Running title Page

Short running title: Predictors of early HbA1c in childhood onset T1D.

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Title Page

Predictors of glycemic control in the first year of diagnosis of childhood onset type 1 diabetes: A systematic review of quantitative evidence.

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Abstract and key word page

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ABSTRACT

Background: Early glycemic control is associated with reduced future vascular complications risk in type 1 diabetes (T1D).

Objective: To systematically review evidence on the predictors of glycemic control within 12 months of diagnosis of childhood onset T1D.

Study design: Inclusion criteria for the electronic search were: interventional and observational studies that assessed and quantified an association between the predictor and glycemic control within 12 months of diagnosis of childhood onset T1D. 17,915 articles were identified from six databases and 20 studies were finally included in the analysis. Harvest plots and narrative synthesis were used to summarize data from intervention (n=0), prospective/retrospective cohort (n=15) and cross-sectional (n=5) studies.

Results: Significant predictors of poorer glycemic control 0-3 months after diagnosis were older age and female gender. Non-white ethnicity, diabetes autoantibody positivity, measures of deprivation and non-private health insurance were potential predictors. Predictors of poorer glycemic control 4 to 12 months after diagnosis were: older age, non-white ethnicity, a single parent family, high HbA1c levels at diagnosis, longer T1D duration and non-intensive insulin therapy. Potential predictors included: family with health issues, clinic factors and co-morbidities at diagnosis.

Conclusions: Most significant predictors of poor glycemic control within twelve months of diagnosis of childhood onset T1D are non-modifiable. These factors need to be recognized and addressed through individualized and multidisciplinary diabetes care. Further research is required to confirm the association of potential predictors with early glycemic control.

PROSPERO registration: CRD42015024546 http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015024546

Key words: Predictors, HbA1c, early glycemic control, type 1 diabetes, children

INTRODUCTION

Poor glycemic control in the first months following the diagnosis in childhood onset Type 1 Diabetes (T1D) tracks in subsequent years (1-4) and is associated with elevated risk of vascular complications in later life (5-11). However, achieving target blood glucose and HbA1c levels during the first few appointments in pediatric diabetes clinics remains a challenge and is not always the focus of discussions with family members (12-14).

Recent systematic reviews have shown that achieving lower HbA1c levels at early stages of the disease through use of intensive insulin therapies in adult T1D patients was beneficial in reducing subsequent vascular complications risk and mortality (15, 16). But these associations and other factors influencing early glycemic control have not been clearly reported in pediatric populations (17-21) .

The aim of our systematic review is therefore to investigate the predictors of glycaemic control in paediatric T1D populations in the first 12 months following diagnosis. The outcomes from our analyses may enable diabetes healthcare practitioners to consider a more focused and individualized approach to achieving HbA1c targets in the early months following the diagnosis of T1D in children and young people.

METHODS

This review is part of a series of systematic reviews of evidence on the determinants and influence of early glycemic control in childhood onset T1D (International Prospective Register for Systematic Reviews -PROSPERO Registration number: CRD42015024546). The study design for the linked reviews is outlined in the published protocol (22). Review methods used are as described by the Evidence for Policy and Practice Information (EPPI) Centre for the rigorous conduct and reporting of systematic reviews for policy and practice (23).

Search strategy, inclusion/exclusion and quality assessment criteria

The search strategy for the linked reviews was designed in consultation with experts after initial iterative scoping searches, to maximize sensitivity and specificity in capturing relevant publications. Three sets of search terms were used relating to population (children and young people diagnosed with TID), exposure (terms to capture observational, intervention, qualitative studies and review articles relating to early diabetes control) and outcome (complications, mortality, change in glycemic levels or metabolic memory). Six electronic databases were double searched in parallel (VMP & HC), from inception to December 2014, without time period or language restrictions, by using a combination of free text and Thesaurus or MeSH (Medical Subject Headings) terms (supplementary table S1). This was supplemented by hand-searching reference lists and contacting authors of included and relevant studies which resulted in identifying nine (24-32) additional studies.

For this review, we defined early glycemic control as HbA1c levels within the first 12 months (subdivided into 0-3 months and 4-12 months) of T1D diagnosis as: 1) mean blood glucose concentrations fall dramatically in the first 3 months after diagnosis following the introduction of insulin therapy and thereafter tend to stabilize (33), 2) blood glucose concentrations during 0-3 months may partly reflect factors that relate to pre-diagnosis, such as access to healthcare, whereas the 4-12 month time period may include factors such as clinic expertise and insulin regimens, 3) diabetes clinics tend to gather and review clinical data of T1D patients at quarterly visits.

Studies that described and quantified the association between early glycemic control AND predictors of early glycemic control in children and young people aged 0 to 19 years at baseline were included (supplementary table S2). We excluded studies of non-humans, populations selected for other diseases; adults aged ≥19 years at baseline and other types of diabetes. We also excluded studies not reporting clinical outcomes or not describing an association with outcomes.

The quality assessment criteria (supplementary table S3) were based on methods described by the EPPI Centre (23) where observational studies were scored based on six items focusing on both internal and external validity. Studies were classified as high, intermediate or low quality based on the number of quality criteria met (for observational studies: low: ≤2; intermediate: 3–4; high: ≥5).

Study selection

To ensure high level of agreement and to minimize reviewer-related biases, a sample of titles, abstracts and articles were double screened (DC, RA and VMP). Full texts of abstracts appearing to meet the inclusion criteria were retrieved for further review and their inclusion/exclusion status was recorded. No foreign language papers were identified. Articles were re-examined (DC, RA and VMP) if there was uncertainty about inclusion criteria and disagreements were resolved at team meetings.

Data extraction

Studies meeting inclusion criteria were quality assessed, data extracted and analyzed by one reviewer (VMP). For quality assurance, all shortlisted studies were double reviewed, data extracted and analyzed by a second reviewer (DC and RA).

For observational studies details of the predictor were extracted and the results were stratified by study design. From prospective or retrospective cohort studies, the association between the predictor and HbA1c at follow up points (from baseline) within 12 months of diagnosis was extracted. For cross sectional studies (XS), the association between the predictor and HbA1c at the reported time point was extracted (supplementary table S4).

Data Synthesis

Data was not meta-analyzed due to heterogeneity between studies and due to the potential influence of exposure on the wider determinants of health outcomes. However, we endeavored to synthesize the complex and diverse evidence graphically in a way similar to a forest plot. Evidence on the direction and strength of the association of predictors and correlates of early glycemic control was summarized using the harvest plot format, which allow a summary of data that cannot be incorporated in a forest plot meta-analysis (34). The harvest plot combines data from several studies and displays the study size, quality and design in addition to demonstrating the effect and direction of the association.

Each harvest plot bar (Figures 2a and 2b) represents a study. Some observational studies reported results of more than one predictor or correlate and were accordingly plotted. Predictors and correlates were grouped based on type (Demographic, biological, behavioral, psychosocial and healthcare). The numerical and alphabetical study id symbol above the bar represents the prospective/retrospective cohort studies and XS studies respectively. The color (black, dark grey and light grey) of bar represented quality of study, with lighter bars representing studies of low quality. The height of bar indicates the study size (small: n <100, medium: 100 to 999, tall: ≥1000) and its position summarizes the direction and strength (statistical significance) of the association (+, 0, -). Statistically non-significant + and - associations were colour-coded in red and blue respectively and grouped under ‘0’. Categorical

and continuous outcome variable results within studies were consistently recoded, such that a + symbolizes higher risk for poor glycemic control and a - symbolizes a lower risk for poor HbA1c levels (35, 36). The weight of the findings between studies was further summarized non-quantitatively as done previously (37, 38), to indicate the significance and greater confidence in the results; where three or more studies consistently reported the direction of the association of a potential predictor.

RESULTS

Search results

The identified articles from individual databases (Medline via OVID, n = 13,039; Embase via OVID, n = 645; Web of Science via Thompson Reuters, n = 2,323; CINAHL via EBSCO, n = 984; Scopus via Elsevier, n = 1,540 and Cochrane library, n = 3,242) were imported into an Endnote file and de-duplicated, which resulted in 17,915 articles for further review. No interventional studies met the inclusion criteria. 20 observational studies were included in the review (Figure 1).

Observational (Cohort and XS) studies characteristics and quality

Evidence from observational (longitudinal cohort: n=15 and XS: n=5) studies, published between 1987 and 2015, have been summarized in supplementary tables S5 and S6 respectively. The observational studies were of high or intermediate quality. Six cohort studies provided high quality evidence (25, 26, 28-30, 32, 39, 40) and fourteen studies (longitudinal: n=9 (27, 31, 41-47) and XS: n=5 (2, 4, 24, 48-50)) provided intermediate quality evidence. None of the studies were of low quality.

There was vast heterogeneity between included studies in terms of study (population, design), outcome (measure, analyses) and follow-up. 10/15 of the longitudinal studies included in our review reported a single HbA1c outcome each during the 0-3 months or 4-12 months follow-up period after diagnosis. 5/15 studies reported more than one HbA1c measurement during the first 12 months of diagnosis as follows: One study reported HbA1c outcome monthly for 12 months (40), another reported monthly for first three months and quarterly thereafter (27). Two further studies reported at 6 and 12 months (45, 47), whereas Sochett et al reported follow-up at 10 days, 1, 3, 6 and 12 months after diagnosis (31). However, for the purpose of this review, from these five studies, only the reported HbA1c outcome values, at or nearest to 3 or 12 months post diagnosis was included in our report.

Geographical mapping and population characteristics of included studies

Eight studies were conducted in USA (24-27, 30, 43-46, 49), one each in Canada (31) and New Zealand (39) and ten in Europe (four (4, 32, 48, 50) from Sweden, two (2, 41) from the UK, one each from Switzerland (47) and Italy (42), one involving seven European countries (28, 29) and one (40) involving 15 European countries and Japan). The total number of participants was approximately 30,818 (longitudinal cohort: 15,975 and XS: 14,843, range 30 (41) to 8190 (50)). Five of the prospective cohort studies had less than 100 participants (31, 41, 45-47). The age range of study population was 0 to 18 years (28, 32, 41, 48).Three studies excluded pre-school aged children (4, 46, 47). Six observational studies (cohort: n=4 (40, 43, 46, 47) and XS: n=2 (2, 4)) were non representative of the general population as they included certain categories of children based on age, ethnicity, mother tongue and T1D duration. Included studies investigated various predictors and correlates of glycemic control in the first year of T1D diagnosis, using a variety of outcome measures.

Predictors and correlates of glycemic control during the first year of diagnosis

0-3 months after diagnosis of T1D (Figure 2a)

Older age (4, 30, 40, 43, 45, 48, 50) and female gender (30, 32, 41, 48, 50) were studied by more than five studies and were significantly associated with poor glycaemic control. At least two out of three studies reported associations with: non-white ethnicity (25, 30), autoantibody positivity (24, 40, 49), measures of deprivation or low socioeconomic status (SES) (25) and non-private health insurance (25, 44). Two studies reported an association with HbA1c diagnostic testing strategies pre 2004 (30) and a spring season of diagnosis (32).

One out of three studies reported an association (24, 49) with C-peptide concentration at diagnosis while two reported no association (28, 31). Evidence on the asssociation with single parent family (25), child's body mass index (BMI) (24, 41, 43, 49, 50), acidosis at diagnosis (43, 50), parental/child's behaviour (47) and clinic factors (25, 43) were insufficient or inconsistent.

