Karolinska
Institutet

**Gestational age and birth weight and the risk of
childhood type 1 diabetes : a population-based cohort
and sibling design study**

**Khashan, Ali S; Kenny, Louise C; Lundholm, Cecilia;
Kearny, Patricia M; Gong, Tong; McNamee, Roseanne;
Almqvist, Catarina**

Gestational age and birthweight and the risk of childhood type 1 diabetes: a population-based cohort and sibling design study

Short title: Gestational age and the risk of type 1 diabetes

Ali S Khashan[1,2*], PhD, Louise C Kenny[2], PhD, Cecilia Lundholm[3], MSc, Patricia M Kearney[1], PhD, Tong Gong[3], MPH, Roseanne McNamee[4], PhD, Catarina Almqvist[3,5], PhD

[1] Department of Epidemiology and Public Health, University College Cork, Cork, Ireland

[2] The Irish Centre for Fetal and Neonatal Translational Research (INFANT), Department of Obstetrics and Gynaecology, University College Cork, Cork, Ireland

[3] Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

[4] Centre for Biostatistics, Institute of Population Health, University of Manchester, Manchester, UK

[5] Astrid Lindgren Children's Hospital, Lung and Allergy Unit, Karolinska University Hospital, Stockholm Sweden

* Department of Epidemiology and Public Health, Western Gate Building, University College Cork, Ireland. Tel: +353 (21) 420 5505; Fax: +353 (21) 420 5469; Email: a.khashan@ucc.ie

Word count (3896)
Number of tables: 4
Number of figures: 1
Online supplementary Appendix 1 and Appendix 2.

1

ABSTRACT (247 words)

Objectives: We investigated the effects of gestational age, birthweight, small for gestational age (SGA) and large for gestational age (LGA) on childhood type 1 diabetes.

Methods: We conducted a population-based cohort study of all singleton live births in Sweden between 1973-2009 and a sibling-control study. Perinatal data were extracted from the Swedish Medical Birth Register. Children with type 1 diabetes diagnosis were identified from the Swedish National Patient Register. Log-linear Poisson regression and conditional logistic regression were used for data analysis.

Results: The study cohort consisted of 3,624,675 singleton live births (42,411,054 person-years). There were 13,944 type 1 diabetes cases during the study period. The sibling-control study consisted of 11,403 children with type 1 diabetes and 17,920 siblings. Gestational age between 33-36 weeks (RR=1.18; [95%CIs: 1.09, 1.28) and 37-38 weeks (RR=1.12; [95%CIs: 1.07, 1.17]) was associated with type 1 diabetes in the cohort study and remained significant in the sibling-control study. SGA (RR=0.83; [95%CIs: 0.75, 0.93]) and LGA (RR=1.14; [95%CIs: 1.04, 1.24]) were associated with type 1 diabetes in the cohort study. The SGA association remained unchanged in the sibling study while the LGA association disappeared. Very low birthweight was associated with a reduced risk of type 1 diabetes.

Conclusions: The findings suggest a small association between gestational age and type 1 diabetes that is not likely due to familial confounding factors. Gestational age and type 1 diabetes may be related to insulin resistance due to early life growth restriction or altered gut microbiota in preterm babies.

INTRODUCTION

Type 1 diabetes is a heterogeneous autoimmune disease characterized by destruction of pancreatic beta cells, resulting in absolute insulin deficiency (1). Although autoimmunity is suggested as the predominant effector mechanism, it is thought that type 1 diabetes precipitates in genetically susceptible persons due to an environmental trigger (2, 3). The prevalence of type 1 diabetes in the USA increased from 1.4 per 1000 in 2001 to 1.93 per 1000 in 2009 (4). Similar trends were observed in European countries (5). In Sweden the incidence of type 1 diabetes increased between 1978 and 2004 but plateaued after 2005 (6).

Several studies found associations between gestational age and birthweight and type 1 diabetes, although the findings are inconsistent. In a recent meta-analysis of 14 case-control studies and four cohort studies, preterm birth (gestational age<37 weeks) was found to increase the risk of type 1 diabetes by 18% (7). The authors highlighted several limitations in the literature such as a lack of consistent adjustment for important confounders. Although the majority of studies reported estimates adjusted for several important confounders, the adjustments varied across studies. It was noted that none of the included studies provided data on birthweight for gestational age. Another recent meta-analysis reported a 17% increased risk of type 1 diabetes among macrosomic infants while low birthweight was not significantly associated with type 1 diabetes (8). The authors noted lack of proper confounding adjustment as a limitation since only half of the 12 included studies provided adjusted estimates of the association between birthweight and type 1 diabetes. Among

3

studies that reported adjusted estimates, only three adjusted for gestational age, and one study adjusted for age and sex only. Significant uncertainty remains, however, about the presence and strength of any association between birthweight and type 1 diabetes (9).

We aimed to examine the effects of gestational age, small for gestational age (SGA), large for gestational age (LGA) and birthweight on childhood type 1 diabetes using population-based Swedish data with information on several potential confounders. We then performed a sibling-control study to assess whether any observed associations in the cohort study were likely to be causal. Sibling control analyses allow us to draw stronger causal inferences about these aspects of pregnancy (10-14). This approach is efficient in accounting for family factors, such as genetics and environmental factors that are shared by siblings. To our knowledge, this is the largest study on this topic to date and the first to utilize sibling control analyses to assess the effects of perinatal risk factors on type 1 diabetes.

