Title Page

Full Title: Effect of early glycaemic control on HbA1c tracking and development of vascular complications after 5 years of childhood onset type 1 diabetes: Systematic Review and Meta-analysis

Short running title: Early glycaemic control and later outcomes.

Veena Mazarello Paes[1, 2], Jessica K Barrett[3], David C Taylor-Robinson[4], Heather Chesters[1], Dimitrios Charalampopoulos[1], David B Dunger[2,5], Russell M Viner[6], Terence J Stephenson[1]

[1]Great Ormond Street Institute of Child Health, University College London, UK

[2]Department of Paediatrics, University of Cambridge, UK

[3]MRC Biostatistics Unit, University of Cambridge, UK

[4]University of Liverpool, UK

[5]Wellcome Trust - MRC Institute of Metabolic Sciences, University of Cambridge, UK

[6]The Royal College of Paediatrics and Child Health, London, UK

Authors details:

1. Veena Mazarello Paes MSc, MPH, MPhil, PhD

UCL Great Ormond Street Institute of Child Health,

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London WC1N 1EH, UK

Department of Paediatrics,

University of Cambridge,

Cambridge, UK

2. Jessica K Barrett MSc, PhD

MRC Biostatistics Unit,

University of Cambridge,

Cambridge, UK

Email: jkb23@medschl.cam.ac.uk

3. David C Taylor-Robinson MB ChB, MPH, PhD, FFPH, MRCPCH

Department of Public Health and Policy

University of Liverpool,

Liverpool, UK

Email: david.taylor-robinson@liverpool.ac.uk

4. Heather Chesters MA, MCLIP

UCL Great Ormond Street Institute of Child Health Library

UCL Great Ormond Street Institute of Child Health,

London WC1N 1EH, UK

Email: h.chesters@ucl.ac.uk

5. Dimitrios Charalampopoulos MD, MPhil, PhD.

UCL Great Ormond Street Institute of Child Health,

London WC1N 1EH, UK

Email: d.charalampopoulos@ucl.ac.uk

6. David B Dunger MD, FMedSci, FRCPCH

Department of Paediatrics,

University of Cambridge,

Cambridge, UK

Wellcome Trust - MRC Institute of Metabolic Sciences,

University of Cambridge,

Cambridge, UK

Email: dbd25@cam.ac.uk

7. Russell M Viner MBBS, PhD, FRCPCH

UCL Great Ormond Street Institute of Child Health,

London, UK

The Royal College of Paediatrics and Child Health

London, UK

Email: r.viner@ucl.ac.uk

8. Terence J Stephenson DM, FRCPCH

UCL Great Ormond Street Institute of Child Health,

London, UK

Email: t.stephenson@ucl.ac.uk

Corresponding author:

Veena Mazarello Paes

UCL Great Ormond Street Institute of Child Health,

1st floor, Wellcome Trust Building,

30 Guilford Street

London WC1N 1EH

UK

Tel: +44 (0)20 7905 2805

Email: veena.paes.14@ucl.ac.uk

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Effect of early glycaemic control on HbA1c tracking and development of vascular complications after 5 years of childhood onset type 1 diabetes: Systematic Review and Meta-analysis.

ABSTRACT

Objective: A systematic review and meta-analysis was conducted to investigate if glycaemic control measured by glycated Haemoglobin (HbA1c) levels near diagnosis are predictive of future glycaemic outcomes and vascular complications in childhood onset type 1 diabetes (T1D).

Methods: Evidence was gathered using electronic databases (MEDLINE, EMBASE, Web of Science, CINAHL, Scopus and Cochrane Library up to February 2017) and snowballing techniques. Studies investigating the association between the exposure "early glycaemic control" and main outcome: "tracking of early control" and secondary outcome: risk of future complications; in children and young people aged 0 to 19 years at baseline; were systematically double-reviewed, quality assessed and outcome data extracted for synthesis and meta-analysis.

Findings: Five studies (N=4227 participants) were eligible. HbA1c levels were sub-optimal throughout the study period but tended to stabilise in a "track" by 6 months after T1D diagnosis. The group with low HbA1c <53mmol/mol (<7%) at baseline had

lower long-term HbA1c levels than the higher HbA1c group. The estimated standardised mean difference between the sub groups showed a reduction of HbA1c levels on average by 1.6% (range -0.95 to -2.28%) from baseline.

Only one study investigated the association between early glycaemic control and development of vascular complications in childhood onset T1D.

Interpretations: Glycaemic control after the first few months of childhood onset T1D, remains stable but sub-optimal for a decade. The low and high HbA1c levels at baseline seem to "track" in their respective tracks during the 10-year follow-up however, the initial difference between groups narrows over time.

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INTRODUCTION

Glycated haemoglobin (HbA1c) levels, a measure for glycaemic control is the main predictor of long-term type 1 diabetes (T1D) outcomes (1-3). HbA1c levels are highest at diagnosis, but improve after insulin treatment and remain stable in most T1D patients. However, a few find it challenging to maintain good glycaemic control despite targeted or intensive interventions, as they go through various stages in life (4, 5).

Studies mainly in adults have shown a link between poor glycaemic control in the early phase following T1D diagnosis and long-term HbA1c levels, with an increased risk of developing vascular complications and mortality (6, 7). The risk of vascular complications is likely to be greater for childhood onset T1D, due to a longer duration of glycaemic exposure (8) and pathophysiological factors such as reduced insulin sensitivity and psychosocial behaviours such as insulin omission (9-11). For childhood onset T1D, some observational studies indicate an association between poor glycaemic control within one or two years of diagnosis and vascular complications in later life (12-14). Others suggest that mean HbA1c levels nearer to

diagnosis are predictive of HbA1c levels in the subsequent years, even lifetime, regardless of the type of insulin regimen (15-17). This phenomenon, also known as glycaemic "tracking", is poorly understood (18). It is unclear exactly when and in whom the phenomenon of "tracking" of HbA1c occurs in childhood onset T1D and if it is due to the natural history of T1D. It is therefore important to investigate the evidence on this phenomenon in order to identify if there exists a window period in the initial phase of T1D diagnosis, during which appropriate resources could be mobilised to deliver targeted interventions to those at risk of developing poorer long-term glycaemic outcomes and vascular complications.

The purpose of our study was to carry out a systematic review and meta-analysis of the evidence assessing the impact of early glycaemic control in children (followed for at least 5 years from diagnosis) on tracking of early control and the risk of developing vascular complications.

METHODS

This review is part of a series of systematic reviews of evidence on the effects of early glycaemic control in childhood onset T1D. The review protocol was registered in PROSPERO (Registration number: CRD42015024546) and a detailed protocol published (19). We followed the review methods for the rigorous conduct and reporting of systematic reviews for policy and practice as described by the Evidence

for Policy and Practice Information (EPPI) Centre (20) which are as per PRISMA guidelines (21).

Search strategy

A refined search strategy was designed after a number of initial iterative scoping searches, with input from experts in the field to maximize capturing of key publications. Three sets of search terms were used relating to population (children and young people diagnosed with T1D), exposure (terms to capture observational, intervention, qualitative studies and review articles relating to early diabetes control) and outcome (complications, mortality, glycaemic tracking i.e. metabolic memory) (additional file 1).

Six electronic databases: (MEDLINE and EMBASE via OVID, Web of Science via Thompson Reuters, CINAHL Plus via EBSCO, Scopus via Elsevier and the Cochrane Library), were double searched in parallel by HC & VMP from inception to December 2014 and updated in February 2017 by using a combination of free text and Thesaurus or MeSH terms (additional file 2). No time-period or language restrictions were applied. All identified articles from electronic databases were imported into Endnote and de-duplicated for further review. This was supplemented by hand-searching of reference lists of studies and reviews, grey literature, personal databases and contacting experts and authors of included studies for additional or unpublished data.

