



**Karolinska
Institutet**

Karolinska Institutet

<http://openarchive.ki.se>

This is a Peer Reviewed Accepted version of the following article, accepted for publication in Pediatrics.

2017-06-14

Mode of obstetrical delivery and type 1 diabetes : a sibling design study

Khashan, Ali S; Kenny, Louise C; Lundholm, Cecilia; Kearney, Patricia M; Gong, Tong; Almqvist, Catarina

Pediatrics. 2014 Sep;134(3):e806-13.

<http://doi.org/10.1542/peds.2014-0819>

<http://hdl.handle.net/10616/45953>

If not otherwise stated by the Publisher's Terms and conditions, the manuscript is deposited under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License (<http://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited, and is not altered, transformed, or built upon in any way.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50

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

Running Title: Delivery and Type 1 Diabetes

Ali S Khashan, PhD^{1,2*}, Louise C Kenny, PhD^{1,2}, Cecilia Lundholm, MSc³, Patricia M Kearney, PhD⁴, Tong Gong, PhD Student³, Catarina Almqvist, PhD^{3,5}

¹ The Irish Centre for Fetal and Neonatal Translational Research (INFANT), University College Cork, Cork, Ireland

² Department of Obstetrics and Gynaecology, Cork University Maternity Hospital, University Cork, Ireland

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

⁴ Department of Epidemiology and Public Health, University College Cork, Cork, Ireland

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

* Author for Correspondence: Department of Obstetrics and Gynaecology, Cork University Maternity Hospital, University Cork, Ireland. Tel: +353 (21) 420 5031; Fax: +353 (21) 420 5025; Email: a.khashan@ucc.ie

Word count (main text): 3465

Word count (abstract): 244

Funding

This work was carried out at the Irish Centre for Fetal and Neonatal Translational Research (INFANT) and was funded in part by Science Foundation Ireland (grant no 12/RC/2272). Financial support was provided through the regional agreement on medical training and clinical research (ALF) between Stockholm County Council and Karolinska Institutet, the Swedish Research Council (grant no 2011-3060) and through the Swedish Initiative for research on Microdata in the Social And Medical sciences (SIMSAM) framework (grant no 340-2013-5867), the Swedish Heart-Lung foundation and the Strategic Research Program in Epidemiology at Karolinska Institutet.

Financial Disclosures: The authors have no financial relationships relevant to this article to disclose.

Conflict of interest: The authors declare that there is no conflict of interest associated with this manuscript.

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

51 **What's known on this subject?**

52

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

57

58 **What this study adds?**

59

60 Use of a very large population-based cohort of 2.6 million children born between
61 1982-2009. The study included information on indication for Caesarean section and
62 performed sibling-control analyses. Although there appears to be an association
63 between CS / IVD and risk, the sibling analysis findings suggest the association is not
64 causal. The findings are crucial evidence to advise women on mode of delivery
65 choice.

66

67

68

69

70

71

72

73

74

75

76

77

78

79

80

81

82

83

84

85

86

87

88

89

90

91

92

93

94

95

96

97

98

99

100

101 **Contributors' Statement**

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

104
105 Louise C Kenny contributed to the study design, interpreted the results and reviewed
106 and revised the manuscript.

107
108 Cecilia Lundholm contributed to the study design and supervised the statistical
109 analysis, interpreted the results and reviewed and revised the manuscript.

110
111 Patricia Kearney contributed to the drafting of the initial manuscript, interpreted the
112 results and reviewed and revised the manuscript.

113
114 Tong Gong contributed to the study design and prepared the study cohort including
115 performing data linkage from several registers and reviewed and revised the
116 manuscript.

117
118 Catarina Almqvist conceptualized and designed the study (with ASK), acquired the
119 permission to access the data and perform the study, interpreted the results and
120 reviewed and revised the manuscript.