4-12 months after diagnosis of T1D (Figure 2b)

Older age (4, 40, 43), non-white ethnicity (25, 39, 40), single parent family (2, 25, 46), high HbA1c levels at diagnosis (40, 42, 43), increasing T1D duration (40, 42, 44, 47) and conventional insulin regimen (no insulin pump used) (25, 43, 44) were each studied by three or more studies and were strongly associated with poor glycaemic control 4-12 months after diagnosis.

Gender (25, 40, 43, 45, 47), C-peptide concentrations (28, 31, 40) and ketoacidosis (25, 40, 43) at diagnosis were not associated with glycaemic control during this period. The role of health insurance (25, 43, 44), SES (2, 39, 47), BMI (2, 25, 40, 41, 43, 44), autoantibody positivity (25), comorbidities (coeliac, thyroid or other disease) (2), child's/parental behaviour (47), parental ill health (2, 39) and clinic factors (2, 25) are unclear due to inconsistentcy of reporting associations or poor evidence.

DISCUSSION

We systematically investigated predictors of glycemic control at 0-12 months following the diagnosis of childhood onset T1D. The identified evidence came from observational studies published between 1987 and 2015 and from more economically developed countries. There have been no interventional studies of these predictors of glycemic control, emphasizing the utility of synthesizing appropriate evidence from a variety of relevant study designs. Also, there was an inconsistency of time points of the reported associations across studies. Furthermore, the associations between predictor and outcomes reported by observational studies should be interpreted with caution as they do not imply causal relationships. However, harvest plot analyses allowed us to meaningfully combine such studies and demonstrate the strength (number of studies supporting the association) and direction (positive or negative) of the associations.

Our review found that older age at diagnosis (>10 years) was associated with poorer glycemic control throughout the first year of diagnosis. This may relate to a complex interaction of factors such as increased insulin resistance (51) and psychosocial changes such as decreased adherence to management plans that occur during adolescence (52).

Female gender was consistently reported by more than five longitudinal studies (4, 30, 32, 41, 48, 50) to be associated with poor early glycaemic control, within first three months of diagnosis, as opposed to no association reported by five out of eight studies after this time period (25, 40, 43, 45, 47). If genuine, this association may partly relate to reduced insulin sensitivity during puberty (53), increased insulin omission, eating disorders and greater psychological disturbances (51, 54, 55) in females compared to males.

The associations between ethnicity (25, 30, 39, 40), low SES (2, 25, 39) and children not living with biological parents (2, 25, 46) and poor early glycemic control is consistent with other studies that did not meet our review inclusion criteria (56-62). The association

between ethnicity and glycemic control may be related to differences in cultural and lifestyle patterns (63), sub-optimal treatments and resistance to changing to new therapies (56) and reduced use of insulin pump therapy (64). Other studies have also shown biological differences between ethnic groups relating to hemoglobin glycation (65, 66).

Higher HbA1c levels at diagnosis were consistently associated with poorer early glycemic control 4-12 months after T1D diagnosis. DKA and higher HbA1c may indicate a delay in the diagnosis of T1D and a later presentation to medical services (67, 68). There have been attempts to increase public and primary care awareness of the symptoms of T1D and the ease of diagnostic tests (69). However government directed initiatives may be required to ensure genuine change in practice and behaviors.

We found that most studies reported no association between C-peptide concentrations and early glycaemic control and this may reflect methodological differences in its measurement. Low C-peptide concentrations as a measure of low endogenous insulin secretion (70) may represent a more aggressive autoimmune destruction of pancreatic beta cells (71) and are associated with higher mean HbA1c levels and future vascular complications (72, 73). These disparities require further investigation.

Our review indicates that the type and dosage of insulin regimen were strong predictors of glycemic control. Absence of pump therapy (43, 44), an insulin dose ≥0.8/kg/day (25) and lower frequency of daily self-monitored blood glucose tests per day (25) were associated with poorer early glycemic control. A complicating factor in interpreting these observations is that earlier use of intensive diabetes therapy may also reflect a category of patients who have a shorter honeymoon period and/or more severe phenotype. It would be important to investigate whether any benefit of early intensive diabetes management through improved HbA1c levels tracks in later years and results in reduced vascular complications risk.

Children with parental health problems and with family history of T1D, had poorer glycemic control (2, 39) which may be due to inherent genetic predisposition to adverse health outcomes (74), but also more likely to be due to behavioral predisposition or behavioral factors such as parental worry about hypoglycemia.

Evidence on the association between clinic factors and early glycemic control was inconclusive (2, 25, 43). Studies have indicated that diabetes teams play a significant role in achieving glycemic targets (75, 76). It is unclear if people with T1D living closer to their diabetes clinic are more likely to attend clinic than those living further away. Non-attendance is associated with poorer adherence to treatment regimens and an elevated risk for diabetes complications (77, 78) particularly in ethnic minorities and those from lower SES in countries with healthcare systems based on the out-of-pocket model. These patients tend to have higher HbA1c and other markers of future vascular diseases and therefore clinic factors needs further investigation.

Two out of three USA based longitudinal studies found that non-private health insurance was significantly associated with poor glycaemic control in the first year of diagnosis (25, 44). Parental and child's behavior in relation to early glycemic control needs further investigation as these were subjectively investigated by one prospective study (47). Month and season of diagnosis in children was associated with early glycemic control and mean HbA1c at diagnosis was observed to be highest in May and lowest in October (32). The mechanisms that explain these associations are unclear and require further investigation.

Strengths and limitations of the review

To our knowledge, this is the first review to robustly investigate published literature on the predictors and correlates of early glycemic control in childhood onset T1D. Furthermore, strict published pre-set systematic review procedures have been adhered to throughout

the process. No period restrictions were applied to literature search strategy and included studies were published between 1987 and 2015 suggesting the encompassment of thorough and up-to-date research in this area. We have taken utmost care to minimize study selection, reviewer related bias. However, publication bias cannot be ruled out. We were unable to meta-analyze the systematically gathered evidence or measure the effect of each predictor in reducing or increasing the HbA1c levels during the first year of diagnosis. However, our review included observational studies and encountered heterogeneity across the studies (varied demographics of the study population, study setting, quality, designs, analyses, outcome and follow-up measures), allowing us to display the details of these differences graphically through harvest plots. The overall quality of the included observational studies was intermediate or high and most of the results from the studies are generalizable, but all of the associations between predictors and outcome cannot be interpreted as showing causal relationships, due to the limitations of the study designs.

CONCLUSIONS AND IMPLICATIONS FOR POLICY/PRACTICE/FURTHER RESEARCH

Quantitative evidence identified characteristics of children with T1D who are at high risk of poor early glycemic control. Characteristics such as age, gender, BMI, ethnicity and SES are not modifiable, however they do help in identifying those children and young people with T1D at high risk, for whom individualized care plans can be put in place to ensure early target HbA1c levels are attained. Biomarkers potentially indicating a delay in diagnosis of T1D (higher HbA1c and DKA at presentation) appear to be associated with poorer subsequent glucose control. Suboptimal glycemic control has been shown to track and therefore puts children at higher risk of developing complications. Intensive insulin therapy has shown beneficial effect in glycemic control during the first year of diagnosis, so implementation of updated clinical practice guidance would be advantageous.

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

T1D: Type 1 diabetes

HbA1c: Hemoglobin A1c

PROSPERO: International Prospective Register for systematic Reviews

EPPI: Evidence for Policy and Practice Information

BMI: Body mass index

SES: Socio economic status

DKA: Diabetic ketoacidosis

DCCT: The Diabetes Control and Complications Trial

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, created the search strategy, searched electronic databases for literature, extracted and analyzed the data and wrote the manuscript. RA was project lead, advised on the trajectories of the project, double reviewed all shortlisted papers and helped revise the manuscript. DC double screened a proportion of titles/abstracts, double reviewed all shortlisted papers and helped revise the manuscript. JE advised on the trajectories of the project, participated in the study design, commented on the results and helped revise the manuscript. TS was overall programme lead, advised on the trajectories of the project, participated in the study design and helped revise the manuscript. DTR participated in the study design, commented on the review methodology 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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REFERENCES

