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Mode of Obstetrical Delivery and Type 1 Diabetes: a Sibling Design Study

Running Title: Delivery and Type 1 Diabetes

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Abbreviations: CS= Caesarean section; T1D= type 1 diabetes; IVD=instrumental vaginal delivery; SGA=small for gestational age; LGA=large for gestational age; BMI=body mass index; ICD=international classification of disease; RR=relative risk; CI=confidence interval; PIN=personal identity number

Keywords: type 1 diabetes, pregnancy, caesarean section, model of delivery, sibling control design

What's known on this subject?

Several studies have reported an association between Caesarean section and childhood type 1 diabetes. Most of these studies lacked important information on indication for Caesarean section and induction of labour. It is unknown whether the reported associations are causal.

What this study adds?

Use of a very large population-based cohort of 2.6 million children born between 1982-2009. The study included information on indication for Caesarean section and performed sibling-control analyses. Although there appears to be an association between CS / IVD and risk, the sibling analysis findings suggest the association is not causal. The findings are crucial evidence to advise women on mode of delivery choice.

Contributors' Statement

Ali S Khashan (ASK) conceptualized and designed the study, performed the statistical analysis and drafted the initial manuscript.

Louise C Kenny contributed to the study design, interpreted the results and reviewed and revised the manuscript.

Cecilia Lundholm contributed to the study design and supervised the statistical analysis, interpreted the results and reviewed and revised the manuscript.

Patricia Kearney contributed to the drafting of the initial manuscript, interpreted the results and reviewed and revised the manuscript.

Tong Gong contributed to the study design and prepared the study cohort including performing data linkage from several registers and reviewed and revised the manuscript.

Catarina Almqvist conceptualized and designed the study (with ASK), acquired the permission to access the data and perform the study, interpreted the results and reviewed and revised the manuscript.

All authors approved the final version to be submitted and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

ABSTRACT (244 words)

Objectives: We investigated the association between CS and type 1 diabetes, and if the association remains after accounting for familial confounding using a sibling-control design.

Methods: We conducted a population-based cohort study of all singleton live births in Sweden between 1982-2009, followed by sibling-control analyses. Type 1 diabetes diagnoses were identified from the Swedish National Patient Register. Mode of delivery was categorized into unassisted vaginal delivery (reference group), instrumental vaginal delivery (IVD), emergency CS and elective CS. The statistical analysis was conducted in two steps; firstly log-linear Poisson regression with aggregated person-years using the full cohort; secondly, conditional logistic regression for sibling-control analyses. The sibling analysis included siblings who were discordant for both mode of delivery and type 1 diabetes.

Results: In the cohort analyses (N=2,638,083), there was an increased risk of childhood type 1 diabetes among children born by elective CS (adjusted RR=1.15, [95% CI: 1.06-1.25]) and IVD (RR=1.14, [1.06, 1.23]) but not emergency CS (RR=1.02, [0.95, 1.11]) when compared to children born by unassisted vaginal birth. However, the effect of elective CS and IVD on childhood type 1 diabetes almost disappeared and became non-significant in the sibling-control analyses.

Conclusions: The present findings suggest a small association between elective CS and IVD and childhood type 1 diabetes. The sibling-control results, however, suggest that these findings are not consistent with causal effects of mode of delivery on type 1 diabetes and may be due to familial confounders such as genetic susceptibility and environmental factors.

INTRODUCTION

Type 1 diabetes (T1D) is increasing in incidence worldwide (1, 2) and the increase is particularly marked in younger children.(3) Environmental factors implicated in the increase in T1D include infections in pregnant women,(4) chemical exposure,(5) increasing maternal age,(6) and variations in vitamin D intake.(7)

The hygiene hypothesis proposes that the global increase in incidence of allergy is due to a lack of exposure to childhood infection.(8)Recently, there is increasing recognition of the pivotal role of the microbiome in the development of the immune system. Mode of delivery is a critical step in determining the infant microbiome. Infants born by elective (pre-labor) Caesarean section (CS) are predominantly colonized by bacteria originating from the hospital environment and maternal skin, whereas those born by vaginal delivery are colonized by bacteria from the mother's birth canal. Indeed, a recent meta-analysis reported a 20% increased risk of T1D among children born by CS compared to those born vaginally.(9) With CS rates at the highest ever recorded (10), any negative effect of CS on the risk of T1D, which is also increasing worldwide would be a public health concern.