METHODS

Study cohort

The study utilised data from the Swedish national registers held by the Swedish National Board of Health and Welfare and Statistics Sweden. Each resident in Sweden is assigned a unique identifier, the Personal Identity Number (PIN), which enables data linkage from various registers and among relatives, such as parents and siblings (15). Using the Swedish Medical Birth Register, we identified almost all singleton live births in Sweden between

4

January 1, 1973 and December 31, 2009. This register contains obstetric, maternal and neonatal data on 96-99% of births in Sweden (16). The sibling-control design study included the children with type 1 diabetes and their siblings. This is a matched case-control study – nested within the overall cohort – where the 'case' has type 1 diabetes, the 'controls' do not and the case and control are siblings.

Exposure variables

Gestational age and birthweight were measured at delivery and recorded in the Medical Birth Register. Gestational age was determined at delivery and calculated using dates from early second trimester ultrasound or calculated by menstrual dating (17) and categorized into very preterm: 22-32; preterm: 33-36; early term: 37-38; term: 39-40 (reference group); and post-term: 41+ weeks. Birthweight was considered erroneous if it was recorded as <500g or >5500g. Birthweight was categorized into: <1500g; 1500-2499; 2500-2999; 3000-3999 (reference group); 4000-5500g. SGA and LGA were defined according to the Swedish weight-based growth standards (18). SGA was defined as a birthweight of 2 standard deviations below the mean and LGA as birthweight of 2 standard deviations above the mean of the sex-specific and gestational age distributions. Children were classified into three categories: SGA, LGA and appropriate for gestational age (AGA; neither SGA nor LGA).

Outcome measure

The Swedish National Patient Register contains records of inpatient diagnoses in Sweden since 1964 (full national coverage since 1987) and

outpatient diagnoses since 2001. The date of onset of type 1 diabetes was defined as the date of the first hospitalization, which led to the diagnosis of type 1 diabetes. Childhood type 1 diabetes, before 15 years of age, was defined according to the International Classification of Diseases (ICD) 8 (250); ICD-9 (250); and ICD-10 (E10). The cohort was followed from the date of birth until onset of type 1 diabetes, 15th birthday, death, migration or December 31, 2009 (end of the study period). The Migration register provided the dates of migration from Sweden while information on date of death was obtained from the Cause of Death register.

Potential confounders

Data on infant sex, maternal age, body mass index (BMI), pre-pregnancy diabetes and gestational diabetes, country of origin, birth order, pre-eclampsia and mode of delivery were obtained from the Medical Birth Register. Maternal BMI is measured at the first antenatal visit which takes place before 15 weeks' gestation in Sweden(19). Data on maternal education level was obtained from the Education register which contains information on the residents' highest level of completed formal education.

Statistical analysis

The statistical analysis to examine the effects of gestational age, birthweight, SGA and LGA on childhood type 1 diabetes was performed in two steps. First, log-linear Poisson regression with aggregated person-years was performed for each exposure variable using the entire cohort. All Poisson models were adjusted for offspring age, as a time dependent variable, year of birth (in one

year categories), birth order and sex, maternal age, BMI, pre-pregnancy diabetes, gestational diabetes, country of origin and education level (these variables were included in the models as presented in Table 1).

The second step aimed to adjust for unmeasured familial environmental and genetic confounding factors shared by siblings using a sibling-control design. Conditional logistic regression was used for the sibling-control analyses with siblings identified through the Multi-Generation Register (20). The conditional logistic regression analysis included siblings where the control was under follow-up and type 1 diabetes free at the age that the sibling with type 1 diabetes was diagnosed. In these analyses, only siblings discordant for each exposure variable categories as well as type 1 diabetes contributed to the measure of association. However, siblings concordant for the exposure variable categories were included in the analysis as they contribute to the potential confounders estimates. The models were adjusted for the same variables as in the Poisson models apart from maternal country of birth, which was the same for both siblings. A sensitivity analysis was performed including full siblings only in the sibling study.

Additional analyses

Considering the complex relationship between birthweight and birthweight for gestational age with gestational age, we repeated the birthweight for gestational age models restricting the analysis to children with gestational age of ≥37 weeks and then more than ≥39 weeks. Similarly, we repeated the gestational age models excluding SGA and LGA children. Between 1973 and 1981 we were able to classify mode of delivery into unassisted vaginal

delivery (VD), instrumental vaginal delivery (IVD) and Caesarean section (CS) while from 1982 data on elective and emergency CS were available and were used to classify CS. Data on maternal BMI were available from 1981 onwards. However, more than 20% of the women who delivered their children from 1981 onwards had missing BMI data. Therefore, we repeated the models from 1982 onwards (to coincide with the more detailed data on mode of delivery) as well as models excluding all women with missing BMI. To assess the potential impact of missing BMI data on the observed association between gestational age and type 1 diabetes, we performed two Poisson regression models including all births from 1981 onwards with know maternal BMI. In the first model we removed maternal BMI and in the second model we included BMI (in addition to the other potential confounders as described in the Tables footnote). Considering that data coverage was complete at the national level from 1987 we repeated the statistical models including births from 1987 onwards.

