregiver supervision” as a relative contraindication.

Figure 1 shows that among socioeconomic factors assessed, “parental educational level”, “family/patient first language being different from that of the

diabetes team", "parental affordability to maintain therapy or having it provided by insurance coverage", and "family income" were mostly considered as relevant factors in the decision-making to start insulin pump. Other socioeconomic factors such as "gender", "religious affiliation", "race, ethnicity, or citizenship", "place of residence (rural versus urban)", and "family social networking (belonging to social support groups)" were mostly found to be totally irrelevant factors. No statistical differences were seen between subgroups.

3.3. Viewpoints on continuous glucose monitoring systems

Almost 95% of the respondents have CGM systems available in their practice; of which, at least 85% have access to more than one brand. Although more than half of people with diabetes agreed to start CGM, only roughly one third of them regularly wear it. Those people whose HCPs were under forty years of age were found to have more access to CGM (57.6 vs. 35.4%, $p=0.019$). A significantly higher percentage of people that use CGM have coverage for it compared with those who do not ($p<0.01$). In the same line, we saw a higher uptake of CGM in those who can count on insurance coverage for CGM when compared with those who do not ($p<0.01$). The percentage of people that agreed/consented to use CGM after it was recommended was affected by coverage for CGM ($p<0.01$), and insurance reimbursement ($p<0.01$).

3.4. Case scenarios

i. *"**One-year-old girl**, during her partial remission phase, receiving 2.5 IU/day of basal long-acting analog insulin, and doing corrections with rapid-acting analogues when needed, has faced two **severe hypoglycemia episodes**, one*

*of them with seizures. She has a **single mother**, **unemployed**, and they live in a country where there is **universal coverage** for CSII and CGM."*

Nearly 80% of the HCP respondents would recommend both insulin pump and CGM, and 18% would only recommend CGM in this scenario (Figure 2i). HCPs from university or academic hospitals were more likely to recommend both insulin pump and CGM than HCPs from other settings, 90.3% and 73%, respectively, p=0.012.

ii. *"**One-year-old girl**, during her partial remission phase, receiving 2.5 IU/day of basal long-acting analog insulin, and doing corrections with rapid-acting analogues when needed, has faced two **severe hypoglycemia episodes**, one of them with seizures. She **lives with her parents in a wealthy village four-hour away from nearest diabetes center**, and family has **full insurance coverage** for CSII and CGM."*

About 84% of the HCP respondents would recommend both insulin pump and CGM, and 12% would only recommend CGM in this scenario (Figure 2ii). HCPs from university or academic hospitals were more likely to recommend both insulin pump and CGM than HCPs from private or public/governmental setting, 93%, 76% and 80%, respectively, p=0.009).

iii. *"A **6-year-old girl** has been suffering blood sugar fluctuations which include one episode of **diabetic ketoacidosis** last month. Her parents are facing a **difficult economic situation** because both are unemployed and **do not have insurance coverage** for diabetes suppliers. The **young parents have not completed their secondary studies**, and family lives in a **deprived area** of a big city."*

Around 15% of the HCP respondents would recommend both insulin pump and CGM, and 39% would only recommend CGM in this scenario; however, 45% of the respondents would not recommend insulin pump nor CGM (Figure 2iii). While 52% of HCPs from university or academic hospital settings would recommend CGM, 33% and 24% of the HCPs from private and public/government hospitals, respectively, would recommend it (p=0.02). Moreover, 46% of the HCPs who follow more than 200 patients would recommend CGM, while 27% of the HCPs who follow less than 200 patients would recommend it (p=0.008).

iv. *"A **6-year-old girl** has been suffering blood sugar fluctuations which include one episode of **diabetic ketoacidosis** last month. The family recently moved to a **new country** where there is **universal healthcare and coverage** for CSII and CGM. The family belongs to a **minority religion** and has **low language comprehension** in their new country."*

Close to 48% of HCPs would recommend both insulin pump and CGM, and 41% would recommend only CGM in this scenario (Figure 2iv). No significant differences were seen between subgroups.