Although several studies investigated the effect of CS on the risk of childhood T1D, the majority did not report separate estimates for elective and emergency CS.(9) More importantly, all the studies relied on adjusting for statistical covariates to account for confounding factors, which only provides qualified support for causal inference because of an inability to account for unmeasured confounders such as home environment or genetic susceptibility. As randomized controlled trials on the mode of delivery in women are unethical, sibling design studies can provide a valid alternative to draw strong causal inferences.(11-14)

This study compares the risk of T1D among children born by elective CS, and for completeness emergency CS and instrumental vaginal delivery (IVD), with those born by vaginal delivery using population-based data from the Swedish national registers. In order to control for genetic and environmental factors that may influence the mode of delivery as well as the risk of disease outcomes including T1D, sibling control analyses have been undertaken.(12, 15) To our knowledge this is the first study to utilise sibling controls to determine the effect of mode of delivery on the risk of T1D.

PATIENTS and METHODS

Study cohort

The study cohort consisted of all singleton live births in Sweden between 1982 and 2009. The study was based on 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 is used uniformly across all services in Sweden.(16) The PIN enables the linkage of data from various registers as well as linkage of data on relatives, such as siblings. Using data from the Swedish Medical Birth Register, we identified almost all children born in Sweden between January 1, 1982 and December 31, 2009. This register contains obstetric, maternal and neonatal data on >99% of births in Sweden.

Exposure

Data on obstetric complications were retrieved from the Medical Birth Register. Mode of delivery was classified into unassisted vaginal delivery, IVD (forceps or vacuum extraction), emergency CS and elective CS. Emergency and elective CS were defined as CS after onset of labor and before onset of labor respectively. Unassisted

vaginal delivery included spontaneous and induced vaginal deliveries. However, from 1990, a new variable for the classification of mode of delivery was recorded with more detail than in the previous years including information about whether labor was spontaneous or induced. Although the main aim was to investigate the effect of elective CS and risk of T1D for completeness we also investigated the association between emergency CS and IVD and risk of T1D. We also explored the confounding effect of gestational age and induction of labor on any observed associations between mode of delivery and childhood T1D.

Outcome measures

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 T1D is defined as the date of the first admission to hospital, which led to the diagnosis of T1D. The primary outcome measure in this study was childhood T1D, before 15 years of age, defined according to the International Classification of Diseases (ICD) 8 (250); ICD-9 (250); and ICD-10 (E10). Secondary outcome measures included T1D at any age (maximum age was 27 years in the study cohort) and any diabetes diagnosis defined according to ICD-8 (250); ICD-9 (250) and ICD-10 (E10-14). The cohort was followed from the date of birth until the onset of the outcome measure, 15^{th} birthday (for the primary outcome only), 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 small for gestational age (SGA), large for gestational age (LGA), gestational age, birth order, pre-eclampsia, infant sex, maternal age, body mass index (BMI), pre-pregnancy diabetes and gestational diabetes were obtained from the Medical Birth Register. 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 investigate the association between mode of delivery and the risk of T1D was performed in two steps. In the first step, log-linear Poisson regression with aggregated person-years was performed using the study cohort. The Poisson model was adjusted for offspring age as a time-dependent variable, year of birth, gestational age and maternal pre-pregnancy diabetes. Further adjustment for birth order, maternal age, BMI, country of birth, education, gestational diabetes, SGA, LGA and pre-eclampsia did not change the results materially and were excluded from the models. These variables were included in the Poisson model as described in Table 1. The second step aimed to adjust for unmeasured familial environmental and genetic confounding factors shared by the siblings using sibling control analyses, which was analysed with conditional logistic regression with the mother as the grouping variable.(15) This analysis included the first two children of the mother, and therefore some of these siblings may have had different fathers, who were discordant for mode of delivery and T1D diagnosis. In addition, the conditional logistic models were restricted to pairs of siblings where the control was under follow-up and T1D free at the age that the sibling with T1D was diagnosed. In this analysis, only siblings

discordant for mode of delivery as well as T1D contributed to the estimates of interest. However, sibling pairs concordant for mode of delivery were included in the analysis as they contribute to the covariate estimates. The conditional logistic regression was adjusted for the same variables as in the Poisson model apart from the maternal country of birth, which was the same for both siblings. The final conditional logistic models were adjusted for year of birth, maternal pre-pregnancy diabetes and gestational age as the other variables did not change the results materially. The statistical analyses were performed for childhood T1D, any T1D and all diabetes in the cohort.

