Perinatal factors and the risk of type 1 diabetes in childhood and adolescence - a register-based case-cohort study in Finland, years 1987-2009

Running title: Perinatal factors and type 1 diabetes

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Abstract

Objectives Our aim was to clarify previously reported associations and to explore new ones between various maternal background and perinatal factors and the risk of type 1 diabetes in childhood.

Methods We identified all children born 1.1.1987-31.12.2008 in Finland and diagnosed with type 1 diabetes by age 16 years or end of 2009 from the Special Reimbursement Register (n=6862). A 10% random sample from each birth year cohort was selected as a reference cohort (n=127216). Information on perinatal factors was obtained from the Finnish Medical Birth Register.

Results Maternal diabetes (HR=6.43; 95% CI 5.35, 7.73), maternal asthma (HR=1.23; 95% CI 1.06, 1.43), child's high birth length for gestational age (HR=1.35; 95% CI 1.22, 1.51 highest vs. lowest quintile) and premature or early term birth (HR=1.21; 95% CI 1.05, 1.39 gestational weeks 33-36 and HR=1.17; 95% CI 1.09, 1.26 gestational weeks 37-38 vs. gestational weeks 39-40) was associated with an increased risk of type 1 diabetes when adjusted for several potential confounders. Maternal smoking during pregnancy (HR=0.72; 95% CI 0.66, 0.77), high number of previous live births (HR=0.65; 95% CI 0.55, 0.76 ≥4 vs. 0 live births), and the child being born small for gestational age (HR=0.80; 95% CI 0.67, 0.96) was associated with a decreased risk of type 1 diabetes.

Conclusions Findings on maternal asthma and high birth length for gestational age increasing the risk of type 1 diabetes are novel and need to be confirmed. Our findings indicate that perinatal factors may play a role in the development of type 1 diabetes.

Key words: Birth length, Child, Cohort studies, Diabetes mellitus type 1, Gestational age

1 INTRODUCTION

Environmental factors across the fetal life, birth and infancy have been suggested to affect the risk of type 1 diabetes.[1] These factors include maternal infections, diet, and conditions in utero and at birth, as well as early exposures of the newborn infant. Perinatal factors are potentially very important in the development of type 1 diabetes as islet autoantibodies can appear at very early age.[2,3] In general, weak, but relatively consistent associations have been reported between Caesarean section,[4] higher birth weight,[5] premature birth,[6] higher maternal age,[7] and having fewer siblings at birth[8] with an increased risk of type 1 diabetes. However, more recent studies indicate that the association related to Caesarean section may be confounded by factors such as maternal type 1 diabetes or pre-pregnancy BMI.[9–11] Other perinatal variables in relation to type 1 diabetes are less extensively studied.

Finland has the highest incidence of type 1 diabetes in the world, much higher incidence than populations of similar genetic background in the neighbouring countries.[12] This makes studying environmental risk factors in Finland highly relevant, especially as a nationwide exploration of the associations between perinatal factors and type 1 diabetes in the general Finnish population is lacking.

Our aim was to investigate the associations between several maternal background, pregnancy and newborn factors and the risk of type 1 diabetes based on nationwide health registers in Finland. We included both previously investigated factors, such as mode of delivery and birth order, as well as seldom reported and novel factors, such as maternal asthma and birth length.

2 METHODS

2.1 Data sources

Data for the present case-cohort study were obtained from nationwide health registers and linked by the unique personal identity codes, assigned to all Finnish citizens shortly after birth. The Special Reimbursement Register and the Population Register maintained by the Social Insurance Institution since 1964 were used to select cases and the reference cohort, respectively. In Finland, patients with certain severe chronic conditions, such as type 1 diabetes and asthma, are entitled to a special reimbursement for the cost of the drugs needed in the treatment. The diagnosis of the disease has to be verified by a physician (adults) or specialist in pediatrics and/or a respective field (children). Further, a medical specialist in the Social Insurance Institution reviews the reimbursement applications. The administrative process for decision-making takes only a couple of weeks, and thus, the date of entitlement decision of the special reimbursement was used as a proxy for the date of diagnosis. Information on insulin purchases [Anatomical Therapeutic Chemical (ATC) code

A10) available in the Drug Prescription Register since 1994 was used to further verify type 1 diabetes cases. The Special Reimbursement Register was used to obtain information on maternal asthma, maternal diabetes and child's asthma. In addition to a physician confirmed diagnosis, a year-round drug treatment, mainly with inhaled corticosteroids and inhaled β_2-agonists as add-on therapy, is a requirement for the special reimbursement for asthma. Information on maternal sociodemographic background, pregnancy and newborn characteristics was derived from the Finnish Medical Birth Register, collected since 1987 and maintained by the Finnish Institute for Health and Welfare. Information on separate Caesarean section types and sustained/quitted smoking during pregnancy was available since 1990. Information on the child's sex and year of birth was available in both registers.