v. *"An **adolescent boy**, from a **racial/ethnic minority group**, diagnosed eight years ago, lives with his grandmother who works as a nurse and is his **only guardian**. Their **health insurance** recently approved him the provision of an intermittent CGM (Libre flash). He has suffered **uncontrolled blood glucose**, despite been on MDI with intensive basal-bolus requiring 1.8 IU/kg/day. Every year he **participates in a regional diabetes camp.**"*

Approximately 55% of the respondents would recommend both insulin pump and CGM in this scenario, and 33% would recommend only CGM (Figure 2v). Nearly

68% of the HCPs who follow more than 200 patients would recommend both therapies, while 47% of the HCP who follow less than 200 patients would recommend them (p=0.04).

vi. *"A **Caucasian adolescent girl**, belonging to a **major racial/ethnic group**, diagnosed eight years ago, lives with her **grandparents who are retired**. Their **health insurance** recently approved her the provision of an intermittent CGM (Libre flash). She has been suffering **uncontrolled blood glucose**, despite been on MDI with intensive basal-bolus requiring 1.8 IU/kg/day. In the village where they live, there are **lacking of social support and counselling**."*

Approximately 38% of the respondents would recommend both insulin pump and CGM in this scenario, and 48% of the respondents would recommend only CGM (Figure 2vi). Nearly 48% of the HCPs who count on diabetes technology coverage would recommend both therapies, while 33% who cannot count on coverage would recommend them (p=0.03).

HCP responses to vignettes i and ii demonstrate that HCPs have similar recommendations about insulin pump and CGM for children and adolescents with diabetes with healthcare coverage/insurance despite family differences in household composition and employment, although HCPs from university or academic hospitals seem to be more likely to recommend both therapies. HCPs recommendations in vignettes iii and iv may have differed because of the absence of insurance coverage in addition to other difficult social circumstances in vignette iii, unlike what was presented in vignette iv where universal healthcare and coverage were present even though the child was from a minority group and had low language comprehension. Although both adolescents in vignettes v and vi had healthcare insurance/coverage, the girl in vignette vi without social support

and counselling was less likely to have an insulin pump recommended by HCPs, especially in those that cannot rely upon healthcare coverage for diabetes technologies.

4. Discussion

We performed an electronic, worldwide, survey with responses from 249 HCPs from 49 different countries to assess their viewpoints on recommending insulin pumps and CGM systems for children and adolescents with type 1 diabetes. Although most HCPs were working at university/academic centers with a considerable number of people with type 1 diabetes, approximately 45% cannot count on their national/regional healthcare system to cover diabetes technologies, and 56% cannot count on insurance companies' reimbursement to cover the cost of diabetes technologies. Even so, our findings suggest that most HCPs are very flexible in recommending insulin pumps and CGMs, but different impressions depended on age, years of practice, clinical setting, number of patients, and availability of coverage for diabetes technology.

Our main finding is significantly more adoption of insulin pumps and CGM systems in those having healthcare or insurance coverage for diabetes devices. Although 95% of HCPs have insulin pumps and CGM systems available at their practice setting, the lack of coverage for them is an immediate explanation for the weak uptake. Countries with universal healthcare and wider availability of diabetes technologies, along with insurance-based countries with coverage for diabetes technologies are more likely to have a higher proportion of people with diabetes using technology, whereas most developing countries, despite holding universal healthcare, do not finance the newest diabetes delivery devices and make access to diabetes technology more limited [14,15,24,25]. However, after cost

and economic concerns, the most commonly reason to turndown technology has been pointed out to be wear-related issues, in line with what was found in our survey [21].

Three large international registries of type 1 diabetes in developed countries demonstrated that less than 50% of youth assessed were receiving pump therapy, and the rate of insulin pump usage was dependent on age group, ethnicity, and gender [24]. In the same line, an international network of pediatric diabetes centers stated that coverage and reimbursement policies for diabetes technologies are very heterogeneous in Europe, which may cause inequality in diabetes management [26,27]. However, the uptake of diabetes technologies may be higher when insurance coverage is approved even when used in people with lower SES[14,28].