Further analyses were performed excluding 1) IVD and CS; 2) children of mothers who had pre-eclampsia; 3) children of mothers who had pre-gestation diabetes; 4) children of women who had gestational diabetes; 5) children of women who were classified as obese (BMI≥30kg/m^2). We performed these analyses to assess whether those factors have any influence on the observed associations as they were found to be associated with type 1 diabetes in previous studies (19, 21, 22). We also repeated the Poisson models including only-children. To examine the distributional assumption of the Poisson regression regarding over-dispersion, we performed negative

binomial regression models. There was no evidence to suggest the distributional assumption was violated therefore the Poisson models results are presented throughout the manuscript. In post-hoc analyses, we repeated the sibling-control models excluding children of women who had pre-gestational or gestational diabetes. Furthermore, we performed detailed post-hoc analyses to examine the association between gestational age and type 1 diabetes using finer gestational age categories. We repeated the Poisson regression analysis using gestational age categorized as 22-29 weeks and in one-week categories thereafter. Gestational age weeks 22-29 were combined in one category due to small number of cases in each week category. Finally, we performed sensitivity analysis to examine the potential effect of unmeasured confounding (see Appendix 2 for details).

RESULTS

The study cohort consisted of 3,624,675 singleton live births with known PIN and gender in Sweden between January 1, 1973 and December 31, 2009 (Figure 1). During the study period (42,411,054 person-years) there were 13,944 childhood type 1 diabetes cases. Mean age at diagnosis was 8.4 years (8.5 in boys and 8.3 in girls). Mothers of children with type 1 diabetes were on average older, had a higher education level and more likely to have pre-pregnancy diabetes. The sibling-control study consisted of 82% (11403/13944) of the type 1 diabetes cases in the cohort study (sibling pairs discordant on type 1 diabetes). The majority of the children with type 1 diabetes that were not included in the sibling analysis were only-children (2163/13944; 15.5%). The maternal characteristics in the sibling-control study

were similar to those of the entire cohort apart from pre-gestation and gestational diabetes, which were more common in the sibling-control study. More details are summarized in Table 1 and Table e1 (Appendix 1).

Gestational age

Gestational age was significantly associated with the risk of type 1 diabetes. Very preterm (RR=0.67; [95% CI: 0.53, 0.84]) and post-term (RR=0.87; [95% CI: 0.83, 0.90]) births were less likely to develop type 1 diabetes while preterm (RR=1.18; [95% CI: 1.09, 1.28]) and early term births (RR=1.12; [95% CI: 1.07, 1.17]) were more likely to develop type 1 diabetes compared to children born at term (Table 2; column 4). All these associations remained statistically significant and almost unchanged in the sibling-control study (Table 2, column 6). We further performed a log-linear Poisson regression to examine the association between gestational age (classified into 1-week categories whenever possible) and type 1 diabetes (Table e2, Appendix 1). These findings suggested that the risk of type 1 diabetes was largest among children born at 34 weeks' gestation. To assess how robust the association is in relation to unmeasured confounding we performed sensitivity analyses using different scenarios. The details of this analysis and the results are presented in Appendix 2.

Birthweight for gestational age

In the cohort study there were significant associations between SGA (RR=0.83; [95% CI: 0.75, 0.93]) and LGA (RR=1.14; [95% CI: 1.04, 1.23]) and the risk of type 1 diabetes (Table 3, column 4). The association between SGA

and type 1 diabetes remained unchanged and statistically significant in the sibling analysis while the association between LGA and type 1 diabetes was no longer statistically significant (Table 3, column 6). Restricting the cohort analyses to early term and term babies did not change the results of SGA or LGA materially.

Birthweight

Very low birthweight (<1500g) children were at lower risk of type 1 diabetes compared to children with normal birthweight (RR=0.66; [95% CI: 0.48, 0.91]) (Table 4, column 4). This association remained statistically significant in the sibling analysis (RR=0.50; [95% CI: 0.31, 0.80])(Table 4, column 6). Further adjustment for gestational age in the sibling control model reduced the association slightly (RR=0.59, [95% CI: 0.33, 1.07]). The other birthweight categories were not associated with type 1 diabetes with most RRs close to unity (Table 4). Of the very low birthweight children 95% were born before 37 weeks' gestation (16,506/17,333). When the analysis was restricted to children born before 37 gestation weeks, the association between very low birthweight (RR=0.47, [95% CI: 0.32, 0.67]) and low birthweight (RR=0.73, [95% CI: 0.60, 0.88]) and type 1 diabetes was statistically significant with larger effect size, although the statistical interaction terms between birthweight and gestational age categories were not statistically significant (p-value for interaction>0.05).

Additional analyses

When the models were repeated for births from 1987 onwards at the cohort level the findings were not materially changed compared to the full cohort models (data not shown). When we repeated the cohort analyses for all the exposure variables excluding birth before 1981 and then excluding all births with missing BMI data, no material change was observed. Repeating the analysis using data on full siblings only did not change the results materially. Additional cohort analyses on the three exposure variables were performed restricting to 1) only-children ; 2) AGA children; 3) unassisted vaginal delivery; 4) mothers with no pre-pregnancy diabetes; 5) mothers with no gestational diabetes; 6) non-obese mothers; and 7) mothers with no pre-eclampsia (Table e3, Appendix 1). Overall, none of these restrictions had any material effect on the findings. Restricting the Poisson models to the first two children per mother did not change the results materially. Excluding diabetes and gestational diabetes from the sibling models did not explain any of the observed associations.