121
122 All authors approved the final version to be submitted and agree to be accountable for
123 all aspects of the work in ensuring that questions related to the accuracy or integrity of
124 any part of the work are appropriately investigated and resolved.

125
126
127
128
129
130
131
132
133
134
135
136
137
138
139
140
141
142
143
144
145
146
147
148
149
150

151 **ABSTRACT** (244 words)

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

155
156 **Methods:** We conducted a population-based cohort study of all singleton live births
157 in Sweden between 1982-2009, followed by sibling-control analyses. Type 1 diabetes
158 diagnoses were identified from the Swedish National Patient Register. Mode of
159 delivery was categorized into unassisted vaginal delivery (reference group),
160 instrumental vaginal delivery (IVD), emergency CS and elective CS. The statistical
161 analysis was conducted in two steps; firstly log-linear Poisson regression with
162 aggregated person-years using the full cohort; secondly, conditional logistic
163 regression for sibling-control analyses. The sibling analysis included siblings who
164 were discordant for both mode of delivery and type 1 diabetes.

165
166 **Results:** In the cohort analyses (N=2,638,083), there was an increased risk of
167 childhood type 1 diabetes among children born by elective CS (adjusted RR=1.15,
168 [95% CI: 1.06-1.25]) and IVD (RR=1.14, [1.06, 1.23]) but not emergency CS
169 (RR=1.02, [0.95, 1.11]) when compared to children born by unassisted vaginal birth.
170 However, the effect of elective CS and IVD on childhood type 1 diabetes almost
171 disappeared and became non-significant in the sibling-control analyses.

172
173 **Conclusions:** The present findings suggest a small association between elective CS
174 and IVD and childhood type 1 diabetes. The sibling-control results, however, suggest
175 that these findings are not consistent with causal effects of mode of delivery on type 1
176 diabetes and may be due to familial confounders such as genetic susceptibility and
177 environmental factors.

178

179

180

181

182

183

184

185

186

187

188

189

190

191 **INTRODUCTION**

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

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

207

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

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

223

224 **PATIENTS and METHODS**

225 Study cohort

226 The study cohort consisted of all singleton live births in Sweden between 1982 and
227 2009. The study was based on data from the Swedish national registers held by the
228 Swedish National Board of Health and Welfare and Statistics Sweden. Each resident
229 in Sweden is assigned a unique identifier, the Personal Identity Number (PIN), which
230 is used uniformly across all services in Sweden.(16) The PIN enables the linkage of
231 data from various registers as well as linkage of data on relatives, such as siblings.
232 Using data from the Swedish Medical Birth Register, we identified almost all children
233 born in Sweden between January 1, 1982 and December 31, 2009. This register
234 contains obstetric, maternal and neonatal data on >99% of births in Sweden.

235

236 Exposure

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

241 vaginal delivery included spontaneous and induced vaginal deliveries. However, from
242 1990, a new variable for the classification of mode of delivery was recorded with
243 more detail than in the previous years including information about whether labor was
244 spontaneous or induced. Although the main aim was to investigate the effect of
245 elective CS and risk of T1D for completeness we also investigated the association
246 between emergency CS and IVD and risk of T1D. We also explored the confounding
247 effect of gestational age and induction of labor on any observed associations between
248 mode of delivery and childhood T1D.

249

250 Outcome measures

251 The Swedish National Patient Register contains records of inpatient diagnoses in
252 Sweden since 1964 (full national coverage since 1987) and outpatient diagnoses since
253 2001. The date of onset of T1D is defined as the date of the first admission to
254 hospital, which led to the diagnosis of T1D. The primary outcome measure in this
255 study was childhood T1D, before 15 years of age, defined according to the
256 International Classification of Diseases (ICD) 8 (250); ICD-9 (250); and ICD-10
257 (E10). Secondary outcome measures included T1D at any age (maximum age was 27
258 years in the study cohort) and any diabetes diagnosis defined according to ICD-8
259 (250); ICD-9 (250) and ICD-10 (E10-14). The cohort was followed from the date of
260 birth until the onset of the outcome measure, 15th birthday (for the primary outcome
261 only), death, migration or December 31, 2009 (end of the study period). The
262 Migration register provided the dates of migration from Sweden while information on
263 date of death was obtained from the Cause of Death register.