Our post hoc analysis evaluated a few variables found to be important in decision-making about insulin pumps and CGM systems. HCPs with more years of experience who are working at centers with larger number of patients and larger multidisciplinary teams may provide different quality of care [26]. In our study, this group of HCPs were more likely to extend flexibility to their patients to start on pumps or turndown this technology, especially when they can count on healthcare/insurance coverage for them. We believe that coverage for diabetes technologies could influence not only the access to these devices, but also HCP's personal impressions on recommending it, as innovative therapies may facilitate the motivation to improve outcomes [2]. For instance, some HCPs were keener to recommend and prescribe them when family income was not an issue.

We assessed HCP's recommendation of insulin pump and CGM systems with two strategies. First, we asked providers to rate the relevance of various

socioeconomic factors in their decision to recommend insulin pumps. Second, we used six case scenarios to explore the same socioeconomic factors. In the first strategy, HCP's viewpoints about the relevance of socioeconomic factors did not seem to vary by presence or absence of healthcare/insurance coverage for diabetes devices. However, with the second strategy, we saw some different viewpoints, especially when diabetes technology coverage was absent. When the coverage for diabetes technology exists, younger age along with severe hypoglycemic episodes seemed to be a factor for greater adoption of pumps and CGMs. School age children with similar social circumstances are more likely to be advised to start on pumps and CGMs if they are covered by healthcare system. For the adolescent group with similar suboptimal glycemic control and coverage for diabetes technologies, the lack of social support and counselling seemed to be associated with less recommendation for starting an insulin pump. Indeed, it is important to highlight that the six case-vignettes were created by the authors, based on their expertise, and supported by the ISPAD, to assess main clinical conditions and different socioeconomic factors that might impact on recommendation of diabetes technologies. However, as the vignettes are not validated in the literature, the results should be read with cautious before being extrapolated into clinical decision-making.

The results of our survey are in line with previous studies that showed that universal coverage for diabetes technology may be as relevant as individuals' metabolic control when HCPs recommend diabetes technologies[24,29,30]. Additionally, some modifiable socioeconomic factors, such as language comprehension, educational level and income would also influence HCPs to recommend technology. However, while unmodifiable socioeconomic factors

such as gender, religious affiliation and race/citizenship seemed to be less important in their decision, background HbA_{1c} level does not appear to influence the initiation of insulin pumps[29].

Given the results of our study, guidelines and educational programs for starting insulin pumps and/or CGMs should address some of the perceived barriers to starting diabetes technologies including language comprehension, parental educational level, and social supports. Video interpretation services and educational material in different languages, for example, should be used during education for families who do not speak the same language as the diabetes team. Educational material should also be adapted so that parents of different educational levels can all be successful.

Our study has some limitations. First, individual responses of HCPs might not be representative of their whole country/region but represent an effort to acknowledge the viewpoints from members of an international medical society. Second, our survey was targeted to HCPs who were ISPAD members, comprising 70% of the respondents; however, the other 30% of respondents were mostly pediatric endocrinologists with more than ten years of practice, who follow less than 100 people with diabetes at their clinic, working in a country/region that lacks coverage/reimbursement for insulin pump and CGM systems. We believe that the dissemination through an open weblink reduced a sampling bias, by surveying HCPs either belonging to ISPAD community or not, and balanced a response (acquiescence) bias that happens when respondents subconsciously or consciously express in less-than-truthful responses, most of them in agreement with the society view, since they belong to the same medical society [31,32].

We conclude that most HCPs are aware of the advantages of using diabetes technologies and are permissive to recommend them to benefit their patients. Although personal's clinical circumstances, language comprehension, educational level, and income affect the recommendation to initiate these technologies, the availability of insurance/coverage for diabetes technology seems to be the biggest factor when HCPs are deciding to recommend them. Therefore, it should be a policy priority to ensure coverage for diabetes technologies, especially in young age groups. Moreover, educational programs, resources, and strategies should be developed so that parental education level and language comprehension are no longer barriers to accessing diabetes technology.