Study selection

Interventional and observational studies with a follow-up of ≥ 5 years from diagnosis of T1D which described and quantified the association between early glycaemic control (defined as glycaemic control within 2 years of diagnosis of T1D) AND long-term glycaemic tracking (defined as settling of HbA1c levels into long-term tracks of either > or < 7% i.e. 53 mmol/mol) and risk of future complications in children and young people aged 0 to 19 years at baseline were included (Additional file 3).

In addition to running electronic database searches in parallel (HC and VMP), sub-samples of papers were double-reviewed (DC and VMP), at each stage of the review process (title and abstract screening, data extraction and quality assessment). The interrater reliability for study selection was substantial (22). Full texts of abstracts appearing to meet the inclusion criteria were retrieved and their status was recorded in a pre-piloted excel spread-sheet, which included specific study details and reasons for exclusion (for excluded studies). No foreign language papers were identified. Articles were re-examined (DC and VMP) if there was uncertainty about inclusion criteria and disagreements were resolved at team meetings.

Data extraction

Data from included studies were extracted, analysed and synthesised by one reviewer (VMP). A proportion of shortlisted studies were also independently double reviewed and data extracted (DC & RA). From observational studies, data on HbA1c

levels were extracted at all available time points from diagnosis. Data on HbA1c tracking and the association between early glycaemic control and chronic complications or markers of chronic complications at follow-up were extracted (additional file 4). Authors of included studies were contacted for clarity and additional information on HbA1c tracking data where necessary. The main outcome of interest was tracking of early glycaemic control based on HbA1c measurements as percentage (DCCT) and/or mmol/mol (International Federation of Clinical Chemistry) units. The secondary outcome of interest was the impact of early glycaemic control on the development of micro and macro vascular complications during the long-term follow-up period.

Quality assessment

The quality of included studies was assessed independently by two reviewers (DC and VMP) using the quality assessment criteria by the EPPI Centre (20). Any disagreements were resolved by consensus. Scores were based on six items focusing on both internal and external validity (additional file 5). Observational studies were classified as high (≥5), intermediate (3-4) or low (≤2) quality based on the number of quality criteria met out of a maximum assessment score of six.

Statistical analysis

Information extracted from included studies were summarised through descriptive narrative synthesis and meta-analysis (23). All statistical analyses were conducted

by one reviewer (VMP) and were verified by a second reviewer (JB). The sample size, mean HbA1c measurements and standard deviation (SD) or standard error (SE) were available at population level and/or for categorised low and high HbA1c groups. Where not reported, the SE of the study at each time point was calculated using the reported SD and the group sample sizes. Baseline period included 3-6 months from T1D diagnosis. Mean HbA1c levels at diagnosis was not included in the main meta-analysis as by definition they were measured prior to exposure of glycaemic control with insulin therapy. The effect sizes and their SE were divided with SD to obtain standardised mean differences (SMD) (24).

The primary outcome was the population mean HbA1c level at baseline (0, 3, 6 months of diagnosis), 1, 2, 3, 5, 7 and 10 years follow up. A further primary outcome was the difference in HbA1c levels between the low HbA1c (<7% at baseline) group (considered the 'treated/exposed' group) and the high HbA1c group (≥7% at baseline) (the 'control' group), reported as standardised mean differences. If multiple measurements of HbA1c were reported at follow-up then these measures were combined within each study before meta-analysis. Heterogeneity between studies was expected and therefore both fixed effects (FE, inverse variance) and random effects (RE, Dersimonian and Laird) models were used to pool the effect sizes and reported using forest plots (25). The heterogeneity between studies was assessed using the χ^2 test for heterogeneity and I^2 statistics (26). The meta-analyses were

carried using the metan command in STATA 15, StataCorp, College Station, Texas 77845 USA.

For glycated haemoglobin, the estimated pooled standardised mean differences were converted into absolute units, to facilitate clinical interpretation, by multiplying the estimate by the pooled SD of all included studies of the meta-analysis.
Furthermore, the long-term population average HbA1c trajectory from each study was plotted alongside the overall estimate at all-time points of follow-up obtained from the meta-analysis. The trajectories of HbA1c sub groups (low v/s high) in each study were also plotted.

The robustness of the meta-analysis to the choice of meta-analysis model was assessed by comparing FE and RE pooled standardised effect sizes. In a sensitivity analysis we excluded studies in pre-school children.

Assessing publication bias using the funnel plots, the Begg's rank correlation test or the Egger's linear regression test was deemed inappropriate as there were insufficient studies included in the review.

Due to the small number of included studies, meta-regression was not appropriate to explore heterogeneity between studies or to investigate if there were other potential factors that could be independently associated with long-term glycaemic control. A

minimum of 10 studies per study level parameter would be needed for meta-regression.

Only one included study assessed the association of micro and macro-vascular complications with early glycaemic control, which precluded a meta-analysis and results of which were narrated separately.

RESULTS

The literature search strategy on glycaemic control in childhood onset T1D identified articles from individual databases (Medline via OVID, n = 14,688; Embase via OVID, n = 843; Web of Science via Thompson Reuters, n = 2,734; CINAHL Plus via EBSCO, n = 1,185; Scopus via Elsevier, n = 2,837 and Cochrane library, n = 4,052). After de-duplication 21,063 articles were screened, out of which 390 were shortlisted for full review (Figure 1). There was good agreement between reviewers on identifying abstracts for full text review. 385 studies were excluded from the systematic review and meta-analysis for reasons shown in figure 1. Five fairly recent studies (24, 27-30) conducted in developed countries (Israel, Scotland, Sweden and USA) with a total of 4227 participants met the inclusion criteria of the systematic review. The studies investigated national (24), regional (27), Children's hospital (29), academic medical centre (30) and clinic (28) level data.

Characteristics of included studies

The Swedish cohort study (24) consisted of 1543 children and adolescents (920 males) from two nationwide population-based Swedish registries (Swedish Paediatric Quality Registry and Swedish National Diabetes Register) covering a period from year 2000 to 2010. The mean age at diagnosis was 13.9 (range 5.0 to 19.0) years and the mean follow-up was for 7.1 ±2.5 (range 1.0 to 12.0) years. The study investigated whether high mean HbA1c values 3-15 months after diagnosis of T1D in childhood was associated with future glycaemic control, albuminuria and retinopathy in early adulthood.

The American study (29) prospectively investigated, between the years 1993 and 2009, whether age at diagnosis, gender, ethnicity, diagnostic era (year of diagnosis) and type of insulin therapy were associated with tracking of glycaemic control at five years follow-up post diagnosis of T1D. A total of 2218 (1166 males) mainly non-hispanic Caucasian (86.1%) children and adolescents participants with a mean age of 9.0 ±4.1 years at diagnosis (range 0 to 20 years), were identified from the Children's Mercy Hospital Type 1 diabetes in paediatrics database, USA. Insulin therapy (split regimen dosing, multiple daily injections and continuous subcutaneous insulin infusion) and diagnostic methods used to analyse HbA1c varied during the study period. Information on the socio-economic status and T1D history in family was not reported.

The other American study (30) followed 138 children (71% males and 91.5% white) at an academic medical centre of Pediatric Endocrinology/Diabetology at Riley Hospital for Children, Indiana, USA and investigated whether long term HbA1c differed as a result of receiving diabetes related education during the years 1998-2002. The mean age at diagnosis was 6.8 ± 3.3 years (age range: 1.1 – 13.9 years). Details of insulin therapy was not reported.

The Scottish study (27) retrospectively investigated HbA1c tracking among 155 children (74 males), aged ≤ 16 years (range 0 to 16 years), from the regional database of the National Health Service (NHS) Highland Paediatric diabetic services followed for a median of 4.10 (range 0 to 15.0) years from diagnosis between the years 1993 and 2012. The cohort had limited ethnic diversity, low use of intensive insulin therapy and no use of pump therapy.