264

265

266 Potential Confounders

267 Data on small for gestational age (SGA), large for gestational age (LGA), gestational
268 age, birth order, pre-eclampsia, infant sex, maternal age, body mass index (BMI), pre-
269 pregnancy diabetes and gestational diabetes were obtained from the Medical Birth
270 Register. Data on maternal education level was obtained from the Education register
271 which contains information on the residents' highest level of completed formal
272 education.

273

274 Statistical analysis

275 The statistical analysis to investigate the association between mode of delivery and
276 the risk of T1D was performed in two steps. In the first step, log-linear Poisson
277 regression with aggregated person-years was performed using the study cohort. The
278 Poisson model was adjusted for offspring age as a time-dependent variable, year of
279 birth, gestational age and maternal pre-pregnancy diabetes. Further adjustment for
280 birth order, maternal age, BMI, country of birth, education, gestational diabetes, SGA,
281 LGA and pre-eclampsia did not change the results materially and were excluded from
282 the models. These variables were included in the Poisson model as described in Table
283 1. The second step aimed to adjust for unmeasured familial environmental and genetic
284 confounding factors shared by the siblings using sibling control analyses, which was
285 analysed with conditional logistic regression with the mother as the grouping
286 variable.⁽¹⁵⁾ This analysis included the first two children of the mother, and therefore
287 some of these siblings may have had different fathers, who were discordant for mode
288 of delivery and T1D diagnosis. In addition, the conditional logistic models were
289 restricted to pairs of siblings where the control was under follow-up and T1D free at
290 the age that the sibling with T1D was diagnosed. In this analysis, only siblings

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

300

301 Sensitivity analyses were performed by excluding children who were SGA, LGA,
302 preterm birth and those of women with pre-eclampsia. Finally, we performed the
303 cohort and sibling control analyses for the primary outcome restricting to births from
304 1990 onwards when the coverage of the national registers was complete and the
305 recording variable for mode of delivery was changed including information on
306 induction of labor. This restriction allowed us to investigate the impact of induction of
307 labor on the T1D and also whether the association between mode of delivery and T1D
308 was dependent on induction of labor. The mode of delivery variable was modified for
309 this analysis to include induction of labor as a separate category. All statistical
310 analyses were performed using Stata 10.0.

311

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

314

315

316 **RESULTS**

317 There were 2,838,056 births in Sweden between January 1, 1982 and December 31,
318 2009. After excluding 74,639 multiple births, 8,343 stillbirths, and 116,991 children
319 with unknown mode of delivery, the final cohort consisted of N=2,638,083. During
320 the study period there were 2,094,481 (79.4%) unassisted vaginal birth, 192,458
321 (7.3%) IVD, 191,646 (7.1%) emergency CS and 159,498 (6.1%) elective CS. Women
322 who had elective CS were more likely to be older, have higher education level
323 attainment and higher BMI compared to women who had unassisted vaginal birth.
324 Both emergency and elective CS were more common in women who had SGA, LGA,
325 preterm birth or pre-pregnancy diabetes. More details on maternal and obstetric
326 characteristics of the study population are summarized in Table 1. In the cohort
327 analyses there were 13,425 children with any diabetes mellitus diagnosis of which
328 10,428 (77.7%) were classified as T1D on or before the 15th birthday (5,530 (53%)
329 boys and 4,898 (47%) girls); 2,395 (17.8%) T1D diagnoses among children aged
330 more than 15 years; and 602 (4.5%) T2D cases. Median age at diagnosis (interquartile
331 range) was 9.8 years (5.7, 14.0). The childhood T1D sibling analysis included 12,174
332 (6,087 with T1D) siblings of which 2,200 (1,100 with T1D) siblings were discordant
333 on both mode of delivery and T1D. Of the 10,428 children with T1D, 1,300 were
334 excluded because the birth order was more than two, 1,936 because the child had no
335 siblings, 797 because the control had shorter follow-up than the case and 308 because
336 the sibling pair was not discordant on T1D. Of the remaining 6,087 children with
337 childhood T1D, only 1,100 were discordant on mode of delivery.