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Figures and Tables

Table 1: Participant's characteristics

Characteristics (n of respondents)	Respondents (%)
Age, years (n=247)	
Under 30	11 (4.5)
30 to 40	104 (42.1)
41 to 50	64 (25.9)
51 to 60	50 (20.2)
Over 60	18 (7.3)
Gender (n=246)	
Female	158 (64.2)
Male	88 (35.8)
Country¥ (n=245)	
India	30 (12.2)
Brazil	26 (10.6)
United States of America	23 (9.4)
Canada	20 (8.2)
Mexico	14 (5.7)
Australia	13 (5.3)
United Kingdom	12 (4.9)
Chile	11 (4.5)
Italy	8 (3.3)
Portugal	7 (2.9)
Belgium	7 (2.9)
Others§	74 (30.2)
Consider themselves to be from minority racial/ethnic group (n=245)	
Yes	30 (12.2)
No	215 (87.8)
Current clinical role (n=245)	
Resident	6 (2.4)
Primary care practitioner, paediatrician, family doctor, or internal medicine doctor	11 (4.5)
Paediatric endocrinology fellow	18 (7.3)
Paediatric endocrinologist/diabetologist	154 (62.9)
Adult endocrinology fellow	1 (0.4)
Adult endocrinologist/diabetologist	24 (9.8)
Nurse practitioner/registered nurse	24 (9.8)
Other (registered nutritionist, dietitian, nutritionist, diabetes educator, mental health professional)	13 (5.3)
Years of practice (n=246)	
Less than 3	42 (17.1)
3 to 5	37 (15)
5 to 10	46 (18.7)
More than 10	121 (49.2)
Main practice setting (n=245)	
Private hospital/outpatient clinic	56 (22.9)
Public or government hospital/outpatient clinic	73 (29.8)
University or academic hospital/outpatient clinic	104 (42.5)
Primary care center	4 (1.6)
General practitioner office	2 (0.8)
Other (Diabetes association)	6 (2.5)
Access to an endocrinologist/diabetologist as a consultant (n=247)	
Yes	56 (22.7)
No	3 (1.2)
She/he is an endocrinologist/diabetologist	188 (76.1)

Number of patients with T1D followed (n=247)	
Less than 100	71 (29.1)
100 to 200	42 (16.9)
201 to 500	59 (23.8)
More than 500	75 (30.2)
Provision of universal health care insurance/coverage for the use of insulin pump and/or CGM systems in your country (n=247)	
Yes	65 (26.3)
No	112 (45.3)
Partially	70 (28.3)
Coverage/reimbursement of private insurance companies for insulin pump and/or CGM systems in your country (n=246)	
Yes	57 (23.2)
No	132 (53.7)
Partially	59 (24)
Member of the International Society for Pediatric and Adolescent Diabetes (ISPAD) (n=247)	
Yes	173 (70)
No	74 (30)

¥ Top 11 country. § Countries with response: Argentina, Bangladesh, Bulgaria, Denmark, Ecuador, Egypt, Finland, Germany, Greece, Haiti, Indonesia, Ireland, Israel, Japan, Liberia, Luxembourg, Malaysia, Malta, Mauritius, Morocco, Myanmar, Netherlands, Norway, Pakistan, Paraguay, Peru, Poland, Republic of Korea, Romania, Saudi Arabia, Serbia, Slovenia, South Africa, Spain, Sweden, Thailand, Turkey, and Uruguay.

Table 2: Percentages of patients counselled by HCP that agreed or consented to start insulin pump therapy.