The Israeli study (28) was a retrospective observational study, investigating HbA1c tracking in 173 mainly Jewish (84.4%) preschool aged children (84 males) aged 0.5 – 6.5 years at diagnosis between 1993 and 2009 at a tertiary level diabetes clinic in Israel, with a median T1D duration of 4.3 years (range 1 to 11 years) and followed up for seven years from T1D onset. All patients were advised on carbohydrate counting, required to perform >6 self- blood glucose measurements per day and both multiple daily injections and insulin pumps were used.

Further details of the data extracted from the five studies included in the systematic review are in Table 1.

Study Quality

The quality of the observational studies was intermediate to high. Two studies were assessed to be “high” quality with a score of five each (24, 29) and the other three were of “intermediate” quality, with scores of four (27, 30) and three (28) out of a possible score of six respectively. No studies included in the review were of low quality.

Early HbA1c levels and long-term tracking of glycaemic control

All five studies included in the review assessed the association between early glycaemic control and later HbA1c levels. Population mean HbA1c was available at various follow-up time points (0, 3, 6, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132 and 156 months after T1D diagnosis). Additionally, four studies provided data on the association between early glycaemic control and later HbA1c levels within sub groups of low and high HbA1c identified at baseline (24, 27-29).

To study the impact of early glycaemic control on later HbA1c levels, data from all five studies could be pooled in the review. The number of studies reporting the effect during each time point of the study period varied. All studies reported sub-optimal estimated mean long-term glycaemic control at all of the investigated time points

during the 10-year follow-up period. The sample size varied from 25 to 2218 and the study periods ranged between years 1993 and 2012. After using the population mean HbA1c and SE in the FE & RE models, the estimated pooled magnitude of the mean HbA1c levels (95% CI) was suboptimal at 11.56% (CI: 11.46, 11.66%) at diagnosis, 7.74% (CI: 7.68, 7.80%) after 3 months 7.61% (CI: 7.47, 7.76%) after 6 months, 7.79% (CI: 7.71, 7.87%) after 1 year, 7.90%(CI: 7.83, 7.98%) after 2 years, 7.94% (CI: 7.86, 8.03%) after 3 years, 8.57% (CI: 8.49, 8.65%) after 5 years, 7.99% (CI: 7.85, 8.12%) after 7 years and 8.59%(CI: 8.24, 8.94%) after 10 years of T1D diagnosis.

The pooled results comparing the effect size results of the FE and RE models were presented in forest plot (Figure 2) and the overall effect estimates were also presented in a graph (supplementary Figure 2). There was variation in glycaemic control between countries in children and adolescents during the 10-year study period. The test for heterogeneity between studies was significantly high (I^2 >69%) at almost all of the follow-up time points in the meta-analysis (χ^2 $p<0.05$).

Further exploratory sub-group analysis indicates that heterogeneity was consistently high between studies, countries and populations.

For the assessment of early glycaemic control (low and high HbA1c identified at baseline) and what followed at various time points during the study period, there

were four studies with data that could be pooled in the review. The HbA1c levels of the low HbA1c group showed better improvement than the high HbA1c group during the study period. The low and high Hba1c levels at baseline seem to "track" in their respective tracks during the 10-year follow-up however, the initial difference between groups narrows over time (Figure 3).

From the FE meta-analysis, the pooled standardised difference in mean HbA1c levels between patients in the low HbA1c group and those in the high HbA1c group with 95% CI was significant at -1.25 (-1.53, -0.97) after 6 months, -0.85 (-0.95, -0.75) after 1 year, -0.84 (-0.95, -0.74) after 2 years, -0.78 (-0.89, -0.66) after 3 years, -0.44 (-0.54, -0.34) after 5 years, -0.75 (-0.94, -0.55) after 7 years and -0.32 (-0.63, -0.02) after 10 years of T1D diagnosis. The treatment effect in absolute units was a reduction of HbA1c levels on average by 1.6% (range -0.95 to -2.28%) from baseline, which may be clinically relevant (Table 2).

The study in pre-school aged children (mean age at diagnosis 3.8 ± 1.6 years) showed better control than the other studies with older children (28).The heterogeneity levels were significantly high (p=0.001) at 1, 2, 3 and 5 years after diagnosis and were lower at follow-up time points 0.5, 7 and 10 years after diagnosis (p>0.7) in the meta-analysis.

The meta-analysis was repeated after excluding the study in pre-school aged children (Supplementary figure 1). The pooled standardised mean difference in HbA1c levels between patients in the low HbA1c group and those in the high HbA1c group with 95% CI was slightly lower at -1.10 (-1.56, -0.65) after 6 months, -0.79 (-0.89, -0.69) after 1 year, -0.78 (-0.89, -0.67) after 2 years, -0.71 (-0.83, -0.59) after 3 years, -0.41 (-0.51, -0.30) after 5 years, -0.72 (-0.92, -0.53) after 7 years and -0.32 (-0.63, -0.02) after 10 years of T1D diagnosis. The treatment effect in absolute units was a reduction of HbA1c levels on an average by 1.49% (range -0.90 to -2.37%) from baseline. The test for heterogeneity showed improved results and was significantly high only at 5 years after diagnosis (p=0.001) in the meta-analysis (Table 2).

Comparing the long–term HbA1c trajectories between studies revealed that the Israeli study in pre-school children yielded better long-term control (supplementary Fig 2). Individual study results suggest that early glycaemic control tracks during the follow-up in the initially low and high HbA1c groups (Supplementary Fig 3)

Since there were only 5 studies in the review, we could not assess publication bias using the funnel plot, the Begg adjusted rank correlation test or the Egger test as there was insufficient power to distinguish real asymmetry from random chance.

Association of early HbA1c levels and complications risk

Only one longitudinal study (24) investigated the association of early glycaemic control and future complications and met the inclusion criteria for the systematic review. The study, adjusted for gender, T1D duration, age at diagnosis, physical activity and smoking) and reported that Swedish children with higher mean HbA1c levels of ≥ 8.7% (≥70 mmol/mol), 3-15 months after diagnosis were significantly more likely to develop macroalbuminuria (OR: 14.3, 95% CI: 2.6 to 78.2, $p<0.01$), microalbuminuria (OR: 1.7, 95% CI: 0.8 to 3.4, $p<0.05$) and retinopathy (OR: 2.0, 95% CI: 1.2 to 3.1, $p<0.01$) in early adulthood (mean age: 21± 2.3 years, range: 18 to 29 years). The study also highlighted the lack of physical activity, smoking and female gender as predictors of poor glycaemic control. However, the role of insulin therapies and other social and family factors on these observations was not reported.

DISCUSSION

We identified five longitudinal studies investigating the impact of early glycaemic control on long-term glycaemic control in children and adolescents (<19 years) followed from diagnosis of T1D. In the meta-analysis of all included 5 studies, the overall mean HbA1c levels in all studies were sub-optimal at all follow-up time points.

The meta-analysis of the four studies comparing initially low v/s high HbA1c groups, indicates that the low HbA1c group showed overall slightly improved control than the

high HbA1c group during the study period. Additionally, the meta-analyses suggests that the overall glycaemic control was stable in a "track" after 6 months of childhood onset T1D diagnosis. The low and high HbA1c levels at baseline also seem to "track" in their respective tracks during the 10-year follow-up. However, the initial difference between groups narrows over time. The number of participants in the low HbA1c group was small and this may have influenced the power to detect group differences.