1. Edge JA, James T, Shine B. Persistent individual tracking within overall improvement in HbA1c in a UK paediatric diabetes clinic over 15 years. Diabetic medicine : a journal of the British Diabetic Association. 2010;27(11):1284-8.
2. Lawes T, Franklin V, Farmer G. HbA1c tracking and bio-psychosocial determinants of glycaemic control in children and adolescents with type 1 diabetes: retrospective cohort study and multilevel analysis. Pediatric diabetes. 2014;15(5):372 - 83.
3. Hofer SE, Raile K, Frohlich-Reiterer E, Kapellen T, Dost A, Rosenbauer J, et al. Tracking of metabolic control from childhood to young adulthood in type 1 diabetes. J Pediatr. 2014;165(5):956-61.e1-2.
4. Samuelsson U, Steineck I, Gubbjornsdottir S. A high mean-HbA1c value 3-15 months after diagnosis of type 1 diabetes in childhood is related to metabolic control, macroalbuminuria, and retinopathy in early adulthood--a pilot study using two nation-wide population based quality registries. Pediatric diabetes. 2014;15(3):229-35.
5. Meigs JB, Nathan DM, Cupples LA, Wilson PW, Singer DE. Tracking of glycated hemoglobin in the original cohort of the Framingham Heart Study. Journal of clinical epidemiology. 1996;49(4):411-7.
6. Hamman RF, Bell RA, Dabelea D, D'Agostino RB, Jr., Dolan L, Imperatore G, et al. The SEARCH for Diabetes in Youth study: rationale, findings, and future directions. Diabetes care. 2014;37(12):3336-44.
7. Rosenbauer J, Dost A, Karges B, Hungele A, Stahl A, Bachle C, et al. Improved metabolic control in children and adolescents with type 1 diabetes: a trend analysis using prospective multicenter data from Germany and Austria. Diabetes care. 2012;35(1):80-6.
8. Petitti DB, Klingensmith GJ, Bell RA, Andrews JS, Dabelea D, Imperatore G, et al. Glycemic control in youth with diabetes: the SEARCH for diabetes in Youth Study. J Pediatr. 2009;155(5):668-72.e1-3.
9. Dabadghao P, Vidmar S, Cameron FJ. Deteriorating diabetic control through adolescence-do the origins lie in childhood? Diabetic medicine : a journal of the British Diabetic Association. 2001;18(11):889-94.
10. Dovc K, Telic SS, Lusa L, Bratanic N, Zerjav-Tansek M, Kotnik P, et al. Improved metabolic control in pediatric patients with type 1 diabetes: a nationwide prospective 12-year time trends analysis. Diabetes technology & therapeutics. 2014;16(1):33-40.
11. Orchard TJ, Nathan DM, Zinman B, Cleary P, Brillon D, Backlund JY, et al. Association between 7 years of intensive treatment of type 1 diabetes and long-term mortality. Jama. 2015;313(1):45-53.
12. Wherrett DK, Chiang JL, Delamater AM, DiMeglio LA, Gitelman SE, Gottlieb PA, et al. Defining Pathways for Development of Disease-Modifying Therapies in Children With Type 1 Diabetes: A Consensus Report. Diabetes care. 2015;38(10):1975-85.
13. Miller KM, Foster NC, Beck RW, Bergenstal RM, DuBose SN, DiMeglio LA, et al. Current state of type 1 diabetes treatment in the U.S.: updated data from the T1D Exchange clinic registry. Diabetes care. 2015;38(6):971-8.
14. RCPCH. National Paediatric Diabetes Audit Report 2012-13. Care processes and outcomes 2014. Available from: http://www.rcpch.ac.uk/system/files/protected/page/NPDA%202012-13%20Core%20Report%202nd%20FINAL%20v%203.3.pdf.
15. Fullerton B, Jeitler K, Seitz M, Horvath K, Berghold A, Siebenhofer A. Intensive glucose control versus conventional glucose control for type 1 diabetes mellitus. Cochrane Database Syst Rev. 2014;2:Cd009122.
16. Kahler P, Grevstad B, Almdal T, Gluud C, Wetterslev J, Lund SS, et al. Targeting intensive versus conventional glycaemic control for type 1 diabetes mellitus: a systematic review with meta-analyses and trial sequential analyses of randomised clinical trials. BMJ open. 2014;4(8):e004806.
17. Shah SC, Malone JI, Simpson NE. A randomized trial of intensive insulin therapy in newly diagnosed insulin-dependent diabetes mellitus. The New England journal of medicine. 1989;320(9):550-4.
18. Hershey T, Bhargava N, Sadler M, White NH, Craft S. Conventional versus intensive diabetes therapy in children with type 1 diabetes: effects on memory and motor speed. Diabetes care. 1999;22(8):1318-24.
19. Franklin VL, Khan F, Kennedy G, Belch JJ, Greene SA. Intensive insulin therapy improves endothelial function and microvascular reactivity in young people with type 1 diabetes. Diabetologia. 2008;51(2):353-60.
20. Perlman K, Ehrlich RM, Filler RM, Albisser AM. Sustained normoglycemia in newly diagnosed type I diabetic subjects. Short-term effects and one-year follow-up. Diabetes. 1984;33(10):995-1001.
21. Wysocki T, Harris M, Wilkinson K, Sadler M, Mauras N, White N. Self-management competence as a predictor of outcomes of intensive therapy or usual care in youth with type 1 diabetes. Diabetes care. 2003;26(7):2043 - 7.
22. Mazarello Paes V, Charalampopoulos D, Khanolkar A, Taylor-Robinson D, Viner R, Edge J, et al. Protocol for systematic review of evidence on the determinants and influence of early glycaemic control in childhood-onset type 1 diabetes. Systematic Reviews. 2015;4(1):159.
23. EPPI. Evidence for Policy and Practice Information (EPPI) and Co-ordinating Centre IoE, University of London. EPPI -Centre Methods for Conducting Systematic Reviews. March 2007, Updated 2010; http://eppi.ioe.ac.uk/cms/LinkClick.aspx?fileticket=hQBu8y4uVwI%3d&tabid=1919&mid=6163. 2007.
24. Redondo MJ, Rodriguez LM, Escalante M, Smith EO, Balasubramanyam A, Haymond MW. Types of pediatric diabetes mellitus defined by anti-islet autoimmunity and random C-peptide at diagnosis. Pediatric diabetes. 2013;14(5):333-40.
25. Redondo MJ, Connor CG, Ruedy KJ, Beck RW, Kollman C, Wood JR, et al. Pediatric Diabetes Consortium Type 1 Diabetes New Onset (NeOn) Study: factors associated with HbA1c levels one year after diagnosis. Pediatric diabetes. 2014;15(4):294-302.
26. Cengiz E, Connor C, Ruedy K, Beck R, Kollman C, Klingensmith G. Pediatric diabetes consortium T1D new onset (NeOn) study: clinical outcomes during the first year following diagnosis. Pediatric diabetes. 2014;15(4):287 - 93.
27. Chase HP, MacKenzie TA, Burdick J, Fiallo-Scharer R, Walravens P, Klingensmith G, et al. Redefining the clinical remission period in children with type 1 diabetes. Pediatric diabetes. 2004;5(1):16-9.
28. Barker A, Lauria A, Schloot N, Hosszufalusi N, Ludvigsson J, Mathieu C, et al. Age-dependent decline of beta-cell function in type 1 diabetes after diagnosis: a multi-centre longitudinal study. Diabetes, obesity & metabolism. 2014;16(3):262-7.
29. Lauria A, Barker A, Schloot N, Hosszufalusi N, Ludvigsson J, Mathieu C, et al. BMI is an important driver of beta-cell loss in type 1 diabetes upon diagnosis in 10 to 18-year-old children. European journal of endocrinology / European Federation of Endocrine Societies. 2015;172(2):107-13.
30. Clements MA, Lind M, Raman S, Patton SR, Lipska KJ, Fridlington AG, et al. Age at diagnosis predicts deterioration in glycaemic control among children and adolescents with type 1 diabetes. BMJ open diabetes research & care. 2014;2(1):e000039.
31. Sochett EB, Daneman D, Clarson C, Ehrlich RM. Factors affecting and patterns of residual insulin secretion during the first year of type 1 (insulin-dependent) diabetes mellitus in children. Diabetologia. 1987;30(7):453-9.
32. Hanberger L, Akesson K, Samuelsson U. Glycated haemoglobin variations in paediatric type 1 diabetes: the impact of season, gender and age. Acta Paediatr. 2014;103(4):398-403.
33. Shalitin S, Phillip M. Which factors predict glycemic control in children diagnosed with type 1 diabetes before 6.5 years of age? Acta diabetologica. 2012;49(5):355-62.
34. Ogilvie D, Fayter D, Petticrew M, Sowden A, Thomas S, Whitehead M, et al. The harvest plot: A method for synthesising evidence about the differential effects of interventions. BMC Medical Research Methodology. 2008;8(1):8.
35. Lakshman R, Mazarello Paes V, Hesketh K, O'Malley C, Moore H, Ong K, et al. Protocol for systematic reviews of determinants/correlates of obesity-related dietary and physical activity behaviors in young children (preschool 0 to 6 years): evidence mapping and syntheses. Systematic reviews. 2013;2:28.
36. Wijndaele K, Lakshman R, Landsbaugh JR, Ong KK, Ogilvie D. Determinants of early weaning and use of unmodified cow's milk in infants: a systematic review. Journal of the American Dietetic Association. 2009;109(12):2017-28.

37. Mazarello Paes V, Hesketh K, O'Malley C, Moore H, Summerbell C, Griffin S. Determinants of sugar-sweetened beverage consumption in young children: a systematic review. Obes Rev. 2015;16(11):903 - 13.
38. Hinkley T, Crawford D, Salmon J, Okely AD, Hesketh K. Preschool children and physical activity: a review of correlates. American journal of preventive medicine. 2008;34(5):435-41.
39. Cutfield SW, Derraik JG, Reed PW, Hofman PL, Jefferies C, Cutfield WS. Early markers of glycaemic control in children with type 1 diabetes mellitus. PloS one. 2011;6(9):e25251.
40. Mortensen HB, Swift PG, Holl RW, Hougaard P, Hansen L, Bjoerndalen H, et al. Multinational study in children and adolescents with newly diagnosed type 1 diabetes: association of age, ketoacidosis, HLA status, and autoantibodies on residual beta-cell function and glycemic control 12 months after diagnosis. Pediatric diabetes. 2010;11(4):218-26.
41. Davis NL, Bursell JD, Evans WD, Warner JT, Gregory JW. Body composition in children with type 1 diabetes in the first year after diagnosis: relationship to glycaemic control and cardiovascular risk. Arch Dis Child. 2012;97(4):312-5.
42. Giordano C, Amato MC, Ciresi A, Citarrella R, Mantione L, Accidenti M, et al. Predictors of microvascular complications in type 1 diabetic patients at onset: the role of metabolic memory. European journal of internal medicine. 2011;22(3):266-74.
43. Viswanathan V, Sneeringer MR, Miller A, Eugster EA, DiMeglio LA. The utility of hemoglobin A1c at diagnosis for prediction of future glycemic control in children with type 1 diabetes. Diabetes research and clinical practice. 2011;92(1):65-8.
44. Beck JK, Lewis TV, Logan KJ, Harrison DL, Gardner AW, Copeland KC. Intensive vs. conventional insulin management initiated at diagnosis in children with diabetes: should payer source influence the choice of therapy? Pediatric diabetes. 2009;10(6):368-73.
45. Hochhauser CJ, Rapaport R, Shemesh E, Schmeidler J, Chemtob CM. Age at diagnosis, gender, and metabolic control in children with type 1 diabetes. Pediatric diabetes. 2008;9(4 Pt 1):303-7.
46. Frey MA, Templin T, Ellis D, Gutai J, Podolski CL. Predicting metabolic control in the first 5 yr after diagnosis for youths with type 1 diabetes: the role of ethnicity and family structure. Pediatric diabetes. 2007;8(4):220-7.
47. Vollrath ME, Landolt MA, Gnehm HE, Laimbacher J, Sennhauser FH. Child and parental personality are associated with glycaemic control in Type 1 diabetes. Diabetic medicine : a journal of the British Diabetic Association. 2007;24(9):1028-33.
48. Samuelsson U, Lindblad B, Carlsson A, Forsander G, Ivarsson S, Kockum I, et al. Residual beta cell function at diagnosis of type 1 diabetes in children and adolescents varies with gender and season. Diabetes/metabolism research and reviews. 2013;29(1):85-9.
49. Redondo MJ, Rodriguez LM, Escalante M, O'Brian Smith E, Balasubramanyam A, Haymond MW. Beta cell function and BMI in ethnically diverse children with newly diagnosed autoimmune type 1 diabetes. Pediatric diabetes. 2012;13(7):564-71.
50. Akesson K, Hanberger L, Samuelsson U. The influence of age, gender, insulin dose, BMI, and blood pressure on metabolic control in young patients with type 1 diabetes. Pediatric diabetes. 2015;16(8):581-6.
51. Amiel SA, Sherwin RS, Simonson DC, Lauritano AA, Tamborlane WV. Impaired insulin action in puberty. A contributing factor to poor glycemic control in adolescents with diabetes. The New England journal of medicine. 1986;315(4):215-9.
52. Bryden KS, Dunger DB, Mayou RA, Peveler RC, Neil HA. Poor prognosis of young adults with type 1 diabetes: a longitudinal study. Diabetes care. 2003;26(4):1052-7.
53. Peveler RC, Bryden KS, Neil HA, Fairburn CG, Mayou RA, Dunger DB, et al. The relationship of disordered eating habits and attitudes to clinical outcomes in young adult females with type 1 diabetes. Diabetes care. 2005;28(1):84-8.
54. Helgeson VS, Siminerio L, Escobar O, Becker D. Predictors of metabolic control among adolescents with diabetes: a 4-year longitudinal study. Journal of pediatric psychology. 2009;34(3):254-70.
55. Wisting L, Froisland DH, Skrivarhaug T, Dahl-Jorgensen K, Ro O. Disturbed eating behavior and omission of insulin in adolescents receiving intensified insulin treatment: a nationwide population-based study. Diabetes care. 2013;36(11):3382-7.
56. Thompson RJ, Agostini K, Potts L, Luscombe J, Christie D, Viner R, et al. Deprivation and ethnicity impact on diabetes control and use of treatment regimen. Diabetic medicine : a journal of the British Diabetic Association. 2013;30(4):491-4.
57. Fredheim S, Delli A, Rida H, Drivvoll AK, Skrivarhaug T, Bjarnason R, et al. Equal access to health care may diminish the differences in outcome between native and immigrant patients with type 1 diabetes. Pediatric diabetes. 2014;15(7):519-27.
58. Deladoey J, Henderson M, Geoffroy L. Linear association between household income and metabolic control in children with insulin-dependent diabetes mellitus despite free access to health care. J Clin Endocrinol Metab. 2013;98(5):E882-5.
59. Zuijdwijk CS, Cuerden M, Mahmud FH. Social determinants of health on glycemic control in pediatric type 1 diabetes. J Pediatr. 2013;162(4):730-5.
60. Carter PJ, Cutfield WS, Hofman PL, Gunn AJ, Wilson DA, Reed PW, et al. Ethnicity and social deprivation independently influence metabolic control in children with type 1 diabetes. Diabetologia. 2008;51(10):1835-42.
61. Kaufman FR, Halvorson M, Carpenter S. Association between diabetes control and visits to a multidisciplinary pediatric diabetes clinic. Pediatrics. 1999;103(5 Pt 1):948-51.
62. Overstreet S, Holmes CS, Dunlap WP, Frentz J. Sociodemographic risk factors to disease control in children with diabetes. Diabetic medicine : a journal of the British Diabetic Association. 1997;14(2):153-7.
63. Kummer S, Stahl-Pehe A, Castillo K, Bachle C, Graf C, Strassburger K, et al. Health behaviour in children and adolescents with type 1 diabetes compared to a representative reference population. PloS one. 2014;9(11):e112083.
64. Senniappan S, Hine P, Tang W, Campbell J, Bone M, Sankar V, et al. The effect of socioeconomic deprivation on efficacy of continuous subcutaneous insulin infusion: a retrospective paediatric case-controlled survey. European journal of pediatrics. 2012;171(1):59-65.
65. Ziemer DC, Kolm P, Weintraub WS, Vaccarino V, Rhee MK, Twombly JG, et al. Glucose-independent, black-white differences in hemoglobin A1c levels: a cross-sectional analysis of 2 studies. Annals of internal medicine. 2010;152(12):770-7.
66. Maruthur NM, Kao WH, Clark JM, Brancati FL, Cheng CY, Pankow JS, et al. Does genetic ancestry explain higher values of glycated hemoglobin in African Americans? Diabetes. 2011;60(9):2434-8.
67. Zucchini S, Scaramuzza AE, Bonfanti R, Buono P, Cardella F, Cauvin V, et al. A Multicenter Retrospective Survey regarding Diabetic Ketoacidosis Management in Italian Children with Type 1 Diabetes. Journal of diabetes research. 2016;2016:5719470.
68. Salardi S, Porta M, Maltoni G, Cerutti F, Rovere S, Iafusco D, et al. Ketoacidosis at diagnosis in childhood-onset diabetes and the risk of retinopathy 20years later. Journal of diabetes and its complications. 2016;30(1):55-60.
69. Diabetes UK: Do You Know The 4T's Of Type 1 Diabetes? 2016 https://www.diabetes.org.uk/the4TS.
70. Oram RA, Jones AG, Besser RE, Knight BA, Shields BM, Brown RJ, et al. The majority of patients with long-duration type 1 diabetes are insulin microsecretors and have functioning beta cells. Diabetologia. 2014;57(1):187-91.
71. Gan MJ, Albanese-O'Neill A, Haller MJ. Type 1 diabetes: current concepts in epidemiology, pathophysiology, clinical care, and research. Current problems in pediatric and adolescent health care. 2012;42(10):269-91.
72. Nathan D, Bayless M, Cleary P, Genuth S, Gubitosi-Klug R, Lachin J. Diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30years: advances and contributions. Diabetes. 2013;62(12):3976 - 86.
73. Lee TH, Kwon AR, Kim YJ, Chae HW, Kim HS, Kim DH. The clinical measures associated with C-peptide decline in patients with type 1 diabetes over 15 years. Journal of Korean medical science. 2013;28(9):1340-4.
74. Bizzarri C, Paladini A, Benevento D, Fierabracci A, Cappa M. Family history and ethnicity influencing clinical presentation of type 1 diabetes in childhood. Journal of endocrinological investigation. 2015;38(10):1141-3.
75. Swift PG, Skinner TC, de Beaufort CE, Cameron FJ, Aman J, Aanstoot HJ, et al. Target setting in intensive insulin management is associated with metabolic control: the Hvidoere childhood diabetes study group centre differences study 2005. Pediatric diabetes. 2010;11(4):271-8.