	Percentage of patients				P value
	< 25%	**25-50%**	**50-75%**	**>75%**	
n of responses by HCP subgroups, (%)					
Age					**NS**
≤ 40 years-old: 85 (44.7)	20 (23.5)	21 (24.7)	21 (24.7)	23 (27.1)	
> 40 years-old: 105 (55.3)	24 (22.9)	17 (16.2)	33 (31.4)	31 (29.5)	
Years of practice					**0.001**
≤ 10 years: 97 (48.0)	36 (37.1)	19 (19.6)	20 (20.6)	22 (22.7)	
> 10 years: 105 (52.0)	14 (13.3)	20 (19.1)	36 (34.3)	35 (35.3)	
Practice setting					**0.008**
Private Hospital: 48 (24.2)	20 (41.7)	13 (27.1)	7 (14.6)	8 (16.7)	
Public/Governmental: 59 (29.8)	14 (23.7)	9 (15.2)	16 (27.1)	20 (33.9)	
University/Academic: 91 (46.0)	15 (16.5)	17 (18.7)	30 (33.0)	29 (31.9)	
Clinic size					**0.020**
≤ 200 patients with T1D: 93 (46.0)	31 (33.3)	19 (20.4)	18 (19.3)	25 (26.9)	
> 200 patients with T1D: 110 (54.0)	19 (17.3)	20 (18.2)	38 (34.5)	33 (30.0)	
Health care coverage					**<0.001**
Universal or partially: 84 (41.4)	40 (47.6)	13 (15.5)	19 (22.6)	12 (14.3)	
No coverage: 119 (58.6)	10 (8.4)	26 (21.8)	37 (31.1)	46 (38.7)	
Insurance reimbursement					**<0.001**
Yes, or partially: 96 (48)	9 (9.4)	22 (22.9)	33 (34.4)	32 (33.3)	
No: 106 (52)	41 (38.7)	17 (16.0)	22 (20.7)	26 (24.5)	
Racial/ethnic minority HCP					**NS**
Yes: 21 (10.4)	6 (28.6)	3 (14.3)	9 (42.9)	3 (14.3)	
No: 181 (89.6)	44 (24.3)	36 (19.9)	47 (26.0)	54 (29.8)	

HCP: healthcare professionals; T1D: type 1 diabetes: NS: non-significant

Table 3: Overview of insulin pumps and continuous glucose monitoring (CGM) systems uptake depending on healthcare coverage or insurance reimbursement.

	Universal or partial healthcare insurance/coverage for diabetes technologies	No healthcare insurance/coverage for diabetes technologies	P value	Private insurance companies cover/reimburse for diabetes technologies	Private insurance companies do not cover/reimburse for diabetes technologies	P value
Use of insulin pump			< 0.0001			< 0.0001
• **Less than 10%**	11.8%	70.6%		20.6%	50.9%	
• **10-30%**	27.7%	4.7%		15.5%	20.8%	
• **30-50%**	33.6%	12.9%		32.0%	17.9%	
• **More than 50%**	26.9%	11.8%		32.0%	10.3%	
Agreement to start on insulin pump			<0.0001			< 0.0001
• **Less than 25%**	8.4%	47.6%		9.4%	38.7%	
• **25-50%**	21.8%	15.4%		22.9%	16.0%	
• **50-75%**	31.1%	22.6%		34.4%	20.7%	
• **More than 75%**	38.9%	14.3%		33.3%	24.5%	
Use of CGM systems			<0.01			<0.01
• **Less than 10%**	11.1%	47.7%		15.4%	43.9%	
• **10-30%**	14.8%	23.9%		13.5%	28.0%	
• **30-50%**	16.7%	14.8%		19.2%	11.2%	
• **More than 50%**	57.4%	14.8%		51.9%	16.8%	
Agreement to start on CGM system			<0.01			<0.01
• **Less than 25%**	3.7%	32.6%		9.8%	28.3%	
• **25-50%**	16.7%	20.9%		11.8%	20.7%	
• **50-75%**	20.4%	26.7%		31.4%	27.4%	
• **More than 75%**	59.3%	19.8%		47.1%	23.6%	
Reason why patients turndown technology:			<0.0001			0.03
• **Family preference for keeping on injections and fingersticks**	7.5%	4.7%		8.2%	4.7%	
• **Fear**	4.2%	3.5%		3.1%	4.7%	
• **Parents cannot afford or maintain therapy**	17.5%	57.6%		26.5%	41.5%	