2.2 Study population and outcome definition

We identified all children born between January 1, 1987 and December 31, 2008 in Finland, who had received a special reimbursement based on diagnosed type 1 diabetes by age 16 years or by the end of year 2009 (n= 7091). A 10% random sample from each birth year cohort (1987–2008) was selected as a reference cohort (n= 131765). Children from multiple pregnancies and those who died in their birthday were excluded from the study population (n= 3923). To further verify type 1 diabetes definition, cases who had no insulin purchases after the special reimbursement (n= 22) were excluded. Thus, the size of the final study population was 6862 children with type 1 diabetes and 127216 children without type 1 diabetes. According to the study design, 742 children with type 1 diabetes were sampled in the reference cohort.

2.3 Exposures

Maternal background factors were maternal age at delivery (<25, 25–29, 30–34 and ≥35 years), smoking during pregnancy [a dichotomous variable (no/yes), and a three-category variable (no, quitted during the first trimester, continued smoking after the first trimester)], maternal diabetes (type 1 or 2, initiated before delivery), maternal asthma (initiated before delivery), and total number of previous pregnancies (any, live births, and pregnancies not terminated to live birth, all categorized as 0, 1, 2, 3, ≥4).

Pregnancy factors were gestational age and mode of delivery [a dichotomous variable (vaginal delivery/Caesarean section) and a four-category variable (normal vaginal delivery, assisted vaginal delivery, planned, and unplanned Caesarean section)]. Gestational age was categorized on the basis of deciles of gestational age (in days) of the children without type 1 diabetes as well as categorized based on gestational weeks according to the classifications of preterm delivery by the WHO[13] and the term delivery by the American College of Obstetricians and Gynecologists

Committee on Obstetric Practice Society for Maternal-Fetal Medicine[14] [≤32 (extremely or very preterm), 33-36 (moderate to late preterm), 37-38 (early term), 39-40 (full term), 41 (late term), ≥42 (post-term)].

Newborn characteristics were birth weight, birth length, ponderal index (birth weight/birth length^3), child's sex, birth decade (1980s, 1990s, 2000s), season of birth [categorised based on month of birth into Winter (December to February), Spring (March to May), Summer (June to August) and Autumn (September to November)], and fetal asphyxia [no/yes (diagnosed based on fetal heart rate using cardiotocography or analysis of the fetal blood sample)].

Both actual birth weight and birth weight for gestational age were used. First, children were categorized according to birth weight on the basis of deciles of the children without type 1 diabetes. Second, birth weight was categorized as in the most recent meta-analysis (<2500 g, 2500–2999 g, 3000–3499 g, 3500–3999 g and ≥4000 g).[5] Third, a variable birth weight for gestational age was constructed using approach by Goldacre.[15] Shortly, for each week of gestational age, and separately for boys and girls, the children were grouped into deciles of birth weight, and finally all information was combined into one composite variable [value 1=smallest, 10=largest]. Fourth, a variable with three categories based on Finnish sex-, plurality- and parity-specific population-based growth curves was constructed (small for gestational age ≤ -2 SD of the mean birth weight for gestational age, appropriate for gestational age = within mean ± 2 SD, large for gestational age ≥ mean + 2 SD).[16] Similar to birth weight, both actual birth length and birth length for gestational age were used, but grouping was based on quintiles in both birth length variables. Ponderal index was categorized into quintiles.

No information on the father was available in the Medical Birth Register. The study was approved by the national data protection authority, the institutions keeping the registers and the Institutional Review Board of the Finnish Institute for Health and Welfare.

2.4 Statistical analysis

To examine the associations between maternal background, index pregnancy and newborn characteristics and the risk of type 1 diabetes we applied a weighted Cox proportional hazard regression using inverse probability weighting to account for the oversampling of the cases. First, we fitted a crude model including only one explanatory variable at a time. Second, we fitted an adjusted model and selected confounding variables for each exposure based on previous knowledge on the underlying mechanisms between the exposure, confounders and the outcome as well as based on the observed associations between these factors in the present data. See the Supplemental Table 1 for the complete list of variables included in the adjusted models. The results are displayed as hazard ratios (HR) and 95% CIs.