76. Raphael JL, Rueda A, Lion KC, Giordano TP. The role of lay health workers in pediatric chronic disease: a systematic review. Academic pediatrics. 2013;13(5):408-20.
77. Osan JK, Punch JD, Watson M, Chan YX, Barrie P, Fegan PG, et al. Associations of demographic and behavioural factors with glycaemic control in young adults with type 1 diabetes mellitus. Internal medicine journal. 2016.
78. Butalia S, Patel AB, Johnson JA, Ghali WA, Rabi DM. Association between diabetic ketoacidosis hospitalizations and driving distance to outpatient diabetes centres in adults with type 1 diabetes mellitus. Canadian journal of diabetes. 2014;38(6):451-5.

Figure 1: Flowchart presenting an overview of the search results.

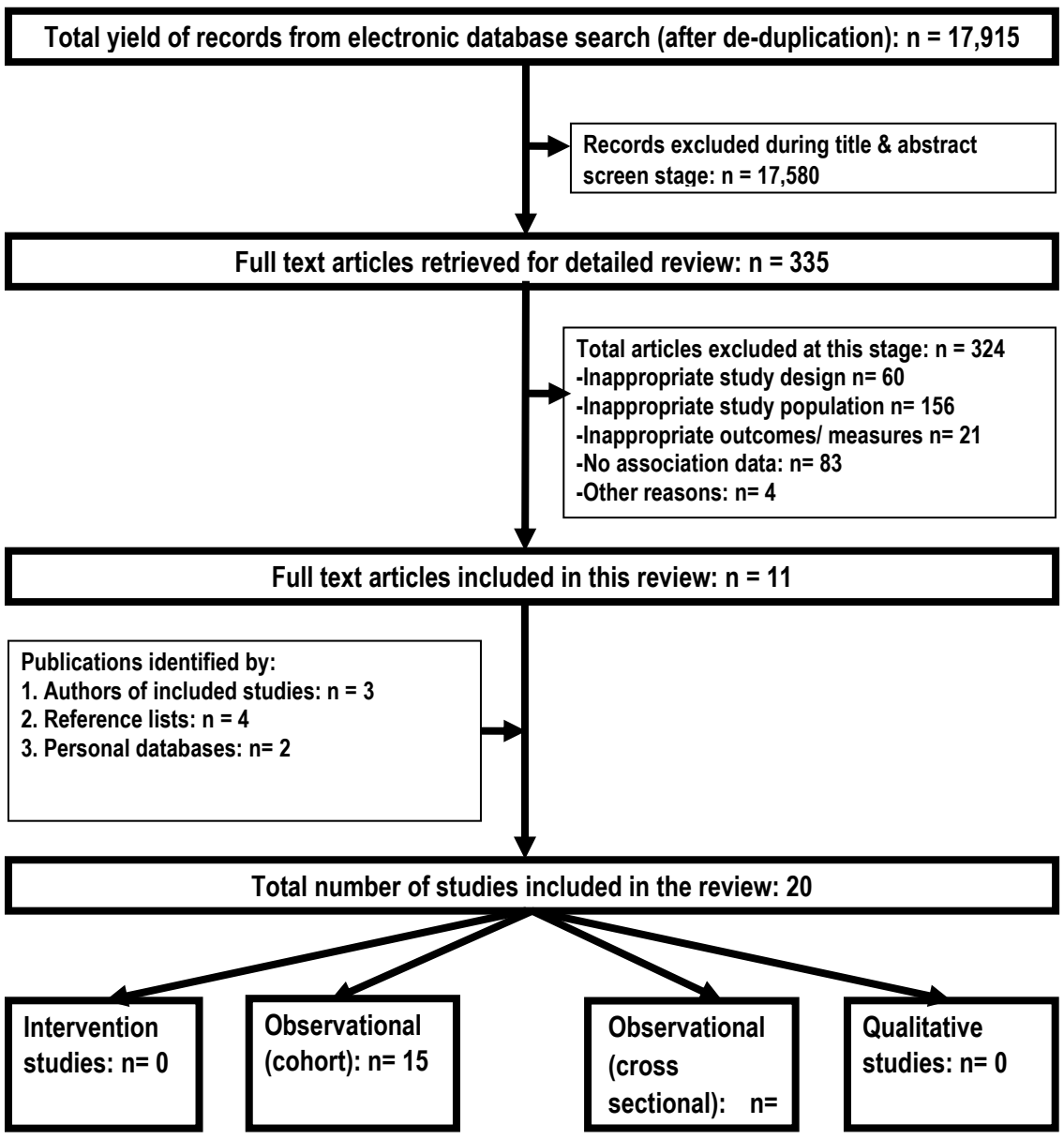


Fig. 2a: Predictors of glycaemic control 0-3 months following diagnosis of type 1 diabetes in children and young people.
(A + denotes HIGHER risk of poor glycaemic control)