Three of the included studies were of intermediate quality while the remaining two were of high quality in reporting potential biases. We adhered to strict systematic review procedures for study selection, data extraction and reporting to minimise reviewer related biases. The age ranges and sample sizes varied between studies which may have influenced the heterogeneity seen in the pooled estimates of long-term glycaemic control. Heterogeneity was reduced when the study in pre-school children was excluded from the meta-analysis.

All studies included in the systematic review were conducted in developed countries, which had dissimilar health system models and this may have impacted the long-term glycaemic outcomes. The study period was between years 1993 and 2012, during which period understanding of the disease and diagnostic methods for HbA1c testing improved. This may have affected the interpretation of the HbA1c measurements. Also, several changes were implemented during this period in diabetes care, practice and management, through introduction of novel fast acting

insulin formulations, intensive insulin treatment and educational interventions. These and the improved diagnostic and clinic factors may have played a role in improving the overall glycaemic trajectories in the participants as reported by other studies (31, 32).

The sub-optimal HbA1c control estimated in the meta-analysis during the follow-up period may be due to more participants with higher HbA1c levels, age (33), endogenous and exogenous factors or biological variation in the glycation phenotypes of children (34-36), psychological factors particularly in older children (37, 38). These are all factors which may also have increased the risk of developing or progression of micro & macrovascular complications in those children as a consequence of those higher HbA1c levels (39).

The DCCT cohort were able to achieve HbA1c levels of 7% (53 mmol/mol) (40) as compared with 8.3% (66 mmol/mol) achieved among more than 25,000 patients from USA (41) and 8.7% (70.1 mmol/mol) achieved by the paediatric population of England and Wales in the UK (42). This highlights the fact that, outside of a clinical trial, achieving glycaemic targets remains difficult. Hence robustly identifying factors early in the life course of childhood onset T1D that influence future glycaemic control and risk of complications remains an important clinical research goal.

Only one study provided evidence that albuminuria and retinopathy were associated with high mean HbA1c ≥ 8.6% (≥ 70mmol/mol) between 3 and 15 months after diagnosis of T1D (24). This is consistent with findings by other studies, which did not meet our inclusion criteria (6, 17, 43, 44). It would be highly relevant for determining future prognosis, if these outcomes could be confirmed in future studies.

Cardiovascular disease is the major cause of death in T1D patients. Pre-symptomatic cardiovascular disease is evident in 100% of young adults with T1D (45) and there is evidence of accelerated atherosclerotic processes (46, 47) and increased severity of cardiovascular disease (48) at an earlier age compared to the general population. Landmark trials show that intensive insulin therapy reduces cardiovascular events in adults (6, 49). Although differences in HbA1c account for most of this benefit, multivariate analyses suggest that part of the reduced risk is mediated by reduction in the incidence of diabetic renal disease (50). In children and young people with T1D, atherosclerosis is present to a greater extent (51) and the prevalence of cardiovascular risk factors is greater (52, 53) than in the general population. Diabetic nephropathy incidence accelerates during adolescence (54). These are all strong indicators of a greatly elevated risk for future vascular diseases. There is currently no evidence base for the effectiveness of ACE Inhibition or statin treatments in adolescents with T1D although, the important AdDIT Trial may inform practice in the coming years (55). Therefore currently, in order to reduce vascular

complications risk, the importance of achieving good glycemic control is arguably greater in childhood compared to adult T1D populations.

The meta-analysis indicates that the overall glycaemic control stabilizes in a “track” after 6 months of childhood onset T1D diagnosis and pre-school aged children had better control throughout the follow-up period. Furthermore, the low and high HbA1c levels at baseline also seem to have metabolic memory, which shows HbA1c “tracking” during the 10-year follow-up despite differences between the high and low groups. This suggests there may be benefits of having good control during the initial few months of diagnosis. However, as these five studies report temporal associations, an experimental study of an intervention soon after diagnosis would be required to prove that better early control results in better later control. This review may also indicate a short window of opportunity to intervene and improve long-term glycaemic outcomes. It may therefore be beneficial to develop clinical and educational strategies to identify and deliver targeted interventions during this early phase to those at risk of having poor glycaemic control and to ensure that the HbA1c targets are maintained in the long-term. There is currently no evidence on effectiveness and timing of focused clinical interventions targeted at changing these tracks (18). It would be useful to gather this evidence and to explore further the mechanisms of this phenomenon in order to deliver best care to newly diagnosed children and adolescents. The findings of this review would be useful to policy makers, health professionals and T1D patients to focus on designing interventions to

prevent sub-optimal glycaemic outcomes and decrease the risk of developing micro and macro vascular complications.

Strengths and limitations of the review

The many strengths of this study include, being to our knowledge, the first systematic review and meta-analysis to rigorously investigate published and unpublished literature on the association of early glycaemic control in childhood onset T1D with glycaemic tracking and future risk of complications. Furthermore, this is the first review to rigorously and systematically search and review all available evidence as per pre-set inclusion/exclusion and quality assessment criteria. We have taken utmost care to minimise study selection, reviewer related and publication bias. All of the included studies were intermediate to high quality.

But, there are limitations to this systematic review which need to be considered. The diabetes diagnosis, care and HbA1c outcome measures have evolved over the years and were not uniform across studies. There was considerable heterogeneity between studies. The comparable follow-up data was not available beyond 10 years. We were unable to investigate if other factors may have confounded the findings. The small number of studies and the short duration of follow-up in studies may have masked the true association with long-term glycaemic control. Although we made every effort to search for unpublished and grey literature, we may have missed some that remain unreported due to unethical practices in reporting or publication bias.

The results of our study may not be generalizable as they were mainly conducted in developed countries with varied health care system models.

Review updating plans

The review will be updated if significant new evidence becomes available and results of the update review will be disseminated through peer-reviewed publications, conference presentations and at meetings.

LIST OF ABBREVIATIONS

HbA1c: Haemoglobin A1c

T1D: Type 1 diabetes

PROSPERO: International Prospective Register for systematic Reviews

DCCT: The Diabetes Control and Complications Trial

EPPI: Evidence for Policy and Practice Information

RE: Random effects model

FE: Fixed effects model

COMPETING INTERESTS

No potential conflict of interest was reported by the authors.

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AUTHORS CONTRIBUTION

VMP was the lead reviewer, designed the study, developed the study protocol, created the search strategy, searched electronic databases for literature, extracted the data, co-ordinated with authors of included studies for additional information, analysed the evidence, drafted the report and is responsible for the article. JB and DTR participated in the study design, contributed to the statistical analysis design and helped revise the manuscript. HC participated in the study design, contributed to the literature search and helped revise the manuscript. DC participated in the study design, contributed to the double review of a proportion of articles and helped revise

the manuscript. DD advised on the project, commented on the analyses and helped revise the manuscript. RV advised on the project, participated in the study design, commented on the analyses and helped revise the manuscript, TS participated in the study design and helped revise the manuscript. All authors contributed to the study design, critical revision of the manuscript and approved the final version.