Sensitivity analyses were performed by excluding children who were SGA, LGA, preterm birth and those of women with pre-eclampsia. Finally, we performed the cohort and sibling control analyses for the primary outcome restricting to births from 1990 onwards when the coverage of the national registers was complete and the recording variable for mode of delivery was changed including information on induction of labor. This restriction allowed us to investigate the impact of induction of labor on the T1D and also whether the association between mode of delivery and T1D was dependent on induction of labor. The mode of delivery variable was modified for this analysis to include induction of labor as a separate category. All statistical analyses were performed using Stata 10.0.

Permission for the study was obtained from the Regional Ethical Review board in Stockholm, Sweden.

RESULTS

There were 2,838,056 births in Sweden between January 1, 1982 and December 31, 2009. After excluding 74,639 multiple births, 8,343 stillbirths, and 116,991 children with unknown mode of delivery, the final cohort consisted of N=2,638,083. During the study period there were 2,094,481 (79.4%) unassisted vaginal birth, 192,458 (7.3%) IVD, 191,646 (7.1%) emergency CS and 159,498 (6.1%) elective CS. Women who had elective CS were more likely to be older, have higher education level attainment and higher BMI compared to women who had unassisted vaginal birth. Both emergency and elective CS were more common in women who had SGA, LGA, preterm birth or pre-pregnancy diabetes. More details on maternal and obstetric characteristics of the study population are summarized in Table 1. In the cohort analyses there were 13,425 children with any diabetes mellitus diagnosis of which 10,428 (77.7%) were classified as T1D on or before the 15th birthday (5,530 (53%) boys and 4,898 (47%) girls); 2,395 (17.8%) T1D diagnoses among children aged more than 15 years; and 602 (4.5%) T2D cases. Median age at diagnosis (interquartile range) was 9.8 years (5.7, 14.0). The childhood T1D sibling analysis included 12,174 (6,087 with T1D) siblings of which 2,200 (1,100 with T1D) siblings were discordant on both mode of delivery and T1D. Of the 10,428 children with T1D, 1,300 were excluded because the birth order was more than two, 1,936 because the child had no siblings, 797 because the control had shorter follow-up than the case and 308 because the sibling pair was not discordant on T1D. Of the remaining 6,087 children with childhood T1D, only 1,100 were discordant on mode of delivery.

The results of the association between mode of delivery and childhood T1D are presented in Table 2. The risk of childhood T1D was moderately increased among children born by elective CS (adjusted RR=1.15; [95% CI: 1.06, 1.25]) or IVD

(adjusted RR=1.14; [95% CI: 1.06, 1.23]) compared to those born by unassisted vaginal delivery. However, there was no evidence for an association between emergency CS and childhood T1D (RR=1.02; [95% CI: 0.95, 1.11]). In the sibling control analysis the effects of elective CS (RR=1.06; [0.85, 1.31]) and IVD (RR=1.07; [95% CI: 0.92, 1.24]) on T1D were no longer significant. Although there was no significant association between emergency CS and T1D, the sibling analysis result is reported for completeness (RR=1.06; 95% CI: 0.88, 1.28). Adjusting for birth order, in particular, in the cohort and sibling analyses did not change the results.

In a sensitivity analysis, we excluded those who had SGA, LGA, preterm birth babies or pre-eclampsia (data not shown). These exclusions had no material effect on the results of the cohort and sibling models. Restricting the analysis to children born from 1990 onwards did not change the results of the cohort or sibling analysis materially. Among children born from 1990 onwards (N=1,863,801), 176,370 (9.5%) babies were exposed to induction of labor. In the cohort analysis, childhood T1D was associated with elective CS (RR=1.12; [95% CI: 1.02, 1.23]) and IVD (RR=1.10; [95% CI: 1.00, 1.20]) but not emergency CS (RR=1.02; [95% CI: 0.93, 1.13]) or induction of labor (RR=1.01; [95% CI: 0.91, 1.15]). When the sibling control analysis was performed the association between childhood T1D and elective CS (RR=1.04; [95% CI: 0.84, 1.29]) and IVD (RR=1.07, [95% CI: 0.92, 1.24]) were no longer significant. Moreover, the association between emergency CS (RR=1.03; 95% CI: 0.85, 1.26) and induction of labor (RR=0.98; [95% CI: 0.81, 1.18) and T1D did not change materially.