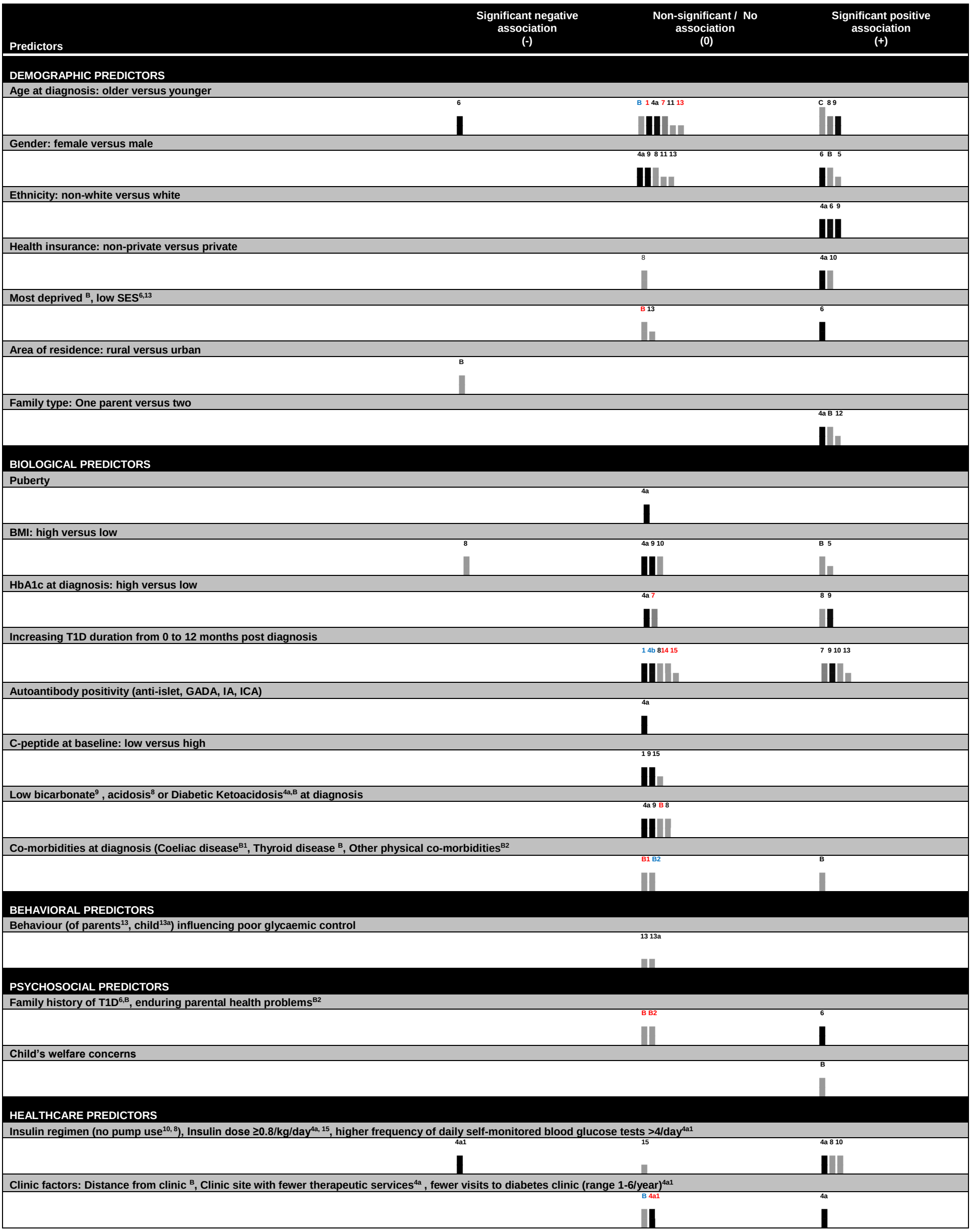
Predictors	Significant negative association (-)	Non-significant / no association (0)	Significant positive association (+)
DEMOGRAPHIC PREDICTORS			
Age at diagnosis: older versus younger		3 1 7 14 13	D C A 2 9 8 11
Gender: female versus male		C 8 11 13	2 3 A D 5
Ethnicity: non-white versus white		E	2 4a
Health insurance: non-private versus private		8	4a 10
SES[13], household income[4a], parental education[4a1]: low versus high		13	4a 4a1
Family type: One parent versus two			4a
BIOLOGICAL PREDICTORS			
BMI (Child [5,8,A,E], parental[A1]): high versus low	A 8		A1 E 5
Autoantibody positivity (anti-islet [E], GADA[9], IA[9], ICA[9])		9	9 E
C-peptide at baseline: low versus high		1 15	E
Diabetic Ketoacidosis at diagnosis		8	A
BEHAVIORAL PREDICTORS			
Behaviour (of parents[13], child[13a]) influencing poor glycaemic control		13 13a	
HEALTHCARE PREDICTORS			
Clinic site with fewer therapeutic services[4a], Intensive Care Unit versus general paediatric ward[8]		8	4a
Diagnostic strategies[2]: pre 2004 versus post; Season of diagnosis[3]: spring versus autumn			2 3

BMI: Body mass index; SES: Socio-economic status; GADA: Glutamic acid decarboxylase antibodies; ICA: Islet cell antibodies; IA: insulin antibodies

Prospective/ retrospective cohort studies: 1: Barker 2014 (28) & Lauria 2015 (29); 2: Clements 2014 (30); 3: Hanberger 2014 (32); 4a, 4a1: Redondo 2014 (25); 4b: Cengiz 2014 (26); 5: Davis 2012 (41); 6: Cutfield 2011 (39); 7: Giordano 2011 (42); 8: Viswanathan 2011 (43); 9: Mortensen 2010 (40); 10: Beck 2009 (44); 11: Hochhauser 2008 (45); 12: Frey 2007 (46); 13: Vollrath 2007 (47); 14: Chase 2004 (27); 15: Sochett 1987 (31)
Cross sectional studies: A, A1: Akesson 2014 (50); B, B1, B2: Lawes 2014 (2); C: Samuelsson 2014 (4); D: Sammuelsson 2013 (48); E: Redondo 2013 (24) & 2012 (49)

Note:
1. Position of bar based on direction and strength of association (statistically significant positive or negative association (+ / -), statistically non- significant (NS) positive or negative association or no association (0), study ID's in red and blue fonts representing NS + and NS - respectively).
2. Results for categorical and continuous outcome variables coded so a + denotes **HIGHER** risk of poor glycaemic control (i.e. higher HbA1c levels is viewed as positive association of predictor/correlate) and a - denoted a **LOWER** risk for poorer glycaemic control.
3. Height of bar represents size of study (small: n <100, medium: 100 to 999, tall: ≥1000)
4. Colour represents quality of study: Black, dark grey and light grey (based on total quality assessment score) - High: met five to six quality criteria, Intermediate: met three or four quality criteria, Low: met two or less quality criteria
5. Study id symbol on top of bar (numerical for prospective/retrospective cohort studies and alphabetical for XS studies).

Figure 2b: Predictors of glycaemic control 4-12 months following diagnosis of type 1 diabetes in children and young people.
(A + denotes HIGHER risk of poor glycaemic control)



T1D: Type 1 diabetes; BMI: Body mass index; SES: Socio-economic status; GADA: Glutamic acid decarboxylase antibodies; ICA: Islet cell antibodies; IA: insulin antibodies

Prospective/ retrospective cohort studies: 1: Barker 2014 (28) & Lauria 2015 (29); 2: Clements 2014 (30); 3: Hanberger 2014 (32); 4a, 4a1: Redondo 2014 (25); 4b: Cengiz 2014 (26); 5: Davis 2012 (41); 6: Cutfield 2011 (39); 7: Giordano 2011 (42); 8: Viswanathan 2011 (43); 9: Mortensen 2010 (40); 10: Beck 2009 (40); 11: Hochhauser 2008; 12 (45): Frey 2007 (46); 13: Vollrath 2007; 14 (47): Chase 2004 (27); 15: Sochett 1987 (31)

Cross sectional studies: A: Akesson 2014 (50); B, B1, B2: Lawes 2014 (2); C: Samuelsson 2014 (4); D: Sammuelsson 2013 (48); E: Redondo 2013 (24) & 2012 (49)

Note:
1. Position of bar based on direction and strength of association (statistically significant positive or negative association (+ / -), statistically non- significant (NS) positive or negative association or no association (0), study ID's in red and blue fonts representing NS + and NS - respectively).
2. Results for categorical and continuous outcome variables coded so a + denotes **HIGHER** risk of poor glycaemic control (i.e. higher HbA1c levels is viewed as positive association of predictor/correlate) and a - denoted a **LOWER** risk for poorer glycaemic control.
3. Height of bar represents size of study (small: n <100, medium: 100 to 999, tall: ≥1000)
4. Colour represents quality of study: Black, dark grey and light grey (based on total quality assessment score) - High: met five to six quality criteria, Intermediate: met three or four quality criteria, Low: met two or less quality criteria
5. Study id symbol on top of bar (numerical for prospective/retrospective cohort studies and alphabetical for XS studies).

Supplementary table S1: Electronic database search strategy

I.	Scopus (via Elsevier) (17/12/2014)
1.	(TITLE-ABS-KEY (({early intensive} OR tight OR glycemic OR glycaemic OR glucose OR diabetes OR strict) W/2 control) OR TITLE-ABS-KEY (insulin W/2 (use* OR injection* OR dose* OR pump*)) OR TITLE-ABS-KEY (glycosylat* OR {HbA1c} OR a1c OR hemoglobin a OR haemoglobin OR {HbA(1c)}) OR TITLE-ABS-KEY ((intensive OR conventional OR standard OR regular OR optimised OR usual OR routine) W/2 (care OR treatment OR therapy OR intervention OR management)) OR TITLE-ABS-KEY (hyperglycaemia OR hypoglycaemia)) AND (TITLE-ABS-KEY OR ({Diabetes complication*} OR {side effects} OR {adverse events} OR glycemia OR glycaemia OR {hyper glycemia} OR {hyper glycaemia} OR hyperglycemia OR hyperglycaemia OR {hypo glycemia} OR {hypo glycaemia} OR hypoglycemia OR hypoglycaemia) OR TITLE-ABS-KEY (ketosis OR {diabetic ketoacidosis} OR dka OR {nonketotic hyperosmolar coma} OR {insulin resistance} OR {autoimmune disease*} OR {auto immune disease}) OR TITLE-ABS-KEY ({urine albumin} OR microalbuminaria OR macroalbuminuria OR {renal disease*} OR {kidney disease*} OR {diabetic nephropathy} OR nephropathy OR dialysis) OR TITLE-ABS-KEY ({foot ulcer} OR amputation) OR TITLE-ABS-KEY (retinopathy OR blindness OR {cardiovascular disease*} OR mi OR {myocardial infarction*} OR stroke* OR {coronary artery disease*}) OR TITLE-ABS-KEY ({cerebrovascular disease*} OR {peripheral vascular disease*} OR {blood pressure} OR bp OR statin* OR death OR mortality)) AND (TITLE-ABS-KEY (pediatric OR paediatric OR child* OR {young people} OR youth OR {young adult*} OR juvenile OR {insulin dependent} OR labile OR brittle OR {sudden onset} OR autoimmune OR {auto immune} OR {non insulin dependent} OR uncontrolled OR {newly diagnosed} OR {new diagnosis} OR {inception diabetes})) AND (TITLE-ABS-KEY (dm1 OR {diabetes mellitus 1} OR {diabetes mellitus} W/2 {type 1}) OR t1d OR t1dm OR iddmor {type 1}) AND TITLE-ABS-KEY (metabolism OR {metabolic memory})
2	TITLE-ABS-KEY (metabolism OR {metabolic memory})
3	(TITLE-ABS-KEY or ({Diabetes complication*} or {side effects} or {adverse events} or glycemia or glycaemia or {hyper glycemia} or {hyper glycaemia} or hyperglycemia or hyperglycaemia or {hypo glycemia} or {hypo glycaemia} or hypoglycemia or hypoglycaemia) or TITLE-ABS-KEY (ketosis or {diabetic ketoacidosis} or DKA or {nonketotic hyperosmolar coma} or {insulin resistance} or {autoimmune disease*} or {auto immune disease}) or TITLE-ABS-KEY ({urine albumin} or microalbuminaria or macroalbuminuria or {renal disease*} or {kidney disease*} or {diabetic nephropathy} or nephropathy or dialysis) or TITLE-ABS-KEY ({foot ulcer} or amputation) or TITLE-ABS-KEY (retinopathy or blindness or {cardiovascular disease*} or MI or {myocardial infarction*} or stroke* or {coronary artery disease*}) or TITLE-ABS-KEY ({cerebrovascular disease*} or {peripheral vascular disease*} or {blood pressure} or BP or statin* or death or mortality))
4	(TITLE-ABS-KEY (({early intensive} or tight or glycemic or glycaemic or glucose or diabetes or strict) W/2 control) OR TITLE-ABS-KEY (insulin W/2 (use* or injection* or dose* or pump*)) OR TITLE-ABS-KEY (glycosylat* or {HbA1c} or A1c or Hemoglobin A or haemoglobin or {HbA(1c)}) OR TITLE-ABS-KEY((intensive or conventional or standard or regular or optimised or usual or routine) W/2 (care or treatment or therapy or intervention or management)) OR TITLE-ABS-KEY (hyperglycaemia or hypoglycaemia))
5	(TITLE-ABS-KEY (pediatric OR paediatric OR child* OR {young people} OR youth OR {young adult*} OR juvenile OR {insulin dependent} OR labile OR brittle OR {sudden onset} OR autoimmune OR {auto immune} OR {non insulin dependent} OR uncontrolled OR {newly diagnosed} OR {new diagnosis} OR {inception diabetes}))
6	(TITLE-ABS-KEY (dm1 OR {diabetes mellitus 1} OR {diabetes mellitus} W/2 {type 1}) OR t1d OR t1dm OR iddmor {type 1})