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

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

349 In a sensitivity analysis, we excluded those who had SGA, LGA, preterm birth babies
350 or pre-eclampsia (data not shown). These exclusions had no material effect on the
351 results of the cohort and sibling models. Restricting the analysis to children born from
352 1990 onwards did not change the results of the cohort or sibling analysis materially.

353 Among children born from 1990 onwards (N=1,863,801), 176,370 (9.5%) babies
354 were exposed to induction of labor. In the cohort analysis, childhood T1D was
355 associated with elective CS (RR=1.12; [95% CI: 1.02, 1.23]) and IVD (RR=1.10;
356 [95% CI: 1.00, 1.20]) but not emergency CS (RR=1.02; [95% CI: 0.93, 1.13]) or
357 induction of labor (RR=1.01; [95% CI: 0.91, 1.15]). When the sibling control analysis
358 was performed the association between childhood T1D and elective CS (RR=1.04;
359 [95% CI: 0.84, 1.29]) and IVD (RR=1.07, [95% CI: 0.92, 1.24]) were no longer
360 significant. Moreover, the association between emergency CS (RR=1.03; 95% CI:
361 0.85, 1.26) and induction of labor (RR=0.98; [95% CI: 0.81, 1.18) and T1D did not
362 change materially.

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

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

369

370 **DISCUSSION**

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

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

398

399 Comparisons with other studies

400 The majority of previous studies on the association between CS and T1D did not
401 report separate estimates for elective and emergency CS. The present findings based
402 on the cohort analysis suggest that the magnitude of the association between CS and
403 T1D is lower than that observed in a recent meta-analysis.(9) The meta-analysis
404 suggested a 23% increased risk of childhood T1D in relation to CS using data from 20
405 studies published before 2008. Two case-control studies using Swedish and Danish
406 data reported about 30% increased risk of T1D among children delivered by CS.(17,
407 18) More recently, Phillips et al., conducted a matched case-control study using a
408 Canadian diabetes database and reported a 40% increase in the risk of childhood T1D
409 in children delivered by CS (elective and emergency combined together).(19) A case-
410 control study using data from Scotland reported a 70% increased risk of T1D among
411 children delivered by CS although most of the association appeared to be related to
412 elective CS.(20) The study was based on children born in 1975-1976 while the
413 present findings are based on three decades. A recent Australian study of more than
414 half a million children found an approximately 30% increased risk of T1D before age
415 6 years among children born by emergency or elective CS.(14) However, several

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

418

419 Strengths and limitations

420 The present study has several strengths. First, the study was based on a very large
421 population-based data of 2.6 million children born in Sweden, which provided
422 adequate statistical power. Second, the data obtained from the national registers were
423 prospectively collected therefore the data on the outcome, exposure and potential
424 confounders are not subject to recall bias. Third, unlike several previous studies on
425 the topic, we were able to classify elective and emergency CS deliveries separately.
426 This classification is crucial for understanding possible mechanisms of any observed
427 associations between CS and T1D.(23) Fourth, the T1D diagnoses were based on
428 ICD-8, 9 and 10 with a known and accurate date of first hospitalisation, which is
429 considered the date of diagnosis. Although full national coverage was achieved from
430 1987 onwards, the sensitivity analyses suggested the results were consistent when the
431 analysis was restricted to births from 1990 onwards. Moreover, the number of T1D
432 cases in the present study are comparable to those reported from the Swedish
433 Childhood Diabetes register between 1977 and 2007 (12,842 vs 12,880). (24)This
434 register has records of almost all incident diabetes cases before 15 years of age as all
435 paediatric departments in Sweden report T1D cases to the register. The Swedish health
436 care system requires all children <15 years who are suspected to have diabetes to be
437 referred to paediatric departments. It is possible, however, that some T2D cases may
438 have been misclassified as T1D. Data on T1D in Sweden is known to be of very high
439 quality.(24) Fifth, we were able to adjust for several potential confounders, which
440 were adjusted for in previous studies. However, maternal diabetes and gestational age