• **Patient does not want to wear something on its body**	65.8%	28.2%		58.2%	42.4%	
• **Unawareness of technology**	3.3%	3.5%		1.0%	5.7%	
• **Reduced diabetes literacy**	0.8%	1.2%		2.0%	0	
• **No available**	0.8%	1.2%		1.0%	0.9%	
Agreement with the statement "All patients, regardless of circumstance, should be offered insulin pump therapy"	85.2%	78.9%	0.12	85.0%	79.6%	0.13
Disagreement with the sentence "No patient, regardless of circumstance, should be offered insulin pump therapy"	87.3%	86.6%	0.70	86.2%	87.7%	0.88
Relevant factors when starting a patient on insulin pump [a]						
• **Extremely relevant:**						
○ **Age**	35.6%	31.9%	0.75	28.2%	39.4%	0.20
○ **History of severe hypoglycemia**	58.9%	55.1%	0.79	50.6%	62.8%	0.32
○ **Suboptimal glycemic control**	44.1%	35.6%	0.07	34.5%	44.8%	0.15
○ **Requirement of small dosage of insulin**	48.4%	51.1%	0.72	50.6%	49.0%	0.87
• **Fairly relevant:**						
○ **Patient or caregiver preference**	31.9%	38.9%	0.27	32.0%	39.1%	0.09
Contraindications to starting a patient on insulin pump [b]						
• **No contraindication:**						
○ **Age less than 3 years old**	86.3%	87.5%	0.62	87.2%	86.7%	0.08
○ **One or more episodes of diabetic ketoacidosis**	50.0%	48.0%	0.96	50.0%	48.1%	0.96
• **Relative contraindication**						

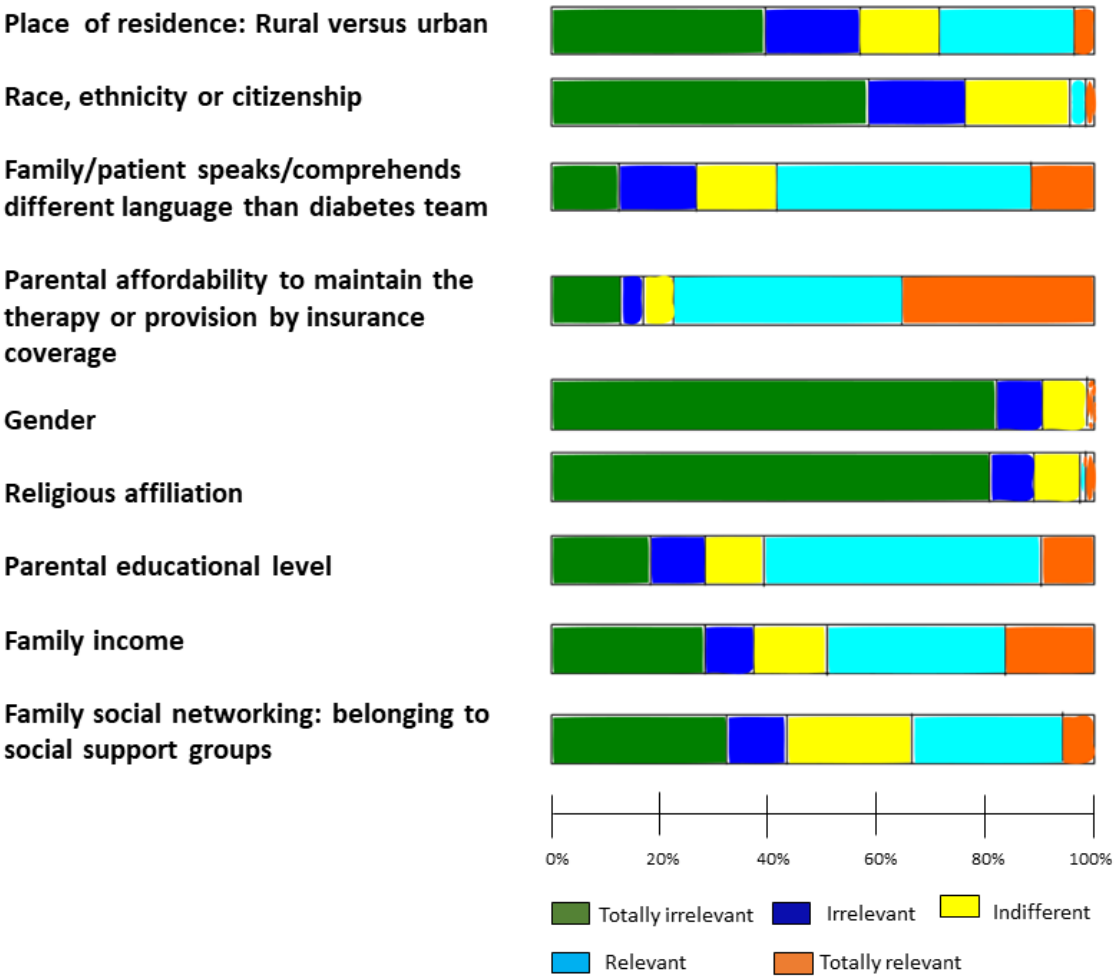
○ **History of infrequent glucose monitoring/no use of CGM**	46.1%	72.0%	0.007	55.4%	65.1%	0.07
○ **Inadequate parental/caregiver supervision**	45.9%	56.0%	0.47	53.4%	48.7%	0.41
• **Absolute contraindication:**						
○ **Infrequent follow-up**	48.7%	49.4%	0.13	41.6%	56.2%	0.17