DISCUSSION

This study investigated the effects of gestational age, birthweight, SGA and LGA on the risk of childhood type 1 diabetes using a large population-based cohort including nearly all births in Sweden over four decades. We used a unique approach by applying both cohort and sibling-control designs using the same population. Preterm and early term birth were associated with an increased risk of type 1 diabetes in the cohort study while very preterm, post-term, SGA and very low birthweight were associated with a reduced risk of

type 1 diabetes. All these associations remained significant in the sibling-control study suggesting a potential causal association.

LGA was associated with an increased risk of type 1 diabetes in the cohort analysis but the association disappeared in the sibling analysis, which suggests that familial factors that are shared between siblings such as genetics and environmental factors might explain, at least partly, this association. There was very little evidence to support an association between birthweight of 1,500 grams or greater and type 1 diabetes.

Comparison with previous literature

The existing literature on birthweight and gestational age and type 1 diabetes is inconsistent. A recent systematic review and meta-analysis identified 18 studies on the association between gestational age and type 1 diabetes (7). Interestingly, all the identified studies were published in the last two decades, reflecting the increasing interest in the effect of perinatal risk factors on type 1 diabetes. The present finding that preterm birth increases the risk of type 1 diabetes in the cohort study is almost the same as the pooled estimate from the meta-analysis. However, the meta-analysis did not report data on very preterm, early term or post term and type 1 diabetes. Another meta-analysis suggested that birthweight>4,000 grams increases the risk of type 1 diabetes by 43% (8). This is inconsistent with the findings of the present study as we found no evidence for type 1 diabetes increased risk among children born with birthweight>4,000 grams. Although LGA children were found to have 14% increased risk of type 1 diabetes in the cohort study, this association was not consistent with a causal association in the sibling analysis. Our findings on

13

low birthweight, however, are consistent with the meta-analysis especially when we restricted the low birthweight analysis to preterm births. Robertson and Harrild reported no association between maternal and neonatal risk factors including birthweight and gestational age and type 1 diabetes in a matched case-control study (23). It should be noted that they found increased odds of type 1 diabetes in children born preterm (<37 weeks) or with low birthweight (<2500 grams), although the results were not statistically significant. This suggests that the apparently inconsistent findings could be related to lack of adequate statistical power in Robertson and Harrild (23). Additionally, we categorized both birthweight and gestational age into more tightly defined groups including very low birthweight and very preterm birth while they used preterm birth as <37 weeks and low birthweight as <2500 grams, which makes the comparison more complicated. The observed association between gestational age and type 1 diabetes is consistent with a large population-based study from Western Australia, which found increased risk of type 1 diabetes in preterm and early term children (24). Haynes et al., also reported a small association between increased birthweight and increased birthweight for gestational age and higher risk of type 1 diabetes, while we found little evidence for such an association. In another large population-based study from Northern Ireland, Cardwell et al., reported an increased risk of type 1 diabetes with higher birthweight which is not consistent with our findings (25). Comparing our gestational age finding, however, is more difficult as Cardwell et al., categorized gestational age as <39 (reference group); 39; 40 and ≥41 weeks' gestation. Contrary to the present findings, Dahlquist et al., (1999), reported no association between

gestational age and type 1 diabetes in the EURODIAB study which included data from seven European studies (26). They also reported reduced risk of type 1 diabetes in low birthweight children but not SGA babies. To our knowledge, ours is the first study to perform a sibling-control study nested within a cohort on this topic, therefore there are no other studies to compare our results.

Strengths and limitations

This study has several strengths. First, the study was based on a very large population-based data of 3.6 million children born in Sweden over four decades, which is, to our knowledge, the most comprehensive study on this topic. Second, the data obtained from the national registers were prospectively collected therefore the data on the outcome, exposures and potential confounders are not subject to recall bias. Third, the type 1 diabetes diagnoses were based on ICD-8, 9 and 10 with a known and accurate date of first hospitalization, which is considered the date of diagnosis. Data on type 1 diabetes in Sweden is known to be of very high quality (27). Fourth, we were able to adjust for several potential confounders, which were adjusted for in previous studies. Finally, in addition to the conventional cohort analyses, sibling control analyses were performed. It is worth noting that the sibling design study can rule out a number of potential explanations for observed associations compared to observational designs using unrelated controls. Moreover, sibling design studies may play an important role in assessing potentially causal associations. In the present study, statistical models of the sibling-control study allowed us to adjust for unmeasured factors that are

shared by siblings such as family environment, diet, lifestyle, maternal characteristics and genetic factors.

The following limitations should be considered when interpreting the study findings. First, we used data on almost all births in Sweden from 1973 and complete nationwide coverage on diagnoses was not achieved until 1987. However, our sensitivity analyses showed that restricting the data to births from 1987 onwards were consistent with the overall results. Second, although we had access to several potential confounders, there was lack of data on several others. For example, we had no data on maternal life style during pregnancy such as physical activity, diet and weight gain. Excessive weight gain during pregnancy, maternal nitrite intake and cod liver oil supplementation have been associated with the risk of type 1 diabetes (28). Furthermore, we had no data on parental and family life style such as family diet and attitude to acquiring health care. However, the risk of residual confounding was reduced by the sibling control analyses. Sibling control statistical models are effective in adjusting for unmeasured familial characteristics that are shared by siblings i.e. maternal and paternal factors that were fixed for each family across pregnancies. Although, these methods cannot rule out unmeasured confounding factors that simultaneously vary between siblings i.e. parental factors that are not permanently fixed for each family and could potentially be different for different pregnancies (29).