II.	Cochrane Library (17/12/2014)
#1	MeSH descriptor: [Diabetes Mellitus, Type 1] explode all trees
#2	DM1 or diabetes mellitus 1 or diabetes mellitus type 1 or T1D or T1DM or IDDM
#3	type 1 or paediatric or child or young people or youth or young adults or juvenile or insulin dependent or labile or brittle or sudden onset or autoimmune or auto immune or non insulin dependent or uncontrolled or newly diagnosed or new diagnosis or inception diabetes
#4	#1 or #2 or #3
#5	MeSH descriptor: [Blood Glucose] explode all trees
#6	MeSH descriptor: [Hemoglobin A, Glycosylated] explode all trees
#7	MeSH descriptor: [Hypoglycemia] explode all trees
#8	MeSH descriptor: [Hyperglycemia] explode all trees
#9	#5 or #6 or #7 or #8
#10	early intensive or tight or glycemic or glucose or diabetes or strict control
#11	insulin use or injection or dose or pump

#12	glycosylate or HbA1c or A1c or Hemoglobin A or HbA1c
#13	intensive or conventional or standard or regular or optimised or usual or routine care or treatment or therapy or intervention or management
#14	#9 or #10 or #11 or #12 or #13
#15	MeSH descriptor: [Diabetes Complications] explode all trees
#16	adverse effects or complications
#17	MeSH descriptor: [Ketosis] explode all trees
#18	MeSH descriptor: [Insulin Resistance] explode all trees
#19	MeSH descriptor: [Autoimmune Diseases] explode all trees
#20	MeSH descriptor: [Albuminuria] explode all trees
#21	MeSH descriptor: [Kidney Diseases] explode all trees
#22	MeSH descriptor: [Dialysis] explode all trees
#23	MeSH descriptor: [Blindness] explode all trees
#24	MeSH descriptor: [Cardiovascular Diseases] explode all trees
#25	MeSH descriptor: [Cerebrovascular Disorders] explode all trees
#26	MeSH descriptor: [Blood Pressure] explode all trees
#27	MeSH descriptor: [Hydroxymethylglutaryl-CoA Reductase Inhibitors] explode all trees
#28	MeSH descriptor: [Mortality] explode all trees
#29	Diabetes complications or side effects or adverse events or glycaemia or hyper glycaemia or hypo glycaemia or ketosis or diabetic ketoacidosis or DKA or nonketotic hyperosmolar coma or insulin resistance or autoimmune disease or urine albumin or urine albumin creatinine ratio or urine albumin excretion or microalbuminuria or macroalbuminuria or renal disease or diabetic nephropathy or nephropathy or dialysis or foot ulcer or amputation or retinopathy or blindness or cardiovascular disease or MI or myocardial infarction or stroke or coronary artery disease or cerebrovascular disease or peripheral vascular disease or blood pressure or BP or statin or death or mortality
#30	#15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29
#31	metabolism
#32	metabolic memory
#33	#31 or #32
#34	#4 and #9 and #14 and #30 and #33

III.	**CINAHL (via EBSCO) (16/12/2014)**
S34	S4 AND S14 AND S30 AND S33
S33	S31 OR S32
S32	"metabolic memory"
S31	MJ metabolism
S30	S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29

S29	diabetes complication or diabetes complication* or side effects or adverse events or glyc#emia or hyper glyc#emia or hyperglyc#emia or hypo glyc#emia or hypoglyc#emia or ketosis or diabetic ketoacidosis or DKA or nonketotic hyperosmolar coma or insulin resistance or autoimmune disease* or urine albumin or microalbuminaria or macroalbuminuria or renal disease* or kidney disease* or diabetic nephropathy or nephropathy or dialysis or foot ulcer or amputation or retinopathy or blindness or cardiovascular disease* or MI or myocardial infarction* or stroke* or coronary artery disease* or cerebrovascular disease* or peripheral vascular disease* or blood pressure or BP or statin* or death or mortality
S28	(MH "mortality+")
S27	(MH "statins+")
S26	(MH "blood pressure+")
S25	(MH "cerebrovascular disorders+")
S24	(MH "stroke+")
S23	(MH "cardiovascular diseases+")
S22	(MH "blindness+")
S21	(MH "dialysis+")
S20	(MH "kidney diseases+")
S19	(MH "Albuminuria")
S18	(MH autoimmune diseases+)
S17	(MH insulin resistance+)
S16	(MH "diabetic angiopathies+") OR (MH "diabetic cardiomyopathies") OR (MH "diabetic coma+") OR (MH "diabetic ketoacidosis") OR (MH "diabetic neuropathies+")
S15	(MH "diabetes mellitus/co")
S14	S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13
S13	(intensive OR conventional OR standard OR regular OR optimi#ed OR usual OR routine) N2 (care OR treatment OR therapy OR intervention OR management)
S12	glycosylat* OR HbA1c OR A1c OR H#emoglobin A OR HbA#1c
S11	insulin N2 (use* OR injection* OR dose* OR pump*)
S10	(“early intensive” OR tight OR glyc#emic OR glucose OR diabetes or strict) N2 control)
S9	(MH "Hyperglycemia+")
S8	(MH "Hypoglycemia+")
S7	MH blood glucose
S6	MH hemoglobin a, glycosylated
S5	(MH "Glycemic Control")
S4	S1 OR S2 OR S3
S3	("type 1" OR p#ediatric OR child* OR "young people" OR youth OR "young adult" OR juvenile OR "insulin dependent" OR labile OR brittle OR "sudden onset" OR autoimmune OR "auto immune" OR "non insulin dependent" OR uncontrolled OR "newly diagnosed" OR "new diagnosis" OR inception) N5 diabetes
S2	DM1 OR "diabetes mellitus 1" OR ("diabetes mellitus" N2 type 1) OR T1D or T1DM or IDDM
S1	(MH "Diabetes Mellitus, Type 1+")

IV.	**Web of Science (via Thomson Reuters) (16/12/2014)**
1	TOPIC: ((DM1 OR "diabetes mellitus 1" OR ("diabetes mellitus" NEAR/2 "type 1") OR T1D or T1DM or IDDM) OR TOPIC: (("type 1" OR p$ediatric OR child* OR "young people" OR youth OR "young adult" OR juvenile OR "insulin dependent" OR labile OR brittle OR "sudden onset" OR autoimmune OR "auto immune" OR "non insulin dependent" OR uncontrolled OR "newly diagnosed" OR "new diagnosis" OR inception) NEAR/5 diabetes)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC Timespan=All years
2	TOPIC: (TOPIC: ((“early intensive” OR tight OR glyc$emic OR glucose OR diabetes or strict) NEAR/2 control) OR TOPIC: (insulin NEAR/2 (use* OR injection* OR dose* OR pump*)) OR TOPIC: (glycosylat* OR HbA1c OR A1c OR H$emoglobin A OR HbA$1c) OR TOPIC: ((intensive OR conventional OR standard OR regular OR optimi$ed OR usual OR routine) NEAR/2 (care OR treatment OR therapy OR intervention OR management)) OR TOPIC: (hyperglyc$emia OR hypoglyc$emia)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC Timespan=All years
3	TOPIC: (TOPIC: (“Diabetes complication*” OR “side effects” OR “adverse events” OR glyc$emia OR “hyper glyc$emia” OR hyperglyc$emia OR “hypo glyc$emia” OR hypoglyc$emia OR ketosis OR “diabetic ketoacidosis” OR DKA OR “nonketotic hyperosmolar coma” OR “insulin resistance” OR “autoimmune disease*” OR “auto immune disease” OR “urine albumin” OR microalbuminaria OR macroalbuminuria OR “renal disease*” OR “kidney disease*” OR nephropathy OR dialysis OR “foot ulcer” OR amputation OR retinopathy OR blindness OR “cardiovascular disease*” OR MI OR “myocardial infarction*” OR stroke* OR “coronary artery disease*” OR “cerebrovascular disease*” OR “peripheral vascular disease*” OR “blood pressure” OR BP OR statin* OR death OR mortality)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC Timespan=All years
4	TOPIC: (TOPIC: (metabolism OR "metabolic memory" OR metabolic))

	Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC Timespan=All years

V.	EMBASE (via OVID) (16/12/2014)
1	exp insulin dependent diabetes mellitus/
2	(DM1 or diabetes mellitus 1 or (diabetes mellitus adj2 type 1) or T1D or T1DM or IDDM).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
3	((type 1 or p?ediatric or child* or young people or youth or young adults or juvenile or insulin dependent or labile or brittle or sudden onset or autoimmune or auto immune or non insulin dependent or uncontrolled or newly diagnosed or new diagnosis or inception) adj5 diabetes).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
4	1 or 2 or 3
5	exp glycosylated hemoglobin/
6	exp glucose blood level/
7	exp hypoglycemia/
8	exp hyperglycemia/
9	((early intensive or tight or glyc?emic or glucose or diabetes or strict) adj2 control).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
10	(insulin adj2 (use* or injection* or dose* or pump*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
11	(glycosylat* or HbA1c or A1c or H?emoglobin A or HbA?1c).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
12	((intensive or conventional or standard or regular or optimi?ed or usual or routine) adj2 (care or treatment or therapy or intervention or management)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
13	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14	diabetic angiopathy/ or diabetic cardiomyopathy/ or diabetic coma/ or diabetic foot/ or diabetic hypertension/ or diabetic ketoacidosis/ or diabetic macular edema/ or diabetic nephropathy/ or diabetic neuropathy/ or diabetic obesity/ or diabetic retinopathy/ or impaired glucose tolerance/ or "maternally inherited diabetes and deafness"/ or nonketotic diabetic coma/ or wolfram syndrome/
15	exp diabetes mellitus/co [Complication]
16	exp diabetes mellitus/si [Side Effect]
17	exp insulin resistance/
18	exp autoimmune disease/
19	exp albuminuria/
20	exp kidney disease/
21	exp dialysis/
22	exp blindness/
23	exp cardiovascular disease/
24	exp cerebrovascular disease/
25	exp blood pressure/
26	exp hydroxymethylglutaryl coenzyme A reductase inhibitor/
27	exp mortality/
28	(Diabetes complication* or side effects or adverse events or glyc?emia or hyper glyc?emia or hyperglyc?emia or hypo glyc?emia or hypoglyc?emia or ketosis or diabetic ketoacidosis or DKA or nonketotic hyperosmolar coma or insulin resistance or autoimmune disease* or urine albumin or microalbuminaria or macroalbuminuria or renal disease* or kidney disease* or diabetic nephropathy or nephropathy or dialysis or foot ulcer or amputation or retinopathy or blindness or cardiovascular disease* or MI or myocardial infarction* or stroke* or coronary artery disease* or cerebrovascular disease* or peripheral vascular disease* or blood pressure or BP or statin* or death or mortality).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
29	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30	memory/
31	metabolic memory.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
32	30 or 31
33	4 and 13 and 29 and 32