When the Poisson and conditional logistic regression models were repeated for the association between mode of delivery and any T1D, i.e. with no age restriction, and any diabetes mellitus in the offspring, the results were consistent with those of

childhood T1D (Tables 3 & 4). However, the RR of the association between emergency CS and any DM was not statistically significance in the sibling analysis (RR=1.14; [95% CI: 0.96, 1.36]).

DISCUSSION

This study investigated the association between mode of delivery and the risk of T1D in a large population-based cohort of children born over 3 decades. There was a small but statistically significant association between elective, but not emergency, CS and childhood T1D. There was also a similar association between IVD and T1D. The associations were independent of maternal and gestational diabetes and several other maternal and obstetric variables. However, siblings within the same family who were delivered by different modes of delivery did not differ with their risk of childhood T1D. These results were consistent for childhood T1D, any T1D and any diabetes mellitus. However, 95% of the cases were T1D which suggest the results are mostly applicable to T1D and should not be generalized to T2D without further research. Moreover, the sibling analysis findings should be interpreted with caution considering the wide CIs. Therefore, the present findings suggest that familial confounding may account for the elevated risk of T1D among children who were delivered by elective CS or IVD. Although the association between elective CS and IVD and T1D cannot be ruled out, the present findings are not consistent with a causal effect of mode of delivery on the risk of T1D. This may reflect the lack of information, and hence the lack of adjustment, on genetics and the lifestyle of the children in this cohort. For example, the family diet, lifestyle and genes that are shared by the siblings may partly explain the observed association between mode of delivery and T1D in the cohort analyses. Such explanations should be considered with caution, as the observed

associations in the cohort analyses were small. (15) Gestational age was one of two main confounders in both the cohort and sibling analyses. Gestational age appeared to affect the association between elective CS and T1D but not emergency CS or IVD and T1D. This may reflect the fact that elective CS is usually performed a week or more before the estimated date of delivery to avoid labor, whereas emergency CS and instrumental vaginal deliveries usually occur during spontaneous or induced labor and are thus more likely to occur closer to or after the estimated date of delivery.

Comparisons with other studies

The majority of previous studies on the association between CS and T1D did not report separate estimates for elective and emergency CS. The present findings based on the cohort analysis suggest that the magnitude of the association between CS and T1D is lower than that observed in a recent meta-analysis.(9) The meta-analysis suggested a 23% increased risk of childhood T1D in relation to CS using data from 20 studies published before 2008. Two case-control studies using Swedish and Danish data reported about 30% increased risk of T1D among children delivered by CS.(17, 18) More recently, Phillips et al., conducted a matched case-control study using a Canadian diabetes database and reported a 40% increase in the risk of childhood T1D in children delivered by CS (elective and emergency combined together).(19) A case-control study using data from Scotland reported a 70% increased risk of T1D among children delivered by CS although most of the association appeared to be related to elective CS.(20) The study was based on children born in 1975-1976 while the present findings are based on three decades. A recent Australian study of more than half a million children found an approximately 30% increased risk of T1D before age 6 years among children born by emergency or elective CS.(14) However, several

previous studies on the topic found no association between CS and childhood T1D (21) including a very large cohort study from Norway.(22)

Strengths and limitations

The present study has several strengths. First, the study was based on a very large population-based data of 2.6 million children born in Sweden, which provided adequate statistical power. Second, the data obtained from the national registers were prospectively collected therefore the data on the outcome, exposure and potential confounders are not subject to recall bias. Third, unlike several previous studies on the topic, we were able to classify elective and emergency CS deliveries separately. This classification is crucial for understanding possible mechanisms of any observed associations between CS and T1D.(23) Fourth, the T1D diagnoses were based on ICD-8, 9 and 10 with a known and accurate date of first hospitalisation, which is considered the date of diagnosis. Although full national coverage was achieved from 1987 onwards, the sensitivity analyses suggested the results were consistent when the analysis was restricted to births from 1990 onwards. Moreover, the number of T1D cases in the present study are comparable to those reported from the Swedish Childhood Diabetes register between 1977 and 2007 (12,842 vs 12,880). (24)This register has records of almost all incident diabetes cases before 15 years of age as all pediatric departments in Sweden report T1D cases to the register. The Swedish health care system requires all children <15 years who are suspected to have diabetes to be referred to pediatric departments. It is possible, however, that some T2D cases may have been misclassified as T1D. Data on T1D in Sweden is known to be of very high quality.(24) Fifth, we were able to adjust for several potential confounders, which were adjusted for in previous studies. However, maternal diabetes and gestational age

appeared to be the only confounders in this study. Sixth, in addition to the conventional cohort analyses, sibling control analyses were performed. Statistical models of sibling pairs discordant for exposure and outcome allowed us to adjust for unmeasured factors that are shared by siblings such as family environment, diet, lifestyle, maternal characteristics and genetic factors.