Potential mechanisms

It has been hypothesized that the effect of preterm and early term birth on the risk of type 1 diabetes may be related to fetal growth restriction (7). Our data however, do not support this hypothesis, as the association was unchanged when SGA children were excluded from the analysis. Another hypothesis suggests that preterm children may have experienced growth restriction in early life and the catch-up growth may result in later insulin resistance (30). It is possible that preterm births experience structural change within organ systems and epigenetic changes leading to higher risk of type 1 diabetes. The observed associations between preterm and early term birth and type 1 diabetes are unlikely to be related to maternal diabetes as this was corrected for in the cohort and sibling analyses. Notably, the results remained unchanged when women with pre-gestation or gestational diabetes were excluded from the analyses. Finally, preterm children have been suggested to have an altered microbiota, which may play a role in the development of type 1 diabetes (31). Kostic et al., performed a study to examine the link between human gut microbiome in infancy and type 1 diabetes in 33 infants genetically predisposed to type 1 diabetes (32). They found a marked drop in alpha-diversity in type 1 diabetes progressors between seroconversion and type 1 diabetes diagnosis. It is interesting that very preterm and very low birthweight babies have been suggested also to have an altered microbiota but they were not associated with an increased risk of type 1 diabetes in the present study (31). Indeed very preterm, SGA and very low birthweight babies appeared to have significantly lower risk of type 1 diabetes. The effects of very preterm and very low birthweight on type 1 diabetes were not studied thoroughly in the past as such a study of rare exposure and rare outcome would require large

cohorts. The biological mechanism of this association is not known but It is possible that it is due to fetal programming where the most vital organs are protected. These findings are worth replicating in other populations as they may generate further hypotheses on the effect of perinatal risk factors on type 1 diabetes.

Conclusion

We found that preterm and early term babies are at increased risk of type 1 diabetes while very preterm birth, very low birthweight and SGA babies at reduced risk of type 1 diabetes. The sibling study suggested that these associations, although small, were not due to familial factors shared by siblings. Further research is warranted to replicate these findings and understand the potential biological mechanisms.

REFERENCES

1.   Vehik K, Dabelea D. The changing epidemiology of type 1 diabetes: why is it going through the roof? Diabetes/metabolism research and reviews. 2011;27(1):3-13.
2.   Atkinson MA, Eisenbarth GS. Type 1 diabetes: new perspectives on disease pathogenesis and treatment. Lancet. 2001;358(9277):221-9.
3.   van Belle TL, Coppieters KT, von Herrath MG. Type 1 diabetes: etiology, immunology, and therapeutic strategies. Physiological reviews. 2011;91(1):79-118.
4.   Dabelea D, Mayer-Davis EJ, Saydah S, Imperatore G, Linder B, Divers J, et al. Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009. JAMA. 2014;311(17):1778-86.
5.   Patterson CC, Dahlquist GG, Gyürüs E, Green A, Soltész G. Incidence trends for childhood type 1 diabetes in Europe during 1989–2003 and predicted new cases 2005–20: a multicentre prospective registration study. The Lancet. 2009;373(9680):2027-33.
6.   Berhan Y, Waernbaum I, Lind T, Möllsten A, Dahlquist G. Thirty years of prospective nationwide incidence of childhood type 1 diabetes the accelerating increase by time tends to level off in sweden. Diabetes. 2011;60(2):577-81.
7.   Li S, Zhang M, Tian H, Liu Z, Yin X, Xi B. Preterm birth and risk of type 1 and type 2 diabetes: systematic review and meta-analysis. Obesity reviews : an official journal of the International Association for the Study of Obesity. 2014;15(10):804-11.
8.   Harder T, Roepke K, Diller N, Stechling Y, Dudenhausen JW, Plagemann A. Birth weight, early weight gain, and subsequent risk of type 1 diabetes: systematic review and meta-analysis. Am J Epidemiol. 2009;169(12):1428-36.
9.   Cardwell CR, Patterson CC. Re: "birth weight, early weight gain, and subsequent risk of type 1 diabetes: systematic review and meta-analysis". Am J Epidemiol. 2009;170(4):529-30; author reply 30-1.
10.   D'Onofrio BM, Rickert ME, Langstrom N, Donahue KL, Coyne CA, Larsson H, et al. Familial Confounding of the Association Between Maternal Smoking During Pregnancy and Offspring Substance Use and Problems. Arch Gen Psychiat. 2012;69(11):1140-50.
11.   Almqvist C, Cnattingius S, Lichtenstein P, Lundholm C. The impact of birth mode of delivery on childhood asthma and allergic diseases--a sibling study. Clin Exp Allergy. 2012;42(9):1369-76.
12.   Obel C, Olsen J, Henriksen TB, Rodriguez A, Jarvelin MR, Moilanen I, et al. Is maternal smoking during pregnancy a risk factor for hyperkinetic disorder?--Findings from a sibling design. International journal of epidemiology. 2011;40(2):338-45.
13.   Khashan AS, Kenny LC, Lundholm C, Kearney PM, Gong T, Almqvist C. Mode of obstetrical delivery and type 1 diabetes: a sibling design study. Pediatrics. 2014;134(3):e806-13.
14.   Donovan SJ, Susser E. Commentary: Advent of sibling designs. International journal of epidemiology. 2011;40(2):345-9.
15.   Ludvigsson J, Otterblad-Olausson P, Pettersson B, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. European journal of epidemiology. 2009;24:659-67.
16.   The Centre of Epidemiology and the National Board of Health and Welfare (http://www.socialstyrelsen).