VI.	Medline (via OVID) (16/12/2014)

1	exp Diabetes Mellitus, Type 1/
2	(((DM1 or diabetes mellitus 1 or diabetes mellitus) adj2 type 1) or T1D or T1DM or IDDM).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
3	((type 1 or p?ediatric or child* or young people or youth or young adults or juvenile or insulin dependent or labile or brittle or sudden onset or autoimmune or auto immune or non insulin dependent or uncontrolled or newly diagnosed or new diagnosis or inception) adj5 diabetes).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
4	1 or 2 or 3
5	exp Blood Glucose/ or exp Hemoglobin A, Glycosylated/ or exp Hypoglycemia/
6	exp Hyperglycemia/
7	((early intensive or tight or glyc?emic or glucose or diabetes or strict) adj2 control).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
8	(insulin adj2 (use* or injection* or dose* or pump*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
9	(glycosylat* or HbA1c or A1c or H?emoglobin A or HbA?1c).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
10	((intensive or conventional or standard or regular or optimi?ed or usual or routine) adj2 (care or treatment or therapy or intervention or management)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
11	5 or 6 or 7 or 8 or 9 or 10
12	exp Diabetes Complications/
13	adverse effects.fs.
14	complications.fs.
15	exp Ketosis/
16	exp Insulin Resistance/
17	exp Autoimmune Diseases/
18	exp Albuminuria/
19	exp Kidney Diseases/
20	exp Dialysis/
21	exp Blindness/
22	exp Cardiovascular Diseases/
23	exp Cerebrovascular Disorders/
24	exp Blood Pressure/
25	exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
26	exp Mortality/
27	(Diabetes complications or side effects or adverse events or glycaemia or hyper glycaemia or hypo glycaemia or ketosis or diabetic ketoacidosis or DKA or nonketotic hyperosmolar coma or insulin resistance or autoimmune disease or urine albumin or urine albumin creatinine ratio or urine albumin excretion or microalbuminuria or macroalbuminuria or renal disease or diabetic nephropathy or nephropathy or dialysis or foot ulcer or amputation or retinopathy or blindness or cardiovascular disease or MI or myocardial infarction or stroke or coronary artery disease or cerebrovascular disease or peripheral vascular disease or blood pressure or BP or statin or death or mortality).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
28	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29	4 and 11 and 28
30	metabolism.fs.
31	metabolic memory.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
32	30 or 31
33	29 and 32

Table S2: Inclusion and exclusion criteria for review of evidence on what factors predict early HbA1c?

Inclusion Criteria	Exclusion Criteria
- Interventional studies (RCT's and non-RCT's) targeting glycaemic control (within 2 years of diagnosis of T1D) and described an association with health outcomes - Non-intervention/observational i.e. cohort and cross sectional (XS) studies that quantified the association between early glycaemic control (within 2 years of diagnosis of T1D) AND risk of future complications in children and young people aged 0 to 25 years at baseline - Qualitative studies that give a deeper background understanding on the topic	- Non-human studies - Selection of population based on other diseases/co-morbidities - Adults aged more than 25 years at baseline. - Studies on T2D - Quantitative studies not reporting clinical outcomes - Quantitative studies that measured glycaemic control but did not describe an association with outcome variables

Table S3: Quality assessment criteria

For observational (prospective/retrospective cohort and cross sectional) studies
Total quality assessment score (**maximum of 6**) was derived for fulfilment of following criteria: 1) More than 50 participants analysed; 2) Studies representing general population 3) Prospective study design 4) Adjusted/multivariate analysis 5) Objective measure of outcome 6) Objective measure of exposure.

Table S4: Details of data extracted from included studies

Observational studies (cross-sectional and prospective/retrospective cohort)
- Study id - Author - Year - Country - Age Range - Average age - Sex (Male: Female ratio) - Ethnicity - Socioeconomic status - Design (Cross sectional/Prospective) - Number of participants - Sample/recruitment e.g general population representative sample or specialist groups, - Exposure examined - Measurement of Exposure - Measurement conducted by Level of glycemic control - Setting (home, primary care, secondary care) - Outcome (complications, metabolic memory - separate row for each outcome investigated), - Measurement of outcome (objective) - Analysis - Effect - Author email - Comments

Table S5: Predictors of early glycaemic control in childhood onset T1D: Evidence from longitudinal studies

REP: Representative; NON REP: Non representative; T1D: type 1 diabetes; BMI: Body Mass Index; SES: Socio-economic status; f/u: Follow up; SD: Standard deviation; ++: statistically significant positive association; + or - : statistically non- significant positive or negative association; /: no association.

No	Author, year and country	Study design/ name	Population and setting	Age range of study population at diagnosis	Follow-up period	Predictor	Outcome	Measure/ analyses	Association	Quality assessment score (max 6) and comments
1	Barker 2014 (28) & Lauria 2015 (29) Seven countries in Europe (Belgium, Leuven, Hungary, Spain, Sweden, Germany, Italy).	Prospective cohort	REP: 842 and 2264 children respectively (58% and 55% males resp.) with T1D from registries/databases in seven European countries (Belgium, Leuven, Hungary, Spain, Sweden, Germany, Italy).	0- 18 years	1 and 5 years	**Biological:** Age at diagnosis 0 - 18 at diagnosis, 1and 5 years f/u **Biological:** fasting C Peptide at diagnosis, 1and 5 years f/u **Biological:** T1D duration 0,1, 5 years	Association with HbA1c levels	Mean (SD) Receiver operating characteristics (ROC) analysis. Mean (SD)	+ HbA1c levels increased with age. Statistical significance not reported / + at diagnosis - at 1 year + at 5 years. Statistical significance not reported	High (5). Did not include adjusted/multivariate analysis
2	Clements 2014 (30) USA	Prospective cohort	REP: 2218 children and young people (52.6% male), Ethnicity: 86.1% non-Hispanic Caucasian, 8.9% non-Hispanic African-American, 5% other or Hispanic), registered between 1993 and 2009 at the Children's Mercy Hospital Type 1 diabetes in paediatrics database, USA	0-20 years Mean age at diagnosis: 9.0 ±4.1 years	1.5 and 5 years	**Biological:** Age at diagnosis 0-20 years **Biological:** Gender: female **Biological:** Duration of T1D 1.5 , 5 years **Biological:** HbA1c levels at diagnosis, 1.5 , 5 years **Psychosocial:** Ethnicity (non- white) **Environmental:** Diagnostic era (pre 2000, 2000-03, 2004-09) **Health services:** Insulin therapy	Association with HbA1c levels	Regression, stratified analyses	++ progressively increased in all age groups, highest in >10 year olds ++ ++ in children > 5 years old ++ progressively increased at diagnosis and f/u ++ at all-time points ++ high levels in pre 2004-2009 group at diagnosis, 1.5 and 5 years ++ HbA1c levels high at diagnosis and rose	High (5). 5 different methods used to analyse HbA1c during the study period

									significantly at f/u	
3	Hanberger 2014 (32) Sweden	Prospective Cohort	REP: 8020 children (4430 males), with type 1 diabetes, who were registered in SWEDIABKIDS registry in Sweden between 2000 and 2010	0-18 years	0-3 years	**Biological:** Age (0-14 years) at diagnosis and 3 year f/u **Biological:** Gender female at diagnosis and f/u **Biological:** HbA1c levels at diagnosis and at f/u **Environmental:** Monthly/seasonal variation at diagnosis and at f/u	Impact of age and gender on variations in HbA1c levels in paediatric T1D at onset and at f/u	ANOVA, mean (SD)	+ at diagnosis and f/u. Statistical significance not reported ++ at diagnosis and f/u. ++ predictors of HbA1c at 3 year f/u **++** Mean HbA1c at diagnosis was significantly highest in May (11%, 97 mmol/mol) and lowest in (October 10.3%, 87 mmol/mol). / at f/u	High (5) Did not include adjusted/multivariate analysis
4a	Redondo 2014 (25) USA	Prospective cohort Paediatric Diabetes Consortium (PDC) T1D New Onset (NeOn) study	REP: 857 participants (49% males), 66% non-Hispanic white and 68% with private health insurance were recruited between 2009 and 2011 in seven centres across USA.	0-19 years Mean age 9.1 ±4.1 years	1 year	**Health services**: Clinic site with less therapeutic approaches **Health services**: fewer visits to diabetes clinic (range 1-6/year) **Health services**: Insulin dose ≥0.8/kg/day **Health services**: Daily self-monitored blood glucose tests >4/day **Psychosocial:** Ethnicity non-white **Psychosocial:** non-private health insurance **Psychosocial:** Lower household income **Psychosocial:** Lower parent education level **Psychosocial:** Not living with both parents	Association with HbA1c at diagnosis	Univariate and multivariate analyses	++ at baseline and f/u + at f/u ++ at f/u - - at f/u ++ at baseline and f/u ++ at baseline and f/u + + at baseline ++ at baseline ++ at baseline and f/u	High (5). Analysis of clinic level factors unclear

4b	Cengiz 2014 (26) USA					**Biological:** DKA at diagnosis **Biological:** Lower age <12 years at diagnosis **Biological:** Gender female **Biological:** Tanner stage **Biological**: higher BMI **Biological:** higher positive anti-islet autoantibodies (GADA,IAA, IA-2) **Biological:** higher HbA1c at diagnosis **Biological:** Duration of T1D at diagnosis, 3, 6, 9 and 12 months			/ at f/u / at f/u / at f/u / at f/u / at f/u / at f/u / at f/u + at diagnosis but – at other time points. Significance not reported.	
5	Davis 2012 (41) UK	Prospective cohort	REP: 30 children (18 males) within 1 week of diagnoses of T1D and N=14 (8 males) controls (age and sex matched siblings/friends) I paediatric clinic. Pre-pubertal: N=19 Pubertal: N=8 Post pubertal: N=3	0-18 years Mean: 10.5 (2.9)	6 weeks and 1 year	**Biological:** Gender female **Biological:** Higher BMI / increased body fat	Association with HbA1c levels at diagnosis and at 1 year f/u	Mean (SD)	++ ++	Intermediate (3) Small sample size, inadequate analysis and exposure of outcomes
6	Cutfield 2011 (39) New Zealand	Prospective cohort	REP: 229 children (52% males) diagnosed with T1D between 2000 and 2008 and in Starbase registry.	0-15 years	At 6 month and at 24 months	**Biological:** Age at diagnosis <10 years old **Biological:** Gender female **Biological:** BMI high **Biological:** T1D in family **Biological:** HbA1c levels at 6months **Psychosocial:** Ethnicity (Non- European,	Effect of predictors on glycaemic control at 6 months and 24 months after diagnosis	Univariate analysis	++ (6months) ++ worst control at 6 months ++ (24 months) ++ worse control in children with First degree relative with T1D (6 months) ++ predictors of HbA1c at 24 months f/u ++ (6 months)	High (5) not adjusted/multivariate analysis