The present study had several limitations. First, we used data on all births from 1982 and complete nationwide coverage was not achieved until 1987. However, our sensitivity analyses showed that restricting the data to births from 1990 onwards were consistent with the overall results. Second, although the cohort analyses were based on the largest cohort of children, to date, the sibling analyses were based on a small number of pairs of siblings due to the fact only siblings discordant on both mode of delivery and T1D contributed to these analyses. Third, 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. 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 analytical methods are effective in adjusting for unobserved familial characteristics that are shared by siblings. Although, these methods cannot rule out unmeasured confounding factors that simultaneously vary between siblings. Fourth, the siblings in this study shared the same mother therefore some of the siblings may be half siblings. This fact would limit the efficiency of the sibling control analyses because half siblings share only half of their genetic background. However, although it could be hypothesized

that the paternal environmental and genetic factors may influence the risk of T1D, it is harder to hypothesize that such factors could influence the mode of delivery.

Mechanisms

There are several plausible explanations for an association between elective CS and T1D. The gut microbiota profile is established at birth. Vaginally-born babies are exposed to bacteria found in the maternal birth canal and rectum that are ingested during the delivery and colonise the neonatal GI tract.(25) Children born by CS (in particular by elective CS) may not be exposed to these bacteria and instead are colonised by bacteria from the mother's skin and hospital environment which results in them having a distinctly different gut microbiota profile compared to children born via vaginal delivery.(25-27) These disturbed microbiota profiles are present one day after birth and can persist for many years.(27) It is hypothesized that the risk of T1D could be increased in children born by elective CS due to the different microbiotic composition.(28) However, the findings from the sibling control analysis suggested that the association between elective CS and T1D is not causal. Children born by IVD, are exposed to microflora, were at increased risk of T1D. Therefore, the gut microbiota is unlikely to play a role in the observed associations at the cohort level. Similarly, the hygiene mechanism is unlikely to play a role in the observed association, considering the lack of evidence for a causal association.(29) Similarly, the association between IVD and T1D appeared to be non-causal and therefore is likely to be explained by maternal or environmental factors.

CONCLUSION

This study demonstrates that children delivered by elective CS or IVD have a small increased risk of T1D. The sibling control analyses, however, suggested the associations were not causal and may be explained by familial or environmental or genetic factors that are shared by the siblings. The present findings have major implications for how to counsel women regarding mode of delivery choice.

REFERENCES

1. Diamond Project Group. Incidence and trends of childhood Type 1 diabetes worldwide 1990-1999. Diabetic Medicine, 2006;23(8):857-66.

2. Maahs DM, West NA, Lawrence JM, Mayer-Davis EJ. Epidemiology of type 1 diabetes. Endocrinol Metab Clin North Am. 2010;39(3):481-97.

3. Patterson CC, Dahlquist GG, Gyurus E, Green A, Soltesz G, Group ES, et al. Incidence trends for childhood type 1 diabetes in Europe during 1989-2003 and predicted new cases 2005-20: a multicentre prospective registration study. Lancet. 2009;373(9680):2027-33.

4. Dahlquist GG, Ivarsson S, Lindberg B, Forsgren M. Maternal enteroviral infection during pregnancy as a risk factor for childhood IDDM. A population-based case-control study. Diabetes. 1995 Apr;44(4):408-13.

5. Hettiarachchi KD, Zimmet PZ, Myers MA. Dietary toxins, endoplasmic reticulum (ER) stress and diabetes. Curr Diabetes Rev. 2008;4(2):146-56.

6. Wagener DK, LaPorte RE, Orchard TJ, Cavender D, Kuller LH, Drash AL. The Pittsburgh diabetes mellitus study. 3: An increased prevalence with older maternal age. Diabetologia. 1983 Aug;25(2):82-5.

7. Vitamin D supplement in early childhood and risk for Type I (insulin-dependent) diabetes mellitus. The EURODIAB Substudy 2 Study Group. Diabetologia. 1999 Jan;42(1):51-4.