For selected exposures, we conducted several sensitivity analyses based on previous studies[17,18] by excluding children according to gestational age, size at birth, mode of delivery, maternal diseases, or maternal smoking during pregnancy. Detailed description on these sensitivity analyses, as well their results are presented in the Supplemental Tables 2-6. Multiple testing was addressed by using a p value adjustment method that controls the false discovery rate (FDR) method[19] (a step-up procedure using 0.05 level as the criterion, 18 tests, R code p.adjust).

The proportionality of the hazards was tested using Schoenfeld residuals. If there was an indication of a violation of the proportional assumption ($p<0.05$), then separate results at age categories based on the distribution of age at diagnosis (quartiles, 0.0-3.9, 4.0-6.9, 7.0-9.9, 10.0-15.9 years) were obtained to illustrate the observed time-varying effect. To examine whether associations between maternal background or perinatal factors and the risk of type 1 diabetes were modified by maternal diabetes or child's sex, an interaction term between the exposures and maternal diabetes or child's sex was included in the models. As we have previously reported that child's prior diagnosis of asthma increases the risk of type 1 diabetes[20] and that several perinatal factors are associated with asthma,[21] we tested the confounding and modifying effect of child's asthma in the main analyses. The dependence of siblings in the data was tested using cluster option in STATA. Missing data were handled by complete case analysis. Analyses were performed using STATA, version 14, (RRID:SCR_012763) and RStudio, version 1.1.463 (RRID:SCR_000432) softwares.

3 RESULTS

The mean age at diagnosis in children with type 1 diabetes (n= 6862) was 7.1 years (SD 3.9), and 25% and 75% of the children were diagnosed by age 3.8 years and 10.2 years, respectively. The mean age at the end of follow-up in children without type 1 diabetes (n=127216) was 11.0 years (SD 5.0). Distribution of maternal background and perinatal factors among children with and without type 1 diabetes are presented in Tables 1-3.

3.1 Maternal background factors and the risk of type 1 diabetes

Maternal diabetes and asthma were associated with an increased risk of type 1 diabetes in the offspring (adjusted HR=6.42; 95% CI 5.35-7.72 and adjusted HR=1.23; 95% CI 1.06, 1.43, respectively), while maternal smoking during pregnancy was associated with a decreased risk of type 1 diabetes, when adjusted for each other as well as for maternal age and child's birth decade (Table 1). When analysing maternal sustained smoking (8.3% of children with type 1 diabetes and 11.3% of children without type 1 diabetes) and quitted smoking (1.4% and 1.9%, respectively) separately, the inverse association was observed with sustained smoking, but not with quitted

smoking (adjusted HR=0.71; 95% CI 0.65, 0.77 and adjusted HR=0.95; 95% CI 0.77, 1.17, respectively). Maternal age was not consistently associated with risk of type 1 diabetes in the adjusted model.

High number of any previous pregnancies was associated with a decreased risk of type 1 diabetes in the adjusted model (Table 1). When assessing separately previous pregnancies ending or not ending to a live birth, an inverse association was observed with previous live births, but not with previous pregnancies not ending up to a live birth (Table 1).

3.2 Pregnancy factors

Gestational age was inversely associated with the of risk of type 1 diabetes after adjustment for maternal age, smoking during pregnancy, diabetes, asthma and previous live births as well as mode of delivery, child's sex, birth weight, birth length and birth decade (Figure 1). When using the conventional categorization of gestational age, the risk of type 1 diabetes was increased in children born at gestational weeks 33-36 or 37-38 compared with children born at gestational weeks 39-40 when adjusted for factors described above (Table 2).

Children born by any Caesarean section were at increased risk of type 1 diabetes when compared with children born with vaginal delivery in the unadjusted model (HR=1.17; 95% CI 1.09, 1.24), but the association diminished when adjusted for maternal age, smoking during pregnancy, diabetes, asthma, number of previous live births, gestational age, child's sex, birth weight, birth length and birth decade (HR=1.02; 95% CI 0.95, 1.10). When assessing vaginal delivery and Caesarean section types separately, the association was stronger for planned than unplanned Caesarean section in the unadjusted model, but both associations diminished in the adjusted model (Table 2).