a. On a scale from not at all relevant to extremely relevant, data were assessed for the most indicated option.
b. On a scale from not at all a contra-indication to an absolute contra-indication, data were assessed for the most indicated option.

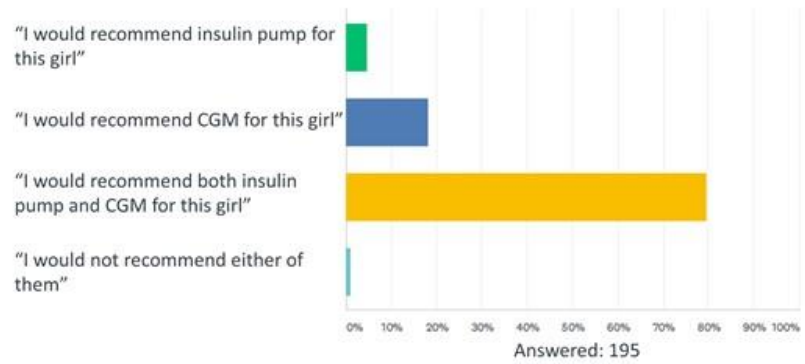
Figure legends:

Figure 1: Relevance of socioeconomic factors when insulin pumps are prescribed or recommended.

Figure 2: Global results on the six different case vignettes assessing factors thought to impact decision to recommend diabetes technologies for pediatric type 1 diabetes. (i) first case scenario; (ii) second case scenario; (iii) third case scenario; (iv) forth case scenario; (v) fifth case scenario; (vi) sixth case scenario.

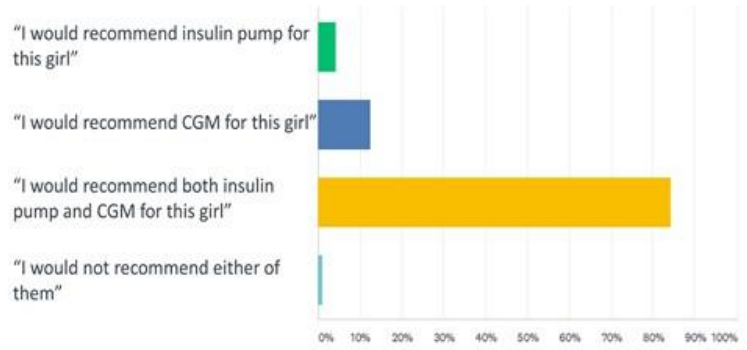

Place of residence: Rural versus urban
Race, ethnicity or citizenship
Family/patient speaks/comprehends different language than diabetes team
Parental affordability to maintain the therapy or provision by insurance coverage
Gender
Religious affiliation
Parental educational level
Family income
Family social networking: belonging to social support groups
0%
20%
40%
60%
80%
100%
Totally irrelevant
Irrelevant
Indifferent
Relevant
Totally relevant