8. Strachan DP. Hay-Fever, Hygiene, and Household Size. British Medical Journal. 1989 Nov 18;299(6710):1259-60.

9. 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

556 diabetes mellitus: a meta-analysis of observational studies. Diabetologia. 2008
557 May;51(5):726-35.
558 10. O'Neill SM, Kearney PM, Kenny LC, Khashan AS, Henriksen TB, Lutomski
559 JE, et al. Caesarean Delivery and Subsequent Stillbirth or Miscarriage: Systematic
560 Review and Meta-Analysis. Plos One. 2013 Jan 23;8(1).
561 11. Susser E, Eide MG, Begg M. Invited Commentary: The Use of Sibship
562 Studies to Detect Familial Confounding. Am J Epidemiol. 2010 Sep 1;172(5):537-9.
563 12. Donovan SJ, Susser E. Commentary: Advent of sibling designs. Int J
564 Epidemiol. 2011 Apr;40(2):345-9.
565 13. Lahey BB, D'Onofrio BM. All in the Family: Comparing Siblings to Test
566 Causal Hypotheses Regarding Environmental Influences on Behavior. Current
567 directions in psychological science, 2010 Oct;19(5):319-23.
568 14. Algert C, McElduff A, Morris J, Roberts C. Perinatal risk factors for early
569 onset of Type 1 diabetes in a 2000–2005 birth cohort. Diabetic medicine,
570 2009;26(12):1193-97.
571 15. Frisell T, Oberg S, Kuja-Halkola R, Sjolander A. Sibling comparison designs:
572 bias from non-shared confounders and measurement error. Epidemiology, 2012
573 Sep;23(5):713-20.
574 16. Ludvigsson J, Otterblad-Olausson P, Pettersson B, Ekbom A. The Swedish
575 personal identity number: possibilities and pitfalls in healthcare and medical research.
576 European journal of epidemiology. 2009;24:659-67.
577 17. Dahlquist G, Kallen B. Maternal-child blood group incompatibility and other
578 perinatal events increase the risk for early-onset type 1 (insulin-dependent) diabetes
579 mellitus. Diabetologia. 1992 Jul;35(7):671-5.

18. Svensson J, Carstensen B, Mortensen HB, Borch-Johnsen K, Danish Study Group of Childhood D. Early childhood risk factors associated with type 1 diabetes--is gender important? European journal of epidemiology. 2005;20(5):429-34.
19. Phillips J, Gill N, Sikdar K, Penney S, Newhook LA. History of cesarean section associated with childhood onset of T1DM in Newfoundland and Labrador, Canada. Journal of environmental and public health. 2012;2012:635097.
20. Patterson CC, Waugh NR, Carson DJ, Cole SK, Hadden DR. A Case-Control Investigation of Perinatal Risk-Factors for Childhood Iddm in Northern-Ireland and Scotland. Diabetes Care. 1994 May;17(5):376-81.
21. 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 Oct;22(10):1698-702.
22. Stene LC, Magnus P, Lie RT, Sovik O, Joner G, Study NCD. No association between preeclampsia or cesarean section and incidence of type 1 diabetes among children: A large, population-based cohort study. Pediatr Res. 2003 Oct;54(4):487-90.
23. Almqvist C, Rejno G. Birth mode of delivery in the modern delivery ward - indication improves understanding of childhood asthma. Clin Exp Allergy. 2013 Mar;43(3):264-7.
24. 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 Aug;34(8):1754-9.
25. Biasucci G, Rubini M, Riboni S, Morelli L, Bessi E, Retetangos C. Mode of delivery affects the bacterial community in the newborn gut. Early Hum Dev. 2010 Jul;86(1):S13-S5.

26. Dominguez-Bello MG, Costello EK, Contreras M, Magris M, Hidalgo G, Fierer N, et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. P Natl Acad Sci USA. 2010 Jun 29;107(26):11971-5.

27. Salminen S, Gibson GR, McCartney AL, Isolauri E. Influence of mode of delivery on gut microbiota composition in seven year old children. Gut. 2004 Sep;53(9):1388-9.

28. Vehik K, Dabelea D. Why Are C-Section Deliveries Linked to Childhood Type 1 Diabetes? Diabetes. 2012 Jan;61(1):36-7.

29. Bach JF, Chatenoud L. The hygiene hypothesis: an explanation for the increased frequency of insulin-dependent diabetes. Cold Spring Harbor perspectives in medicine. 2012 Feb;2(2):a007799.