3.3 Newborn characteristics

We did nor observe a consistent association between actual birth weight, categorized in deciles, and the risk of type 1 diabetes (Figure 2A). When using a conventional categorization, low birth weight (<2500 g) was associated with a decreased risk of type 1 diabetes, but high birth weight was not, when adjusted for maternal age, smoking, diabetes, asthma, previous live births, mode of delivery, gestational age, child's sex, birth decade, and birth length (Supplemental Table 5). High birth weight for gestational age, categorized in deciles, was associated with an increased risk of type 1 diabetes in the unadjusted model, but the association weakened in the adjusted model (Figure 2B). Being born as small for gestational age was associated with a decreased risk (HR=0.75; 95% CI 0.64, 0.89), while being born as large for gestational age was associated with an increased risk of type 1 diabetes (HR=1.37; 95% CI 1.22, 1.54) compared with children being born as average for

gestational age in the unadjusted model. After adjustment for the confounders described above, the association with small for gestational age remained (HR=0.80; 95% CI 0.67, 0.96), while the association with large for gestational age diminished markedly (HR=1.12; 95% CI 0.98, 1.27) (overall p=0.013).

High actual birth length and birth length for gestational age were associated with an increased risk of type 1 diabetes in the unadjusted models, and adjustment for maternal age, smoking, diabetes, asthma, previous live births, mode of delivery, gestational age, child's sex, birth decade, and birth weight did not substantially change the results (Figure 3A and B). Ponderal index was not associated with type 1 diabetes (data not shown).

Male sex and later birth decade were associated with an increased risk of type 1 diabetes after adjustment for maternal age, smoking, diabetes, asthma, previous live births, gestational age, mode of delivery, child's sex, birth weight, birth length, and birth decade (Table 3). Season of birth and fetal asphyxia were not associated with the risk of type 1 diabetes (Table 3).

3.4 Sensitivity analysis

The association between maternal asthma and offspring's type 1 diabetes remained after excluding prematurely born or small for gestational age children (adjusted HR=1.34; 95% CI 1.14, 1.58 and adjusted HR=1.27; 95% CI 1.08, 1.50, respectively). In addition, sensitivity analyses for gestational age, mode of delivery, birth weight and birth length using different exclusions (described in the Supplemental Table 2) did not substantially change the main results (Supplemental Tables 2-6).

We observed deviations from proportional hazards assumption for variables maternal previous live births, child's birth weight for gestational age in the three categories and sex. In general, the associations between these factors and the risk of type 1 diabetes were stronger or present at earlier ages than at older ages, except for sex, where the increased risk of type 1 diabetes in boys was observed only in the oldest age group (Table 4). No other follow-up time interactions were observed. We did not observe effect modification by maternal diabetes, child's sex or asthma on the associations between perinatal factors and the risk of type 1 diabetes. In addition, accounting for multiple testing (Supplemental Table 7), sibling dependence or further adjusting for child's asthma did not substantially change the results (data not shown).

4 DISCUSSION

In this large, population-based sample from the Finnish nationwide health registers, we investigated associations between several maternal and perinatal factors and child’s later risk of type 1 diabetes. Most consistent associations with an increased risk of type 1 diabetes were found for being born moderate to late preterm or early term (gestational weeks 33-38), high birth length, maternal

asthma, and maternal diabetes. Further, being born as small for gestational age was consistently associated with a decreased risk of type 1 diabetes. In addition, high number of previous live births and sustained smoking during pregnancy were associated with a decreased risk of type 1 diabetes in the offspring.

Strengths of the present study include a large, nationwide sample and a linkage of comprehensive information from population-based registers using the unique personal identity codes. The identification of type 1 diabetes and asthma through the Special Reimbursement Register can be considered reliable, as the requirement for the special reimbursement was based on clinical diagnosis and the eligibility for the reimbursement does not depend on family's/maternal socioeconomic situation, area of residence or place of treatment. Therefore, we are likely to have captured all children with type 1 diabetes diagnoses during the study period. Other strengths include the large number of perinatal exposures, careful adjustments for the potential confounders and possibility to conduct several well-powered sensitivity analyses. Limitations of the study include that we were not able to include some factors potentially relevant in the development of type 1 diabetes, like maternal and child's infections, diet and genetic risk. Thus, residual confounding potentially exists. In addition, our asthma definition did not include mild asthma, and mechanisms underpinning the observed associations could not be further investigated.