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Figure 1: Stages of systematic review of evidence on long-term glycaemic control

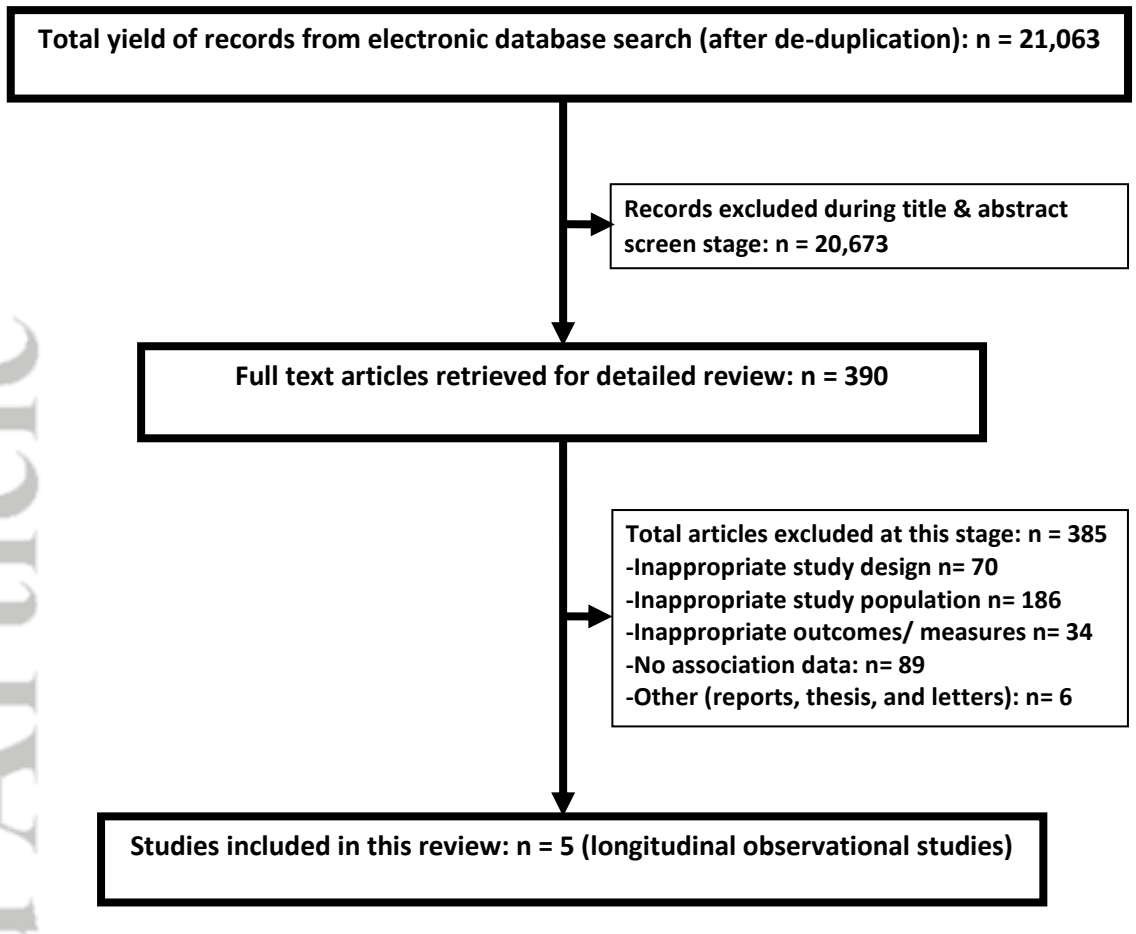
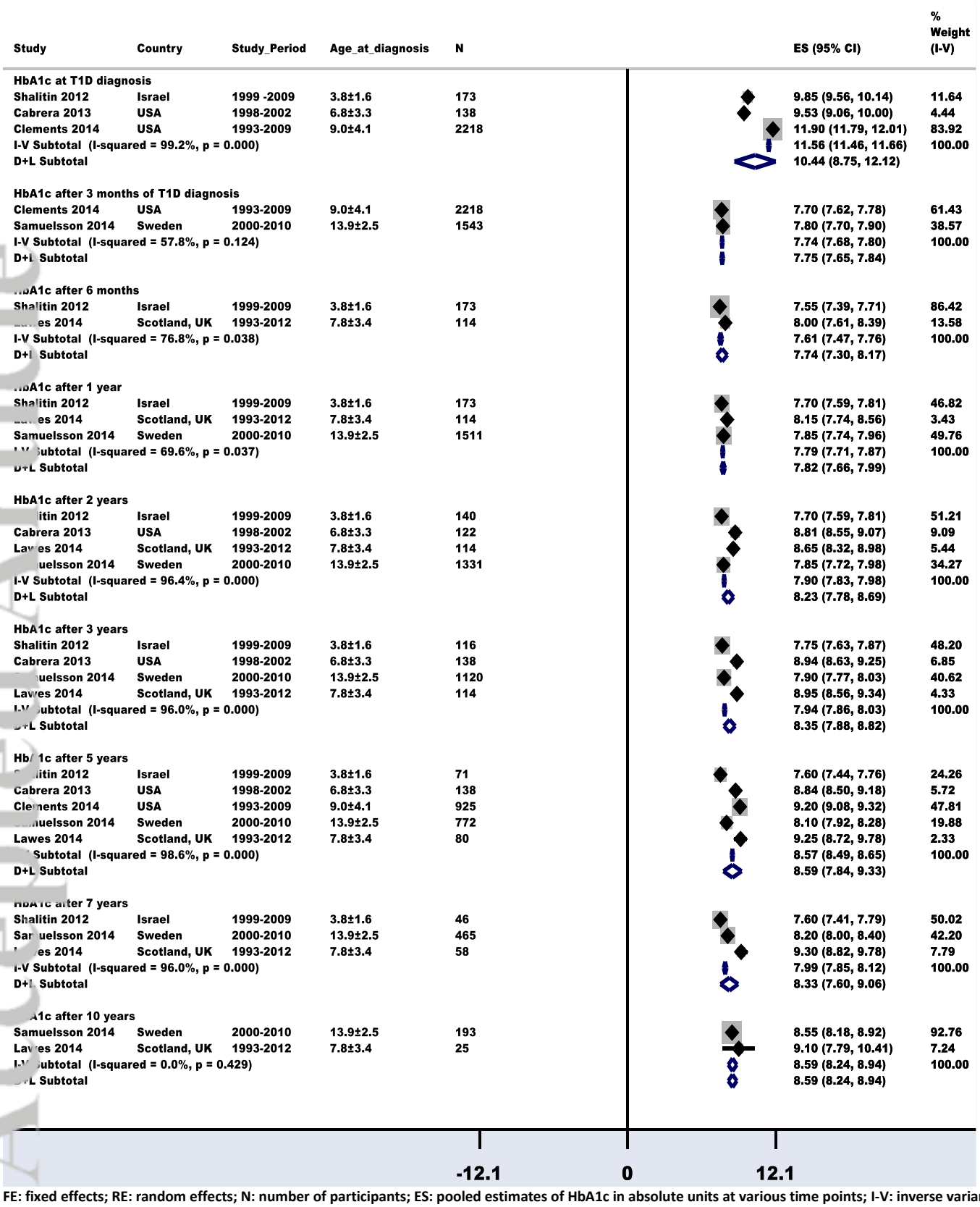
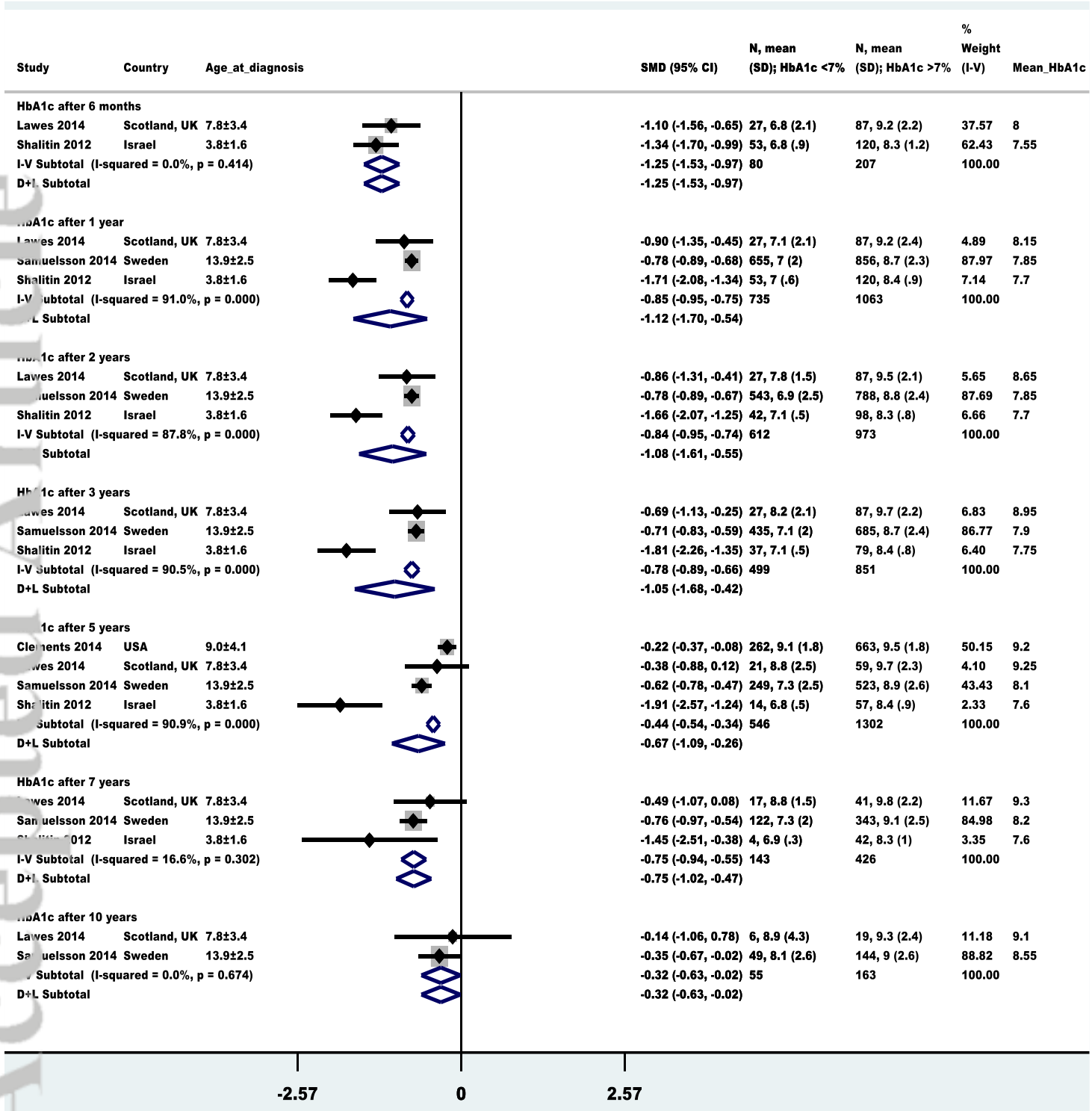