Table 1: Maternal characteristics and obstetric outcomes in relation to mode of delivery

	Unassisted vaginal, n (%)	Emergency caesarean section, n (%)	Elective caesarean section, n (%)	Instrumental vaginal, n (%)
Total population	2,094,481	191,646	159,498	192,458
Maternal characteristics				
Age				
<20	53,117 (2.5)	3,753 (2.0)	1,743 (1.1)	4,809 (2.5)
20-24	402,946 (19.2)	30,381 (15.8)	16,078 (10.1)	37,535 (19.5)
25-29	742,504 (35.4)	61,116 (31.9)	43,229 (27.1)	69,218 (36.0)
30-34	609,694 (29.1)	59,200 (30.9)	54,877 (34.4)	55,434 (28.8)
35-39	244,121 (11.7)	29,961 (15.6)	34,180 (21.4)	21,647 (11.2)
40+	42,074 (2.0)	7,229 (3.8)	9,375 (5.9)	3,814 (2.0)
missing	25 (0.0)	6 (0.0)	16 (0.0)	1 (0.0)
BMI				
Underweight	67,753 (3.2)	4,309 (2.2)	4,020 (2.5)	5,758 (3.0)
Normal	1,056,836 (50.5)	82,018 (42.8)	73,172 (45.9)	102,005 (53.0)
Overweight	301,552(14.4)	34,785 (18.1)	29,921 (18.8)	30,305 (15.7)
Obese	104,820 (5.0)	17,405 (9.1)	15,205 (9.5)	9,870 (5.1)
Missing	563,520 (26.9)	53,129 (27.7)	37,180 (23.3)	44,520 (23.1)
Education				
≤9 years	331,420 (15.8)	28,475 (14.9)	22,349 (14.0)	22,636 (11.8)
High school	957,081 (45.7)	84,975 (44.3)	69,890 (43.8)	85,613 (44.5)
University	593,220 (28.3)	57,744 (30.1)	51,337 9 (32.2)	64,752 (33.6)
Missing	212,760 (10.2)	20,452 (10.7)	15,922 (10.0)	19,457 (10.1)
Country of birth				
Sweden	1,772,915 (84.6)	157,896 (82.4)	132,907 (83.3)	163,113 (84.7)
Other Nordic	72,067 (3.4)	6,827 (3.6)	5,415 (3.4)	5,763 (3.0)
Other	249,499 (11.9)	26,923 (14.0)	21,176 (13.3)	23,582 (12.2)
Pre-pregnancy diabetes				
No	2,087,249 (99.6)	188,786 (98.5)	156,289 (98.0)	191,079 (99.3)
Yes	7,232 (0.4)	2,860 (1.5)	3,209 (2.0)	1,379 (0.7)
Gestational diabetes				
No	2,084,950 (99.5)	189,159 (98.7)	156,860 (98.3)	191,132 (99.3)
Yes	9,531 (0.5)	2,487 (1.3)	2,638 (1.7)	1,326 (0.7)
Obstetric outcomes				
Infant sex				
Male	1,059,904 (50.6)	105,045 (54.8)	81,315 (50.1)	111,069(57.7)
Female	1,034,573 (49.4)	86,599 (45.2)	78,183 (49.0)	81,388 (48.5)
unknown	4	2	0	1
Birthweight for gestational age				
AGA	1,981,654 (94.6)	167,087 (87.2)	137,056 (85.9)	180,925 (94.0)
SGA	39,031 (1.9)	13,083 (6.8)	9,980 (6.3)	5,072 (2.6)
LGA	64,922 (3.1)	9,866 (5.1)	11,437 (7.2)	5,519 (2.9)
Missing	8,874 (0.4)	1,610 (0.8)	1,025 (0.6)	942 (0.5)
Gestational age				
39-40	1,149,229 (54.9)	64,570 (33.7)	37,753 (23.7)	93,604 (48.6)
22-32 weeks	8,631 (0.4)	8,040 (4.2)	7,074 (4.4)	330 (0.2)
33-36 weeks	71,886 (3.4)	19,155 (10.0)	14,945 (9.4)	4,771 (2.5)
37-38	339,172 (16.2)	40,192 (21.0)	91,778 (57.5)	21,987(11.4)
41+	521,833 (24.9)	59,235 (30.9)	7,681 (4.8)	71,462 (37.1)
Missing	3,730 (0.2)	454 (0.2)	267 (0.2)	304 (0.2)
Pre-eclampsia				
No	2,050,513 (97.9)	177,662 (92.7)	147,316 (92.4)	185,452 (96.4)
Yes	43,968 (2.1)	13,984 (7.3)	12,182 (7.6)	7,006 (3.6)
Birth order				
1	1,068,784 (51.0)	134,560 (70.2)	73,479 (46.1)	162,644 (84.5)
2	742,147 (35.4)	43,292 (22.6)	58,904 (36.9)	24,855 (12.9)
3	221,005 (10.5)	10,422 (5.4)	20,833 (13.1)	4,022 (2.1)
4+	62,545 (3.0)	3,372 (1.8)	6,282 (3.9)	937 (0.5)