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

446

447 The present study had several limitations. First, we used data on all births from 1982
448 and complete nationwide coverage was not achieved until 1987. However, our
449 sensitivity analyses showed that restricting the data to births from 1990 onwards were
450 consistent with the overall results. Second, although the cohort analyses were based
451 on the largest cohort of children, to date, the sibling analyses were based on a small
452 number of pairs of siblings due to the fact only siblings discordant on both mode of
453 delivery and T1D contributed to these analyses. Third, although we had access to
454 several potential confounders, there was lack of data on several others. For example,
455 we had no data on maternal life style during pregnancy such as physical activity, diet
456 and weight gain. Furthermore, we had no data on parental and family life style such as
457 family diet and attitude to acquiring health care. However, the risk of residual
458 confounding was reduced by the sibling control analyses. Sibling control analytical
459 methods are effective in adjusting for unobserved familial characteristics that are
460 shared by siblings. Although, these methods cannot rule out unmeasured confounding
461 factors that simultaneously vary between siblings. Fourth, the siblings in this study
462 shared the same mother therefore some of the siblings may be half siblings. This fact
463 would limit the efficiency of the sibling control analyses because half siblings share
464 only half of their genetic background. However, although it could be hypothesized

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

467

468 Mechanisms

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

487

488

489

490 **CONCLUSION**

491
492 This study demonstrates that children delivered by elective CS or IVD have a small
493 increased risk of T1D. The sibling control analyses, however, suggested the
494 associations were not causal and may be explained by familial or environmental or
495 genetic factors that are shared by the siblings. The present findings have major
496 implications for how to counsel women regarding mode of delivery choice.

497

498

499

500

501

502

503

504

505

506

507

508

509

510

511

512

513

514

515

516

517

518

519

520

521

522

523

524

525

526

527

528

529

530

531 **REFERENCES**

532

533 1. Diamond Project Group. Incidence and trends of childhood Type 1 diabetes

534 worldwide 1990-1999. *Diabetic Medicine*, 2006;23(8):857-66.

535 2. Maahs DM, West NA, Lawrence JM, Mayer-Davis EJ. Epidemiology of type

536 1 diabetes. *Endocrinol Metab Clin North Am*. 2010;39(3):481-97.

537 3. Patterson CC, Dahlquist GG, Gyurus E, Green A, Soltesz G, Group ES, et al.

538 Incidence trends for childhood type 1 diabetes in Europe during 1989-2003 and

539 predicted new cases 2005-20: a multicentre prospective registration study. *Lancet*.

540 2009;373(9680):2027-33.

541 4. Dahlquist GG, Ivarsson S, Lindberg B, Forsgren M. Maternal enteroviral

542 infection during pregnancy as a risk factor for childhood IDDM. A population-based

543 case-control study. *Diabetes*. 1995 Apr;44(4):408-13.

544 5. Hettiarachchi KD, Zimmet PZ, Myers MA. Dietary toxins, endoplasmic

545 reticulum (ER) stress and diabetes. *Curr Diabetes Rev*. 2008;4(2):146-56.

546 6. Wagener DK, LaPorte RE, Orchard TJ, Cavender D, Kuller LH, Drash AL.