Figure 2: Summary of FE & RE models: Pooled estimates of overall glycaemic control at follow-up



FE: fixed effects; RE: random effects; N: number of participants; ES: pooled estimates of HbA1c in absolute units at various time points; I-V: inverse variance; D+L: DerSimonian and Laird

Figure 3: Summary of FE & RE models: Estimated SMD of HbA1c levels with 95% CI between the low (exposed to glycaemic control) and high (unexposed to glycaemic control) HbA1c groups during various time-points of follow-up



SMD: standardised mean difference; CI: confidence interval; N: number of participants; SD: standard deviation; I-V: inverse variance; D+L: DerSimonian and Laird

Table 1: Description of longitudinal studies investigating the impact of early glycaemic control on long-term HbA1c and risk of complications in childhood onset T1D

No	Author, year, country and study period	Study design and data source	Population	Age range of study population	Follow-up period	Treatment	Outcome and measure	Definition of early HbA1c	Statistical Analyses	Association	Quality score (max 6) and comments
1	Samuelsson 2014 Sweden 2000 - 2010	Retrospective/Prospective pilot study National databases (paediatric plus adult) Swedish paediatric diabetes quality registry (SWEDIABKIDS) and the national diabetes register (NDR). Mean visits in SWE: 19.5 Mean visits in NDR: 4 Mean age in SWE: 13.9±2.5 years Mean age in NDR: 21.0±2.3 years	**Generalizability**: Non rep **Sample size**: 1543 children and adolescents. **Males**: 920 **Ethnicity**: NR **SES**:NR **Family history of T1D**:NR 5-9 yr olds: N= 89 (5.8%) 10-14 yr olds: N= 769 (49.8%) 15-19 yr olds: N= 685 (44.4%) Mean HbA1c adjacent to diagnosis: 8.6% (≥70mmol/mol) Mean HbA1c months 3-15 in relation to age at diagnosis: 5-9 yr olds: 7.5% ± 1.1 (58.7 ± 12) 10-14 yr olds: 7.2% ± 1.2 (55.3 ± 13) 15-19 yr olds: 7.04%	5-19 years Mean age at diagnosis: 13.9 ± 2.5 years.	1-12 years Mean: 7.1 ±2.5 years	NR	Metabolic control (HbA1c) and detection of albuminuria, retinopathy in early adulthood Standardised assay for HbA1c. Urine albumin excretion. Physical activity levels	HbA1c values between 3 and 15 months after diagnosis	**1) MVLR:** Mean HbA1c in NDR (dependent) and Mean HbA1c months 3-15 after diagnosis (independent: **a) Unadjusted**: R-square 0.159, Beta Coefficient 0.466; 95% CI (0.408 – 0.525); t=15.6; p=0.001 **b) Adjusted** (for age at diagnosis, gender, duration of diabetes, smoking PA)**:** R-square 0.206, Beta Coefficient 0.414; 95% CI (0.355 – 0.473); t=13.2; p=0.001 **2) LR unadjusted OR with 95% CI** a) HbA1c group 6.8 – 8.6% (51-69mmol/mol); Ref ≤ 6.7% (≤50mmol/mol): i) Macroalbuminuria: 1.3 (0.3 - 6.0) ii) Microalbuminuria: 0.9 (0.5 -1.4) iii) Retinopathy: 1.6 (1.2 – 2.1); p<0.01 b) HbA1c group ≥ 8.7% (≥70 mmol/mol); Ref ≤6.7% (≤50mmol/mol): i) Macroalbuminuria: 12.3 (3.2 - 46.8); p<0.01 ii) Microalbuminuria: 2.0 (1.1 -3.8), p<0.05 iii) Retinopathy: 2.6 (1.7 – 3.8); p<0.01 **3) LR adjusted (gender, duration of T1D, age at diagnosis, PA and smoking) OR with 95% CI** a) HbA1c group 6.8 – 8.6% (51-69mmol/mol); Ref ≤6.7%	++ Children with poor metabolic control adjacent to diagnosis had higher HbA1c levels in adulthood. ++ micro and macroalbuminuria and retinopathy in early adults seen in patients with high mean HbA1c during 3-15 mo post diagnosis. ++ HbA1c levels higher in young children as compared to pubertal children (12 y for girls and 14 y for boys) + girls had higher HbA1c levels + PA levels lower in patients with high HbA1c levels, micro/macro albuminuria and retinopathy +Smoking observed in patients with high HbA1c levels, micro/macro albuminuria and retinopathy	High (5) non-representative child population. Children < 5 years not included