17.	National Board on Health and Welfare. The Swedish Medical Birth Register - A summary of content and quality. Centre for Epidemiology, Stockholm, Sweden. 2003;Report 112-3.

18.	Maršál K, Persson PH, Larsen T, Lilja H, Selbing A, Sultan B. Intrauterine growth curves based on ultrasonically estimated foetal weights. Acta Paediatrica. 1996;85(7):843-8.

19.	Hussen HI, Persson M, Moradi T. Maternal overweight and obesity are associated with increased risk of type 1 diabetes in offspring of parents without diabetes regardless of ethnicity. Diabetologia. 2015;58(7):1464-73.

20.	Ekbom A. The Swedish Multi-generation Register. Methods Mol Biol. 2011;675:215-20.

21.	Cardwell CR, Stene LC, Joner G, Cinek O, Svensson J, Goldacre MJ, et al. Caesarean section is associated with an increased risk of childhood-onset type 1 diabetes mellitus: a meta-analysis of observational studies. Diabetologia. 2008;51(5):726-35.

22.	Henry E, Patterson C, Cardwell C. A meta‐analysis of the association between pre‐eclampsia and childhood‐onset Type 1 diabetes mellitus. Diabetic Medicine. 2011;28(8):900-5.

23.	Robertson L, Harrild K. Maternal and neonatal risk factors for childhood type 1 diabetes: a matched case-control study. BMC public health. 2010;10(1):281.

24.	Haynes A, Bower C, Bulsara MK, Finn J, Jones T, Davis E. Perinatal risk factors for childhood Type 1 diabetes in Western Australia–a population‐based study (1980–2002). Diabetic Medicine. 2007;24(5):564-70.

25.	Cardwell C, Carson D, Patterson C. Parental age at delivery, birth order, birth weight and gestational age are associated with the risk of childhood Type 1 diabetes: a UK regional retrospective cohort study. Diabetic Medicine. 2005;22(2):200-6.

26.	Dahlquist GG, Patterson C, Soltesz G. Perinatal risk factors for childhood type 1 diabetes in Europe - The EURODIAB substudy 2 study group. Diabetes Care. 1999;22(10):1698-702.

27.	Dahlquist GG, Nystrom L, Patterson CC, Grp SCDS, Grp DISS. Incidence of Type 1 Diabetes in Sweden Among Individuals Aged 0-34 Years, 1983-2007 An analysis of time trends. Diabetes Care. 2011;34(8):1754-9.

28.	Virtanen S, Knip M. Nutritional risk predictors of beta cell autoimmunity and type 1 diabetes at a young age. The American journal of clinical nutrition. 2003;78(6):1053-67.

29.	Frisell T, Oberg S, Kuja-Halkola R, Sjolander A. Sibling comparison designs: bias from non-shared confounders and measurement error. Epidemiology. 2012;23(5):713-20.

30.	Tinnion R, Gillone J, Cheetham T, Embleton N. Preterm birth and subsequent insulin sensitivity: a systematic review. Arch Dis Child. 2014;99(4):362-8.

31.	Groer MW, Luciano AA, Dishaw LJ, Ashmeade TL, Miller E, Gilbert JA. Development of the preterm infant gut microbiome: a research priority. Microbiome. 2014;2:38.

32.	Kostic A, Gevers D, Siljander H, Vatanen T, Hyötyläinen T, Hämäläinen A, et al. The Dynamics of the Human Infant Gut Microbiome in Development and in Progression toward Type 1 Diabetes. Cell Host Microbe. 2015;17(2):260-73.

Figure 1: Flowchart of study population

3,731,304 births (1973-2009)

Exclusions:
12,105 stillbirths; 90,219 multiple births; 98 unknown infant sex; 9 children with missing maternal unique PIN;

4198 were excluded because their follow-up ended on the same day of birth (4021 children died on the first day of life and 177 were born on 31 December 2009).