Our finding that premature birth is associated with increased risk of type 1 diabetes is in line with results from a recent meta-analysis.[6] In addition, the observed effect estimates were almost identical with the estimates from two recent, large, register-based studies from Sweden[17] and UK.[15] Our findings remained similar after exclusion of mothers with diabetes and children born with Caesarean section indicating an independent association. Previously discussed mechanisms for the association include different gut microbiota, catch-up growth and insulin resistance, which all have been linked to both premature birth and type 1 diabetes.[15,17] Shared genetics between preterm birth and type 1 diabetes is not a likely explanation, since prematurity is mostly explained by non-genetic factors and the few genes linked to prematurity have not been linked to type 1 diabetes.[22]

Higher birth length was associated with an increased risk of type 1 diabetes and higher birth length for gestational age showed even more clear association with an increased risk of type 1 diabetes. These associations remained after adjustment for several potential confounders including birth weight, as well as in the sensitivity analyses after excluding preterm or early term births, instrumental births, maternal diabetes, asthma and smoking during pregnancy. Some evidence on a positive association between birth length and type 1 diabetes has been reported in two case-control studies,[23,24] but to our knowledge, the association between birth length for gestational age and the risk of type 1 diabetes has not been reported in population based cohort studies before. Faster linear growth in childhood has been linked to risk of type 1 diabetes,[24–27] and our findings suggests that

linear growth already in the utero may play a role in the development of type 1 diabetes. One potential mechanism underpinning the association between birth length and type 1 diabetes include the overload hypothesis, which suggests that higher insulin needs and insulin production related to faster growth could make the pancreatic beta cells vulnerable to triggers leading autoimmune reactions.[28] In addition, shared genetics between faster growth and risk of type 1 diabetes has been suggested. HLA genotypes indicating high risk of type 1 diabetes have been linked to higher birth length.[24,29] In the general population, single nucleotide polymorphisms at HLA loci have also been linked to higher birth and infant length.[30] Thus, genetics at the HLA loci might explain part of the positive association between birth length and type 1 diabetes, however the part is likely to be small.

Our observations that born small for gestational age or with low actual birth weight was associated with a decreased risk of type 1 diabetes are in line with previous studies.[15,17] Born large for gestational age was associated with increased risk of type 1 diabetes when unadjusted, however, this association seemed to be confounded by other perinatal factors. This was particularly evident when adjusted for birth length, as the association between high birth weight and type 1 diabetes diminished, while the association with low birth weight remained more stable. Thus, the fact that we adjusted for birth length while others did not, might at least partly explain that we did not observe association between high birth weight and type 1 diabetes while others did. The protective association for being born small for gestational age may reflect the same phenomena as that related to higher birth length for gestational age.

Our finding on Caesarean section is in line with the most recent studies concluding that the association is likely largely explained by confounding.[10,11,18]

We observed that maternal diabetes and maternal asthma were associated with an increased risk of type 1 diabetes in the offspring. The association between maternal diabetes and type 1 diabetes in the offspring is well established reflecting a genetic component of the disease.[31] However, the association between maternal asthma during pregnancy and long-term health outcomes in the offspring, other than respiratory outcomes, has received less attention. Maternal asthma during pregnancy has been associated with an increased risk of wide range of childhood diseases including endocrine and metabolic disorders,[32] but, as far as we know, the association between maternal asthma and type 1 diabetes in the offspring has not been reported previously. Potential mechanisms underpinning this association include maternal asthma medication and the effect of maternal asthma on infant gut microbiota. Prenatal inhaled corticosteroids have been associated with an increased risk of endocrine and metabolic disorders in the child,[33] and suggestive evidence exists on prenatal corticosteroids increasing the risk of type 1 diabetes in the child.[34] Koleva et al[35] recently reported differences in infant gut microbiota composition in infants affected

by prenatal asthma compared to infants not affected by maternal asthma. Gut microbiota, in turn has been suggested to play a role in the development of type 1 diabetes.[36]

High number of maternal previous live births, reflecting high birth order, was associated with a decreased risk of type 1 diabetes in the offspring, particularly with type 1 diabetes diagnosed before 4 years of age. These findings are in line with the pooled results from most recent meta-analysis reporting a decreased risk of type 1 diabetes with increasing birth order.[8] The suggested potential mechanisms underpinning the association between birth order and type 1 diabetes involve prenatal exposures that depend on maternal parity, like maternal immunity, and postnatal exposures acquired from older siblings, like infections or other microbial exposures.[8]

Our finding that maternal sustained smoking during pregnancy was associated with a decreased risk of type 1 diabetes in the offspring is in line with the most recent, large cohort study.[37] This Norwegian study provided, for the first time, robust evidence that the inverse association between maternal smoking during pregnancy and type 1 diabetes in the offspring is likely due to in utero effect and not from unmeasured confounding factors as previously suggested. Despite the potential protective effect of maternal smoking on the development of type 1 diabetes in the offspring, the well-established adverse effects of smoking on pregnancy outcomes should not be disregarded.