			± 1.3 (50.5 ± 14)						(≤50mmol/mol): i) Macroalbuminuria: 0.6 (0.1 - 6.9) ii) Microalbuminuria: 0.9 (0.6 -1.7) iii) Retinopathy: 1.4 (1.1 – 1.9); p<0.05 b) HbA1c group ≥ 8.7% (≥70 mmol/mol); Ref ≤ 6.7% ≤50mmol/mol): i) Macroalbuminuria: 14.3 (2.6 - 78.2); p<0.01 ii) Microalbuminuria: 1.7 (0.8 -3.4) iii) Retinopathy: 2.0 (1.2 – 3.1); p<0.01		
2	Clements 2014 USA 1993 - 2009	Prospective cohort The Children's Mercy Hospital Type 1 diabetes in paediatrics database, USA.	**Generalizability**: Rep **Sample size**: 2218 children and adolescents. **Males**: 1166 **Ethnicity**: 86.1% non-Hispanic Caucasian, 8.9% non-Hispanic African-American, 5% other or Hispanic), **SES**:NR **Family history of T1D**:NR	0-20 years Mean age at diagnosis: 9.0 ±4.1 years	5 years	Stratified by diagnostic era which included the following regimen as first line therapy Pre 2000: Split regimen dosing 2000-2003: multiple daily injections 2004-2009: Continuous subcutaneous insulin infusion	1)Association with HbA1c levels at diagnosis, 1.5 and 5 year f/u by diagnostic age, ethnicity, and diagnostic era Various methods used to measure HbA1c during the study period i.e. HPLC, Boronate affinity. 2) Effect of insulin therapy on HbA1c tertiles i.e. Children with <7%	HbA1c during first 3 months of diagnosis and/or 4 – 12 months after diagnosis Three groups of patients based on baseline HbA1c: a) <7, b) 7 to 9, c) >9.	**Mean (SD)** 1st HbA1c after 3months of diagnosis 7.7 ± 1.9 (60.7 ±20.8 mmol/mol) V/S mean HbA1c in the 5th year after diagnosis 9.2 ± 1.8 (106.6 ±28.0 mmol/mol) Comparison of mean 1st HbA1c after 3months of diagnosis V/S mean HbA1c in the 5th year after diagnosis by HbA1c tertiles < 7, 7-9 and > 9 % (< 53, 53 -75 and >75 mmol/mol) (1) HbA1c in children with < 7: mean 6.2 ± 0.5 (n = 871) v/s 9.1 ± 1.8 (n = 609 missing) (2) HbA1c 7 – 9: mean 7.9 ± 0.6 (n = 940) v/s 9.1 ± 1.5 (n=483 missing) (3) HbA1c > 9: mean 10.7 ± 1.8 (n = 407) v/s 9.8 ± 2.0 (n=201 missing) **Regression, stratified analyses** Effect of insulin therapy: Children with <7% (53mmol/mol) at diagnosis had higher HbA1c levels during 1.5 years after diagnosis across all age groups.	++ Significant increase in HbA1c levels by increasing age of diagnosis with ≥10 year olds experiencing poorer glycaemic control. Younger patients had better control across all HbA1c sub categories p<0.001 The group with HbA1c <7 has steeper increase for the first 1.5 years. However, it seems all three groups ended at about the same level at 5 years except for the patients who were diagnosed at >10 years old of the HbA1c >9 group. ++ 0-4 year old did not show much change in HbA1c trajectory over 5 years, but progressive increase in HbA1c levels in all age groups, highest in >10 year olds (p<0.001). Highest HbA1c inflection point is at around 1.5 years post diagnosis ++ Small but statistically significant differences within gender subgroups across diagnostic age groups (p<0.0001). ++ HbA1c levels were higher in non-Hispanic black patients (p value for race/ethnicity x age interaction <0.001	High (5) 5 different methods used to analyse HbA1c during the study period

							(<53mmol/mol), 7-9% (53-75mmol/mol) and >9% (>75%)		Overall HbA1c levels rose yearly by 1.83% (1.72 to 1.94) (20.0 mmol/mol (18.8 to 20.2). HbA1c rise was less steep but significant in children with baseline HbA1c between 7% (53mmol/mol) and 9% (75mmol/mol) (0.81% (0.69 to 0.92) (8.9 mmol/mol (7.5 to 10.1))). Patients with baseline HbA1c >9% (75mmol/mol) had stable or improved control at 1.5 years post diagnosis with an overall yearly decline of -0.68% (-0.87 to -0.49) per year (-7.4 mmol/mol (-9.5 to -5.3) Non- Hispanic black v/s non-Hispanic white mean (SD): 10.2% (±2.5) (88.0 ±27.3 mmol/mol) and 8.4% (±1.4) (68.0 ±15.3 mmol/mol) Pre 2000 era mean (SD): 8.9% (±1.5) (73.8 ±16.4 mmol/mol) 2000-2003 mean (SD): 8.7% (±1.6) (71.6 ±17.5 mmol/mol) 2004-2009 mean (SD): 8.1% (±1.7) (65.0 ±18.6 mmol/mol)	Also rate of HbA1c levels rise during 1.5 years post diagnosis was greater in non- Hispanic black patients in each age sub group. ++ high levels in pre 2004-2009 group at diagnosis, 1.5 and 5 years p<0.001.	
3	Lawes 2014 North of Scotland, UK Jan 1993 – Aug 2012	Retrospective cohort Regional database (paediatric) from NHS Highland Paediatric diabetic services, North of Scotland,	**Generalizability:** Non rep **Sample size**: 155 children ≤ 16 years. **Males**: n= 74. **Ethnicity**: limited ethnic diversity **SES** and **family history of T1D**: study reports as nationally comparable	0-16 years Median baseline age: 7.9 (range 4.5 to 10.9 years).	Up to 15 years Median f/u: 4 years 10 months	Lower use of intensive insulin (basal bolus) regimens. No patients on pump therapy.	HbA1c trends and association with 6 month HbA1c Bayer DCA 2000 near-patient analyser 3121 HbA1c measurements	Baseline HbA1c defined as HbA1c at or nearest to 6 months from diagnosis	**LMR**: 0.9% (10mmol/mol) increase at 6 month HbA1c was associated with 0.5% (0.4-0.6%) or 5.3mmol/mol (4.5-6.2) increase at all subsequent time points (95% CI: p<0.001) A 2.4% (1.1 to 3.6%) or 26 mmol/mol (12 to 39) increase in HbA1c was seen at 10 year f/u in patients from highest 6 months HbA1c quintile (8.6 vs 6.2% or 94 vs 68mmol/mol) p<0.001 Cross-correlation coefficients for 6-months HbA1c on linear and	++ Significant mean HbA1c levels and shape of trajectories after adjusting for patient and observation level predictors. ++A higher 6 month HbA1c was associated with slow but sustained HbA1c deterioration with T1D duration as compared to lower 6 month HbA1c Time independent variables significantly associated with poorer glycaemic control were age at diagnosis, living with <2 biological parents, proximity to urban clinic, neighbourhood deprivation, child with	Intermediate (4) Retrospective study design. Non-rep - excluded patients with < 1 year f/u from diagnosis. Included only patients from North Scotland.