3,624,675singleton live births with known sex and known maternal PIN

13944 children with Type 1 diabetes

21,488 children with any Diabetes

Gestational age analysis
N=3,616,628
8047 births with missing gestational age

Birthweight for gestational age analysis
N=3,605,655
19,020 births with missing birthweight and/or gestational age
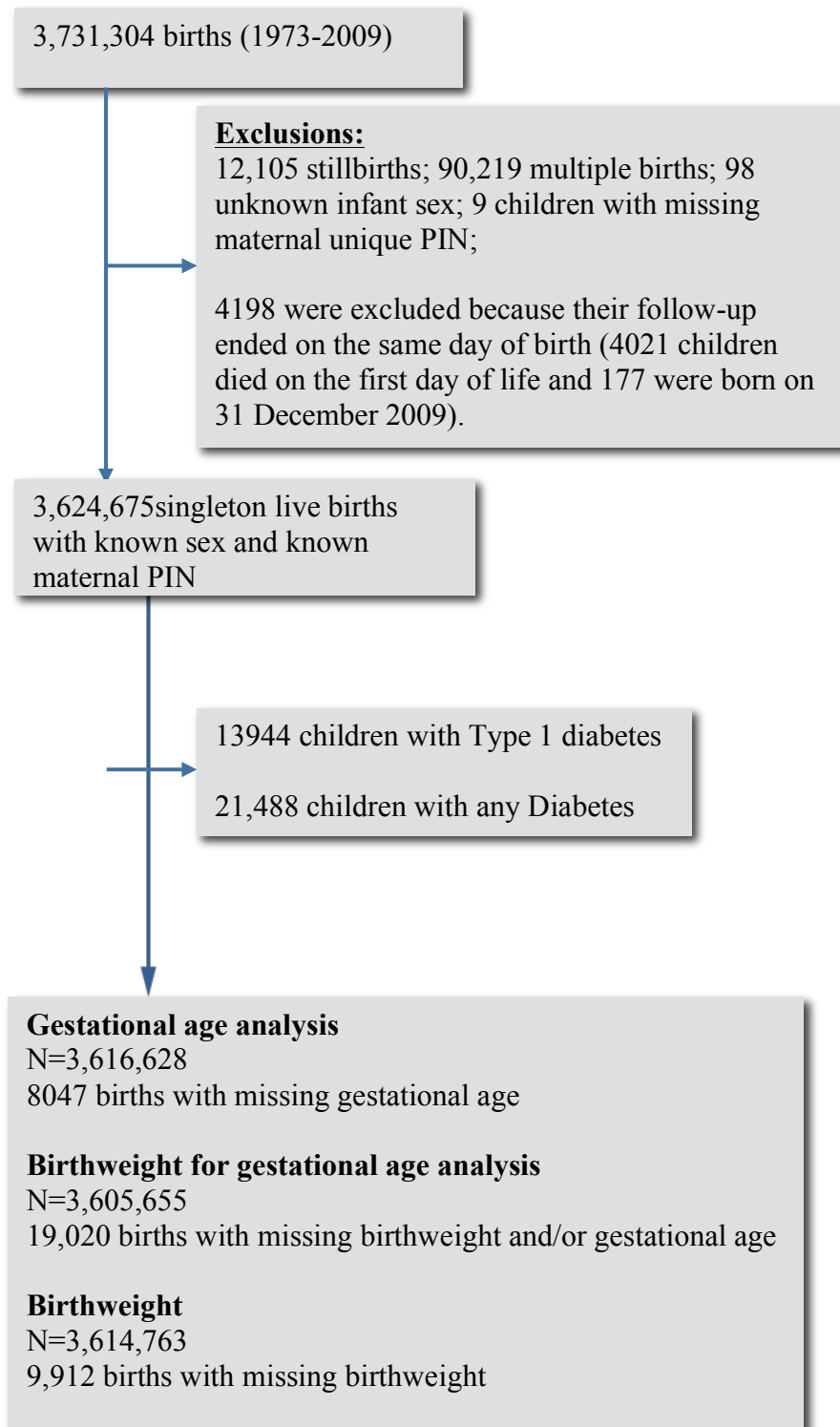
Birthweight
N=3,614,763
9,912 births with missing birthweight

Table 1: maternal characteristics in relation to childhood type 1 diabetes

Potential confounders	Cohort Study		Sibling Study	
	No type 1 diabetes n(%)	Childhood type 1 diabetes, n(%)	No type 1 diabetes n(%)	Childhood type 1 diabetes, n(%)
	n=3,610,731	n=13,944	n=17,920	n=11,403
Maternal Age				
<20	119,097 (3.3)	392 (2.8)	734 (4.1)	332 (2.9)
20-24	759,591 (21.0)	2,986 (21.4)	4,229 (23.6)	2,567 (22.5)
25-29	1,276,985 (35.4)	5,042 (36.2)	6,246 (34.8)	4,207 (36.9)
30-34	987,944 (27.4)	3,762 (27.0)	4,410 (24.6)	3,022 (26.5)
35-39	394,022 (10.9)	1,498 (10.7)	1,948 (10.9)	1,105 (9.7)
40+	73,092 (2.0)	264 (1.9)	353 (2.0)	170 (1.5)
Maternal BMI (1982-2009) (kg/m^2)				
Normal	1,368,687 (37.9)	5,006 (35.9)	6,507 (36.3)	4,326 (37.9)
Underweight	84,234 (2.3)	288 (2.1)	459 (2.6)	257 (2.2)
Overweight	416,586 (11.5)	1,551 (11.1)	2,082 (11.6)	1,331 (11.7)
Obese	155,200 (4.3)	592 (4.2)	825 (4.6)	503 (4.4)
Missing	717,041 (19.9)	3,342 (24.0)	4,458 (24.9)	2,891 (25.3)
Births before 1981	868,983 (24.1)	3,165 (22.7)	3,589 (20.0)	2,095 (18.4)
Maternal Education				
≤9 years	743,753 (20.6)	2,975 (21.3)	4,003 (22.3)	2,230 (19.6)
High school	1,592,921 (44.1)	7,012 (50.3)	8,731 (48.7)	5,813 (51.0)
University	920,961 (25.5)	3,257 (23.4)	3,907 (21.8)	2,760 (24.2)
Missing	353,096 (9.8)	700 (5.0)	1,279 (7.1)	600 (5.3)
Maternal Country of birth				
Sweden	3,072,713 (85.1)	12,747 (91.4)	16,355 (91.3)	10,484 (91.9)
Other Nordic	150,938 (4.2)	573 (4.1)	703 (3.9)	436 (3.8)
Other	387,080 (10.7)	624 (4.5)	862 (4.8)	483 (4.2)
Maternal Pre-gestation diabetes				
No	3,593,342 (99.5)	13,595 (97.5)	17,572 (98.1)	11,160 (97.9)
Yes	17,389 (0.5)	349 (2.5)	348 (1.9)	243 (2.1)
Maternal Gestational diabetes				
No	3,590,867 (99.5)	13,695 (98.2)	17,667 (98.8)	11,229 (98.5)
Yes	19,864 (0.5)	249 (1.8)	253 (1.4)	174 (1.5)