Table 2: The association between mode of delivery and childhood type 1 diabetes (before age 15)

Mode of delivery	TYPE 1 DIABETES, n in cohort analysis	Partially adjusted, RR(95% CI)[a]	Adjusted RR(95% CI)[b]	Sibling cohort adjusted RR(95% CI)[c] 2,200 siblings[d]
Unassisted vaginal birth	8,242	Reference [1]	Reference [1]	Reference [1]
Elective caesarean section	678	**1.31(1.21,1.41)**	**1.15(1.06,1.25)**	1.06(0.85, 1.31)
Emergency caesarean section	725	1.07(0.99,1.16)	1.02(0.95,1.11)	1.06(0.88, 1.28)
Instrumental vaginal birth	783	**1.13(1.05,1.22)**	**1.14(1.06,1.23)**	1.07(0.92, 1.24)

a adjusted for offspring age and calendar year as time dependent variables using Poisson regression with aggregated person-years

b adjusted for offspring age as a time dependent variable, year of birth, gestational age and maternal diabetes using Poisson regression with aggregated person-years

c adjusted for year of birth, maternal diabetes and gestational age using conditional logistic regression

d number of siblings discordant on mode of delivery and childhood T1D

Table 3: The association between mode of delivery and type 1 diabetes in the offspring (no age restriction)

Mode of delivery	TYPE 1 DIABETES, n in cohort analysis	Partially adjusted, RR(95% CI)[a]	Adjusted for RR(95% CI)[b]	Sibling cohort adjusted RR(95% CI)[c] 2,576 siblings[d]
Unassisted vaginal birth	10,179	Reference [1]	Reference [1]	Reference [1]
Elective caesarean section	801	**1.30(1.21,1.40)**	**1.15(1.07,1.24)**	1.00(0.82, 1.22)
Emergency caesarean section	901	**1.08(1.01,1.16)**	1.03(0.96,1.11)	1.08(0.90, 1.30)
Instrumental vaginal birth	942	**1.13(1.05,1.21)**	**1.13(1.06,1.21)**	1.08(0.94,1.24)

a adjusted for offspring age and calendar year as time dependent variables using Poisson regression with aggregated person-years

b adjusted for offspring age as a time dependent variable, year of birth, gestational age, and maternal diabetes using Poisson regression with aggregated person-years

c adjusted for year of birth, maternal diabetes and gestational age using conditional logistic regression

d number of siblings discordant on mode of delivery and any T1D

Table 4: The association between mode of delivery and any diabetes diagnosis in the offspring

Mode of delivery	TYPE 1 DIABETES, n in cohort analysis	Partially adjusted, RR(95% CI)[a]	Adjusted RR(95% CI)[c]	Sibling cohort adjusted RR(95% CI)[c] 2,676 siblings[d]
Unassisted vaginal birth	10,641	Reference [1]	Reference [1]	Reference [1]
Elective caesarean section	856	**1.33(1.24,1.43)**	**1.17(1.08,1.25)**	1.03(0.85,1.26)
Emergency caesarean section	957	**1.10(1.03,1.18)**	1.04(0.97,1.11)	1.14(0.96, 1.36)
Instrumental vaginal birth	971	**1.11(1.04,1.19**	**1.12(1.05,1.19)**	1.07(0.94,1.23)

a adjusted for offspring age and calendar year as time dependent variables using Poisson regression with aggregated person-years

b adjusted for offspring age as a time dependent variable, year of birth, gestational age, and maternal diabetes using Poisson regression with aggregated person-years

c adjusted for year of birth, maternal diabetes and gestational age using conditional logistic regression

d number of siblings discordant on mode of delivery and DM