			40% patients lived in remote/rural areas.					quadratic growth identified sustained effects on trajectories of glycaemic control (p<0.001)	welfare concerns and with thyroid disease. Time dependent covariates: mental health problems, major adverse life events, clinic non- attendance, lower BMI SDS (particularly in girls), were associated with higher HbA1c levels.	Attrition rate was high (approx. 80%) at 10 year f/u
4	Shalitin 2012 Israel Jan 1999 – May 2009	Retrospective cohort Diabetes clinic database within a tertiary hospital - the National Center for Childhood Diabetes, Schneider Children's Medical Center of Israel.	**Generalizability:** Non rep **Sample size**: 173 pre-school aged children 0.5 to 6.5 years **Males** = 84 **Ethnicity**: Jews=84.4%, Arabs=12.1% and Ethiopian Jews=3.5% **SES:** only parental marital status reported **Family history of T1D**: NR Mean duration of diabetes: 4.9 ±2.8 years or median 4.3 (range 1 – 11 years)	0.5 – 17 years Mean age at diagnosis: 3.8 ± 1.6 years	0 – 7 years	All patients were advised on carbohydrate counting, required to perform self- blood glucose measurements at least 6 times/day and several different types of insulin regimen (multiple daily injections or continuous subcutaneous insulin infusion) were used.	HbA1c trends (in patients with <7.5% (n=53) and ≥7.5% (n=120) HbA1c) and association with HbA1c at onset Capillary HbA1c measured every 3 months by automated immunochemical technique using Bayer DCA 2000; reference range 4.3 – 5.8%. During f/u: HbA1c <7.5% : n=53 (30.6% patients) HbA1c ≥7.5% : n=120 (69.4% patients) Attrition rate	HbA1c at T1D onset	**MLRA:** OR=0.44; 95% CI0.26-0.72; p=0.002 and OR=0.09; 95% CI 0.04-0.24; P<0.001 for every 1% increase in HbA1c at 0.5 and 1 year after T1D onset. **HbA1c in patients with <7.5% :** At onset: 9.5 ±2.1 (n=53) At 0.5 years after onset: 6.8 ±0.9 (n=53) At 1 years after onset: 7.0 ±0.6 (n=53) At 2 years after onset: 7.1 ±0.5 (n=42) At 3 years after onset: 7.1 ±0.5 (n=37) At 4 years after onset: 7.2 ±0.6 (n=26) At 5 years after onset: 6.8 ±0.5 (n=14) At 6 years after onset: 6.8 ±0.3 (n=11) At 7 years after onset: 6.9 ±0.3 (n=4) HbA1c at last visit: 7.3±0.7 **HbA1c in patients with >7.5% :** At onset: 10.2 ±1.8 (n=120) At 0.5 years after onset: 8.3 ±1.2 (n=120) At 1 years after onset: 8.4 ±0.9 (n=120) At 2 years after onset: 8.3 ±0.8 (n=98) At 3 years after onset: 8.4 ±0.8 (n=79) At 4 years after onset: 8.4 ±0.8 (n=68)	++ Lower HbA1c values at 0.5 and 1 year after T1D onset, predicted achievement of HbA1c target of <7.5%. ++ comparison of HbA1c between below target and above <7.5% target in patients was significant ++ Patients with celiac disease (n=21) had lower mean HbA1c compared to those without (n=152). 7.5 ±0.8% vs 8.0 ±0.8%, p=0.01 + children from single parent family and those with more DKA events had higher HbA1c levels, but this was not statistically significant There were no statistically significant differences between groups in Gender, ethnicity, age at diagnosis, presence of diabetes antibodies, and presence of DKA at onset, mean number of SBGM and insulin regimen type (MDI or CSSII).	Intermediate (3) retrospective study design; non-representative child population. Children < 0.5 years and >6.5 years at baseline not included, analyses. Attrition rate was 62, 66 and 73% at 5, 6 and 7 year f/u respectively.

						was 62, 66 and 73% at 5, 6 and 7 year f/u respectively.		At 5 years after onset: 8.4 ±0.9 (n=57) At 6 years after onset: 8.4 ±0.9 (n=47) At 7 years after onset: 8.3 ±1.0 (n=42) HbA1c at last visit:8.4±1.0		
5	Cabrera 2013 USA 1998 –2002	Retrospective cohort Electronic clinical database of the Section of Pediatric Endocrinology/Diabetology at Riley Hospital for Children, Indiana, USA	**Generalizability:** Rep **Sample size**: 138 children 1.1 – 13.9 year old **Males** = 71 **Ethnicity**: white=91.5%, other=8.5% **SES:** parental marital status and insurance type reported **Family history of T1D**: NR Mean duration of diabetes: 5 years	1.1 – 13.9 years Mean age at diagnosis: 6.8 ± 3.3 years	0 – 5 years	Patients with initial T1D education from academic medical center (AMC) V/S non-AMC patients Insulin therapy: NR	HbA1c levels at 0, 2, 3 and 5 years after diagnosis in AMC v/s non AMC referred patients. Initial A1C by either by Bayer DCA2000 or by HPLC at the central lab. All patients subsequently had their A1C determined by the Bayer DCA2000 at follow-up clinic visits. A1C levels were obtained from the records of subsequent clinic visits, and mean A1C was calculated for years 2, 3, and 5	HbA1c at T1D onset	**Mean (SE):** At diagnosis: 9.53(0.24) **GEE Mean(SE):** at 2 years: 8.81(0.09) at 3 years:8.94(0.12) at 5 years: 8.84(0.12) **Correlations of A1C values over time for all individual patients (p<0.001)** Change from 2 to 3 years (n=130): 0.648 Change from 2 to 5 years (n=130): 0.524 Change from 3 to 5 years (n=138): 0.520	The A1C was also highly consistent in each patient over time. / Long-term glycaemic control was independent of whether initial education was delivered at an AMC or non-AMC. / Formal education and location at time of diagnosis do not appear to play a significant role in long-term glycaemic control.	Intermediate (4) retrospective study design; analyses. Attrition rate appears to be 8 at 2 and 3 years

						from date of diagnosis.				

T1D: Type 1 diabetes; NON REP: Non representative of general population; SD: standard deviation; BMI SDS: Body mass index standard deviation score; PA: physical activity; MVLR: Multivariate linear regression; LMR: linear multilevel regression; MLRA: Multiple logistic regression Analysis; GEE: Generalised estimating equation; CI: confidence intervals; LR: logistic regression; OR: Odds ratio; ++: statistically significant positive association; + or - : statistically non- significant positive or negative association

Table 2: Summary of pooled standardised mean differences in HbA1c levels between low and high HbA1c groups

	MA with all 4 studies			**Sensitivity MA (after excluding study in pre-school children)**		
T1D duration	**SMD (95% CI)**	**HbA1c % (95% CI)**	**Heterogeneity (I^2)**	**SMD (95% CI)**	**HbA1c % (95% CI)**	**Heterogeneity (I^2)**
after 6 months of T1D diagnosis	-1.25 (-1.53, -0.97)	-2.28% (-2.79%, -1.77%)	0.0%, p=0.41	-1.10 (-1.56, -0.65)	-2.37% (-3.35%, -1.40%)	0.0%, p=0.01
after 1 year of T1D diagnosis	-0.85 (-0.95, -0.75)	-2.02% (-3.06%, -0.97%)	91.0%, p=0.001	-0.79 (-0.89, -0.69)	-1.74% (-1.96%, -1.52%)	0.0%, p=0.61
after 2 years of T1D diagnosis	-0.84 (-0.95, -0.74)	-1.76% (-2.63%, -0.90%)	87.8%, p=0.001	-0.78 (-0.89, -0.67)	-1.48% (-1.69%, -1.27%)	0.0%, p=0.73
after 3 years of T1D diagnosis	-0.78 (-0.89, -0.66)	-1.75% (-2.80%, -0.70%)	90.5%, p=0.001	-0.71 (-0.83, -0.59)	-1.48% (-1.73%, -1.23%)	0.0%, p=0.93
after 5 years of T1D diagnosis	-0.44 (-0.54, -0.34)	-1.25% (-2.03%, -0.48%)	90.9%, p=0.001	-0.41 (-0.73, -0.09)	-0.90% (-1.60%, -0.20%)	85.7%, p=0.001
after 7 years of T1D diagnosis	-0.75 (-0.94, -0.55)	-1.19% (-1.62%, -0.74%)	16.6%, p=0.30	-0.72 (-0.92, -0.53)	-1.48% (-1.89%, -1.09%)	0.0%, p=0.40
after 10 years of T1D diagnosis	-0.32 (-0.63, -0.02)	-0.95% (-1.87%, -0.06%)	0.0%, p=0.67	-0.32 (-0.63, -0.02)	-0.95% (-1.87%, -0.06%)	0.0%, p=0.67

MA: Meta-analysis; SMD: standardised mean difference, T1D: Type 1 diabetes; HbA1c: Glycated Haemoglobin