Table 2: The association between gestational age and childhood type 1 diabetes

Gestational age, weeks	Type 1 diabetes, n	Partially adjusted, RR(95% CI)[a]	Adjusted, RR(95% CI)[b]	Type 1 diabetes, n[d]	Sibling study with full adjustment, RR(95% CI)[c]
Very preterm: 22-32	72	0.71(0.56, 0.90)	0.67(0.53, 0.84)	54	0.57(0.39, 0.83)
Preterm: 33-36	716	1.26(1.17, 1.36)	1.18(1.09, 1.28)	551	1.16(1.02, 1.32)
Early term: 37-38	2,785	1.14(1.09, 1.19)	1.12(1.07, 1.17)	2,245	1.10(1.03, 1.18)
Term: 39-40	7,082	Reference [1]	Reference [1]	5,856	Reference [1]
Post-term: ≥41	3,260	0.88(0.84, 0.91)	0.87(0.83, 0.90)	2,677	0.93(0.87, 1.00)

a The model was adjusted for offspring age and year of birth as time dependent variables
b The model was adjusted for offspring age as time dependent variables, year of birth, maternal age, education, BMI, country of origin, pre-gestation diabetes, gestational diabetes and infant sex. Covariates were included in the models categorized as presented in Table 1. Year of birth was included in the models as categorical in one year categories. Offspring age was included in the Poisson models as a time-dependent variable.

c adjusted as in b without maternal country of origin
d number of TYPE 1 DIABETES cases in sibling pairs discordant on the outcome

Table 3: The association between birthweight for gestational age and childhood type 1 diabetes

Birthweight for gestational age	Type 1 diabetes, n	Partially adjusted, RR(95% CI)[a]	Adjusted, RR(95% CI)[b]	Type 1 diabetes, n[d]	Sibling study with full adjustment, RR(95% CI)[d]
Birthweight for gestational age					
AGA	12,969	Reference [1]	Reference [1]	10,634	Reference [1]
SGA	329	0.84(0.75, 0.93)	0.83(0.75, 0.93)	235	0.83(0.69, 0.99)
LGA	586	1.31(1.21, 1.42)	1.14(1.04, 1.24)	489	1.00(0.87, 1.15)

a The model was adjusted for offspring age and year of birth as time dependent variables
b The model was adjusted for offspring age as time dependent variables, year of birth, maternal age,
education, BMI, country of origin, pre-gestation diabetes, gestational diabetes and infant sex. Covariates were included in the models as presented in Table 1. Year of birth was included in the models as categorical in one year categories. Offspring age was included in the Poisson models as a time-dependent variable.
c adjusted as in b without maternal country of origin
d number of TYPE 1 DIABETES cases in sibling pairs discordant on the outcome

Table 4: The association between birthweight and childhood type 1 diabetes

Birthweight (in grams)	Type 1 diabetes, n	Partially adjusted, RR(95% CI)[a]	Adjusted, RR(95% CI)[b]	Type 1 diabetes, n[d]	Sibling cohort full adjustment, RR(95% CI)[d]
<1500	39	0.70(0.51,0.96)	0.66(0.48,0.91)	28	0.50(0.31, 0.80)
1500-2499	383	0.97(0.88,1.08)	0.95(0.86,1.05)	289	0.94(0.80, 1.12)
2500-2999	1,534	1.01(0.95,1.06)	1.02(0.97,1.08)	1,168	1.03(0.94, 1.13)
3000-3999	9,351	Reference [1]	Reference [1]	7,705	Reference [1]
4000-5500	2,610	1.06(1.01,1.11)	1.01(0.96,1.05)	2,193	0.94(0.87, 1.01)

a The model was adjusted for offspring age and year of birth as time dependent variables
b The model was adjusted for offspring age as time dependent variables, year of birth, maternal age, education, BMI, country of origin, pre-gestation diabetes, gestational diabetes and infant sex. Covariates were included in the models as presented in Table 1. Year of birth was included in the models as categorical in one year categories. Offspring age was included in the Poisson models as a time-dependent variable.

c adjusted as in b without maternal country of origin
d number of TYPE 1 DIABETES cases in sibling pairs discordant on the outcome