i



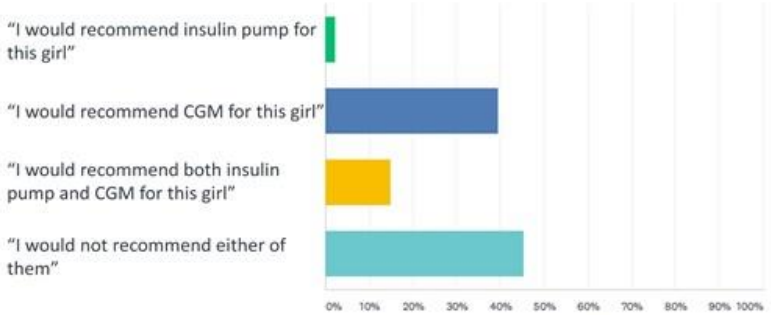
Answered: 195

ii



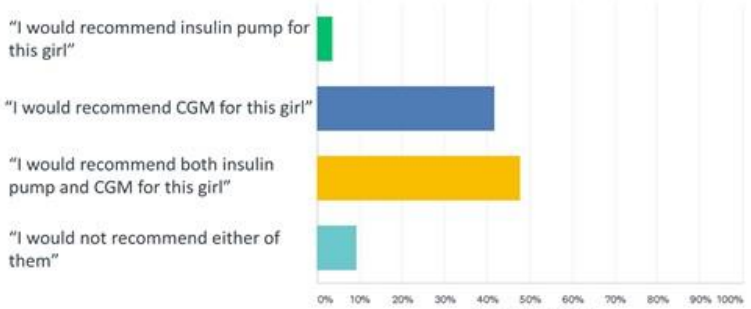
Answered: 195

iii



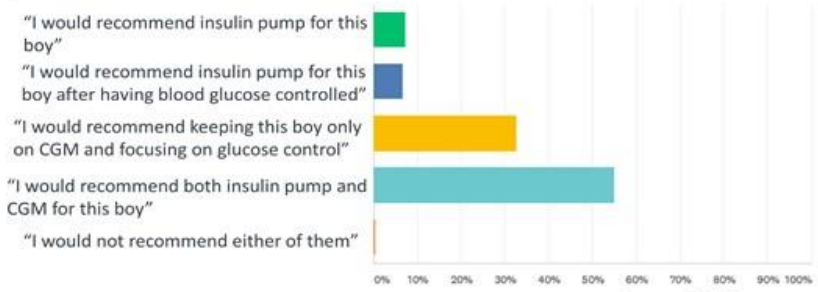
Answered: 195

iv



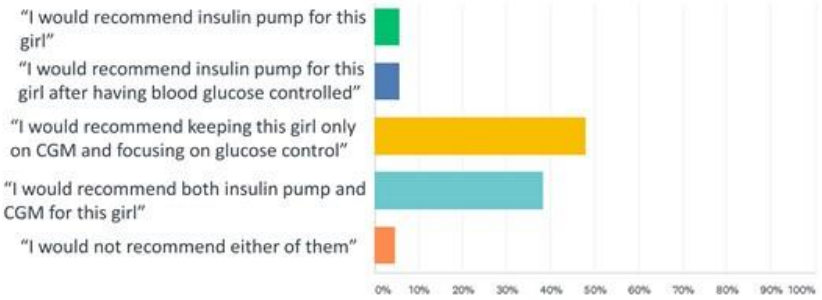
Answered: 195

v



Answered: 196

vi



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