						Maori, Pacific islanders) **Psychosocial:** SES low **Psychosocial:** Child not living with both biological parents			++ (6 months) ++ (24 months)	
7	Giordano 2011 (42) Italy	Prospective cohort	REP: 251 children (59% males) with T1D from Sicily, who were hospitalised between 1991 and 2005 were recruited and prospectively followed if T1D treatment naïve.	0-23 years Mean age 15.2 ±2.8 years	1 and >10 years	**Biological:** Age at diagnosis 0 - 15 **Biological:** Higher HbA1c at diagnosis **Biological:** T1D duration 1, 10 years	Association with HbA1c levels	Mean (SD), Univariate ANOVA	+ + at 1 year f/u but ++ HbA1c levels higher in children < 15 years old ++	Intermediate (4) inadequate analysis and measure of outcome/exposure
8	Viswanathan 2011 (43) USA	Retrospective Cohort	NON REP: 120 children (44% male), Ethnicity: 92% Caucasian, 6.7% African-American), hospitalised in 2003 at the tertiary care centre at Riley Hospital for Children with Type 1 diabetes and in paediatrics database.	1-17 years Mean age 7.6 ±3.9 years	6 weeks, 1, 2, 3 and 4 years	**Biological:** Age at diagnosis 0 - 17 **Biological:** Duration of T1D **Biological:** BMI low **Health Services:** ICU patients versus general paediatric floor patients at diagnosis **Biological:** Acidosis (serum bicarbonate) at diagnosis **Biological:** Gender female **Health services:** Pump therapy **Psychosocial:** health insurance	Association with HbA1c levels	Mean (SD), correlation	++ HbA1c levels increased with age ++ at diagnosis, / at 1 and 2 years, ++ at 3 years and + at 4 year f/u ++ / / / - - /	Intermediate (4) non representative population, inadequate study design and analysis
9	Mortensen 2010 (40) Multinational (Europe and Japan)	Prospective cohort Hvidoere Remission Phase Study	NON REP: 275 children (48% males, 84% White caucasian) diagnosed with T1D between 1999 and 2000, from 18	0-17 years Range: 0.2-16.8 years Mean: 9.1 years	Monthly for 12 months from diagnosis	**Biological:** Age at diagnosis **Biological:** Duration of T1D > 3 months	Association with HbA1c levels	Mean (SD),one way analysis of variance and multiple	++ Significantly higher in ≥ 10 year olds compared to 5-9.9 year olds at diagnosis, 9 and 12 months. ++ HbA1c levels dropped	High (5) Mainly in white Caucasians

			centres representing 15 countries in Europe and Japan.			**Biological:** HbA1c levels at diagnosis **Biological:** Presence of antibodies Glutamic acid decarboxylase antibodies (GADA), Islet cell antibodies (ICA) , insulin antibodies (IA) **Biological:** Gender **Biological:** Standard bicarbonate **Biological:** BMI **Biological:** C peptide **Psychosocial:** Ethnicity (non-white Caucasians)		regression (at 12 months)	significantly at 3 months and then gradually increased across all age groups. ++ predictors of HbA1c at 12 months ++ presence of GADA predictor of HbA1c at 12 months + presence of ICA and IA / at 12 months / at 12 months / at 12 months / at 12 months ++ at 12 months	
10	Beck 2009 (44) USA	Retrospective cohort	REP: 105 newly diagnosed children (69% with private insurance), managed with intensive insulin (>4 inj/day): n=51 (59% male) or conventional insulin (<3 inj/day), n=54 (46% male) were retrospectively identified from an outpatient academic paediatric endocrinology practice.	0-18 years	12, 15 and 18 months	**Biological:** Duration of T1D (12, 15 and 18 months) **Health services:** Conventional insulin regimen (ref: intensive) **Health services:** Health Insurance (ref: Private)	Association with HbA1c levels	percentage (SEM), ANOVA ANOVA Chi-square analysis	++ The overall HbA1c mean was significantly higher (ANOVA) in both groups especially conventional treatment group ++ The overall HbA1c mean at diagnosis (post hoc analysis), 12, 15, and 18 month was significantly higher (ANOVA) ++ The overall HbA1c mean significantly higher at diagnosis, 12, 15, and 18 months in conventional treatment group (Chi-square analysis). However, 69 vs. 48% participants had private insurance and intensive insulin treatment.	Intermediate (3) population (84% Caucasian), retrospective study design, inadequate analysis

11	Hochhauser 2008 (45) USA	Retrospective cohort	REP: 59 children diagnosed with T1D between 1992 and 2005 at the Division of pediatric endocrinology and diabetes at Mount Sinai medical centre.	0-19 years	Every 6 months after diagnosis for 3 years	**Biological:** Age at diagnosis **Biological:** Gender female	Effect on HbA1c levels at diagnosis, 6, 12, 24 and 36 months post diagnosis	Analyses of variance	++ Levels at diagnosis higher in children aged 13+ / at other time points + girls generally had higher levels but those aged 6-12 years had higher levels of HbA1c levels at diagnosis	Intermediate (4). Retrospective study design, baseline characteristics do not indicate which patients were included in longitudinal analyses.
12	Frey 2007 (46) USA	Prospective cohort of a convenience sample	NON REP: 71 children (49% male), Ethnicity: 51% White, 49% African-American), with T1D, recruited from a university affiliated teaching hospital in a major Midwestern city in USA	7-19years Mean age 12.8 ±2.9 years	At 1, 2 and 5 years	**Psychosocial:** Ethnicity non white **Psychosocial:** Single parent family **Psychosocial:** Low family income **Biological:** Higher HbA1c at diagnosis **Biological:** Age at diagnosis 7 - 19 **Biological:** Tanner stage **Biological:** Higher BMI	Association with HbA1c levels at 24 months	Regression modelling	++ ++ at 1, 2 and 5 years + ++ + + +	Intermediate (4). Population selection and study design inadequate
13	Vollrath 2007 (47) Switzerland	Prospective cohort	NON REP: 64 German speaking children with new onset T1D and their parents were recruited from four children's hospitals in Switzerland	6-16 years	At 4-6 weeks, 6 12 and 24 months post diagnosis	**Biological:** Duration of T1D (6 – 24 months) **Biological:** Gender female **Biological:** Age at diagnosis **Psychosocial:** SES **Psychosocial:** Personality characteristics of child influencing glycaemic control	Effects on HbA1c levels at 1, 6,12 and 24 months	Correlation, T test, p values, multiple regression	++ poorer glycaemic control with increasing duration of T1D (6 months v/s 2 years) / no difference in HbA1c levels between boys and girls +NS correlation between age and HbA1c / no difference in HbA1c levels between families from low, middle and upper SES - - conscientiousness / agreeableness	Intermediate (3). Non generalizable population, subjective outcome measures and analyses

						Psychosocial: Personality characteristics of parents influencing glycaemic control			/ Extraversion / Neuroticism - - agreeableness (mothers) / conscientiousness / agreeableness / Extraversion / Neuroticism	
14	Chase 2004 (27) USA	Prospective cohort	REP: 552 children (57% males) with T1D from 1997 to 2001 and registered at the Barbara Davis Center for Childhood Diabetes in Denver, CO.	0- 18 years	At month 0, 1, 2-4, 5-7, 8-10 and 11-13	**Biological:** Age at diagnosis 0 – 18 **Biological:** Duration of T1D 1 year	Association with HbA1c levels	Mean (SD)	+ HbA1c levels increased with age at diagnosis +	Intermediate (3) Unclear population selection method, inadequate analyses and outcomes
15	Sochett 1987 (31) Canada	Prospective cohort	REP: 33 children newly diagnosed with T1D and followed up at Diabetes Clinic at the hospital for sick children, Toronto	0.5-17.5 years	10 days, 1, 3, 6 and 12 months after diagnosis	**Biological:** C Peptide **Biological:** HbA1c levels **Health services**: Insulin dose ≥0.8/kg/day	Association with HbA1c levels	ANOVA	/ from 1 -12 months + at 3 – 12 months / from 1 -12 months	Intermediate (4). Small sample size and inadequate analysis

Table S6: Correlates of early glycaemic control in childhood onset T1D: Evidence from cross sectional studies

REP: Representative; NON REP: Non representative; XS: cross sectional study design; BMI: Body Mass Index; SDS: Standard deviation score; DKA: Diabetic ketoacidosis; f/u: Follow up; T1D: type 1 diabetes; ++: statistically significant positive correlation; + or - : statistically non- significant positive or negative correlation; /: no correlation.

No	Author, year and country	Study design/ name	Population and setting	Age range	Correlate	Outcome	Measure	Association	Quality assessment score (max 6) and comments
A	Akesson 2014 (50) Sweden	XS prospective	REP: 8190 children(4508 males), diagnosed with T1D before 2011 and in SWEDIABKIDS registry in Sweden	0-18 years	**Biological:** low pH **Biological:** low BMI SDS **Biological:** low blood pressure systole SDS **Biological:** low blood pressure diastole SDS **Biological:** Gender female **Biological:** Mother's BMI high **Biological:** Father's BMI high	Association with HbA1c at diagnosis	B coefficient with 95% CI and p value	++ ++ + + ++ ++ ++	Intermediate (4) XS study design and inadequate analysis
B	Lawes 2014 (2) Scotland, UK	XS Retrospective	NON REP: 155 children ≤ 16 years from NHS Highland Paediatric diabetic services, North of Scotland, diagnosed between Jan 1993 and Aug 2011 and receiving care between Nov 2008 and Aug 2012.40% patients lived in remote/rural areas.	0-16 years	**Biological :** Gender female **Biological :** Age at diagnosis <11 years **Biological :** T1D in family **Biological : high** BMI SDS at diagnosis **Biological :** DKA at diagnosis **Biological :** Coeliac disease **Biological :** Thyroid	association with baseline 0-6 month from diagnosis) HbA1c	Univariate, multivariate linear, logistic and cox regression models	++ + + ++ + + ++	Intermediate (3) Retrospective XS study design, excluded patients with < 1 year f/u from diagnosis. Included only patients from North Scotland.

					disease **Biological :** Other physical comorbidity **Psychosocial :** Most deprived Scottish Index of Multiple Deprivation quintile **Psychosocial :** Living with < 2 biological parents **Psychosocial :** Subject of child welfare concerns **Psychosocial :** enduring parental health problem **Health Service:** distance from clinic hub **Health Service:** Insulin regimen at 2 year f/u **Environmental:** living remotely			- + ++ ++ + - + for 3 to 4 doses per day (ref 1 dose/day) - for 2 doses per day (ref 1 dose/day) - -	
C	Samuelsson 2014 (4) Sweden	XS prospective	NON REP: 1543 children and adolescents (920 males) from Swedish paediatric diabetes quality registry (SWEDIABKIDS) and the national diabetes register (NDR) Age 5-9 years: N= 89 (5.8%) Age 10-14 years: N= 769	5-19 years	**Biological:** Age at diagnosis < 10 years **Biological:** Gender female	Association with HbA1c levels at 3-15 months after diagnosis	Mean, p value	++ at diagnosis and at f/up + at diagnosis	Intermediate (4) XS study design, non-representative child population (children < 5 years not included and very few children diagnosed before the age of 10)

			(49.8%) Age 15-19 years: N= 685 (44.4%) Mean age at diagnosis: 13.9 years. Mean duration of T1D at f/u: 7.1 years Mean HbA1c adjacent to diagnosis: ≥70mmol/mol (8.6)%						
D	Sammuelsson 2013 (48) Sweden	XS prospective *The Better Diabetes Diagnosis*	REP: 3824 children newly diagnosed with T1D in 2005 from 43 Swedish paediatric clinics	0-18 years	**Biological:** age at diagnosis 6-15 year olds **Biological:** Gender female	Effect on HbA1c at diagnosis	Mean SD	++ ++	Intermediate (4). XS study design and inadequate analysis
E	Redondo 2013 (24) & 2012 (49) USA	XS prospective	REP: 607 and 524 children respectively, aged < 19 years and newly diagnosed with T1D at Texas children's hospital		**Biological:** anti-islet autoantibody expression **Biological:** Beta-cell function preservation with C-peptide <2ng/mL **Biological:** BMI high **Psychosocial:** Ethnicity non white	Association with HbA1c at diagnosis	Mean SD	++ ++ ++ +	Intermediate (4). XS study design and inadequate analysis