547 The Pittsburgh diabetes mellitus study. 3: An increased prevalence with older

548 maternal age. *Diabetologia*. 1983 Aug;25(2):82-5.

549 7. Vitamin D supplement in early childhood and risk for Type I (insulin-

550 dependent) diabetes mellitus. The EURODIAB Substudy 2 Study Group.

551 *Diabetologia*. 1999 Jan;42(1):51-4.

552 8. Strachan DP. Hay-Fever, Hygiene, and Household Size. *British Medical*

553 *Journal*. 1989 Nov 18;299(6710):1259-60.

554 9. Cardwell CR, Stene LC, Joner G, Cinek O, Svensson J, Goldacre MJ, et al.

555 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, Ekblom 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.

- 580 18. Svensson J, Carstensen B, Mortensen HB, Borch-Johnsen K, Danish Study
581 Group of Childhood D. Early childhood risk factors associated with type 1 diabetes--
582 is gender important? *European journal of epidemiology*. 2005;20(5):429-34.
- 583 19. Phillips J, Gill N, Sikdar K, Penney S, Newhook LA. History of cesarean
584 section associated with childhood onset of T1DM in Newfoundland and Labrador,
585 Canada. *Journal of environmental and public health*. 2012;2012:635097.
- 586 20. Patterson CC, Waugh NR, Carson DJ, Cole SK, Hadden DR. A Case-Control
587 Investigation of Perinatal Risk-Factors for Childhood Iddm in Northern-Ireland and
588 Scotland. *Diabetes Care*. 1994 May;17(5):376-81.
- 589 21. Dahlquist GG, Patterson C, Soltesz G. Perinatal risk factors for childhood type
590 1 diabetes in Europe - The EURODIAB substudy 2 study group. *Diabetes Care*. 1999
591 Oct;22(10):1698-702.
- 592 22. Stene LC, Magnus P, Lie RT, Sovik O, Joner G, Study NCD. No association
593 between preeclampsia or cesarean section and incidence of type 1 diabetes among
594 children: A large, population-based cohort study. *Pediatr Res*. 2003 Oct;54(4):487-90.
- 595 23. Almqvist C, Rejno G. Birth mode of delivery in the modern delivery ward -
596 indication improves understanding of childhood asthma. *Clin Exp Allergy*. 2013
597 Mar;43(3):264-7.
- 598 24. Dahlquist GG, Nystrom L, Patterson CC, Grp SCDS, Grp DISS. Incidence of
599 Type 1 Diabetes in Sweden Among Individuals Aged 0-34 Years, 1983-2007 An
600 analysis of time trends. *Diabetes Care*. 2011 Aug;34(8):1754-9.
- 601 25. Biasucci G, Rubini M, Riboni S, Morelli L, Bessi E, Retetangos C. Mode of
602 delivery affects the bacterial community in the newborn gut. *Early Hum Dev*. 2010
603 Jul;86(1):S13-S5.

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

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

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

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

616
617
618
619
620
621
622
623
624
625
626
627
628
629
630
631
632
633
634
635
636
637
638
639

640
641

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 (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)

642
643
644
645
646
647

648 **Table 2:** The association between mode of delivery and childhood type 1 diabetes
 649 (before age 15)
 650

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)

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

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

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

656 d number of siblings discordant on mode of delivery and childhood T1D
 657
 658
 659
 660
 661
 662
 663
 664
 665
 666
 667

668 **Table 3:** The association between mode of delivery and type 1 diabetes in the offspring
 669 (no age restriction)
 670

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)

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

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

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

676
 677 d number of siblings discordant on mode of delivery and any T1D
 678
 679
 680
 681
 682

683 **Table 4:** The association between mode of delivery and any diabetes diagnosis in the
 684 offspring
 685

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)

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

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

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

691 d number of siblings discordant on mode of delivery and DM

692
693
694
695
696
697
698
699
700
701
702
703
704
705
706
707
708
709
710
711
712
713
714
715
716
717
718