We observed stronger associations with shorter follow-up with maternal previous live births and being born small for gestational age with the development of type 1 diabetes compared with longer follow-up. These findings may indicate that if these factors play a role in the disease process, the role may be most important with type 1 diabetes that develops at early ages. This, in turn, may reflect heterogeneity of type 1 diabetes or that the associations dilute over time. The finding that male sex was associated with an increased risk of type 1 diabetes only at early adolescence, and not in earlier childhood, is in line with previous finding in Finland[38] and supports the age-dependent sex difference.

Findings from the present study can be considered generalizable to Finnish pediatric population as almost all children diagnosed with type 1 diabetes, and a large, randomly selected reference population were studied. Similarity of the results with other Nordic cohorts supports wider generalizability, however, generalizability to other populations is unclear. The strengths of the observed associations between perinatal factors and the risk of type 1 diabetes were relatively small, except that with maternal diabetes. In addition, as type 1 diabetes is a relatively rare disease, the observed associations, if causal, may have only a small impact on the absolute risk. Although many of the perinatal factors included in the present study are not easily modifiable, our findings can be used for more precise identifying of high-risk individuals for the prevention of type 1

diabetes. In addition, our results highlight that several perinatal factors as well as age-interaction are relevant to acknowledge in further studies assessing risk factors for type 1 diabetes.

In conclusion, premature birth, high birth length, maternal diabetes and maternal asthma were associated with an increased risk of type 1 diabetes in the offspring. High number of maternal previous live births and smoking during pregnancy as well as newborn infant's small birth weight for gestational age were associated with a decreased risk of type 1 diabetes. These findings are in line with observations from other European cohorts, although the direct association between birth length for gestational age and maternal asthma and type 1 diabetes has not been reported before.

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Table 1 Maternal background factors and the risk of type 1 diabetes in the offspring born 1987-2008 in Finland

Background factor	Children with type 1 diabetes (n= 6862)		Children without type 1 diabetes (n= 127216)		Unadjusted model		Adjusted model†		*P* value‡
	No	%	No	%	HR	(95% CI)	HR	(95% CI)	
Maternal age (years)									0.327
<25	1322	19.3	25822	20.3	1.00		1.00		
25-29	2446	35.7	43532	34.2	1.08	(1.01, 1.16)	1.05	(0.98, 1.12)	
30-34	2065	30.1	37553	29.5	1.11	(1.04, 1.20)	1.07	(0.99, 1.15)	
≥35	1029	15.0	20309	16.0	1.08	(0.99, 1.17)	1.03	(0.95, 1.03)	
Maternal smoking during pregnancy									<0.001
No	5876	85.6	104300	82.0	1.00		1.00		
Yes	794	11.6	19584	15.4	0.71	(0.66, 0.77)	0.72	(0.66, 0.77)	
Missing information	192	2.8	3332	2.6					
Maternal diabetes									<0.001
No	6698	97.6	126696	99.6	1.00		1.00		
Yes	162	2.4	520	0.4	6.49	(5.42, 7.77)	6.42	(5.35, 7.72)	
Maternal asthma									0.006
No	6662	97.1	123572	97.1	1.00		1.00		
Yes	200	2.9	3644	2.9	1.26	(1.09, 1.45)	1.23	(1.06, 1.43)	
Number of maternal previous pregnancies (all)									<0.001
0	2175	31.7	39598	31.1	1.00		1.00		
1	2156	31.4	38669	30.4	0.99	(0.93, 1.05)	0.98	(0.92, 1.04)	
2	1354	19.7	24047	18.9	0.99	(0.92, 1.06)	0.96	(0.89, 1.03)	
3	630	9.2	12263	9.6	0.90	(0.83, 0.99)	0.86	(0.80, 0.97)	
≥4	514	7.5	12078	9.5	0.80	(0.72, 0.88)	0.77	(0.69, 0.86)	
Missing information	33	0.5	561	0.4					
Number of maternal previous live births									<0.001
0	2806	40.9	51851	40.8	1.00		1.00		
1	2418	35.2	42937	33.8	1.02	(0.96, 1.07)	0.99	(0.94, 1.05)	
2	1084	15.8	20179	15.9	0.95	(0.89, 1.02)	0.92	(0.85, 0.99)	
3	344	5.0	6650	5.2	0.94	(0.84, 1.06)	0.92	(0.81, 1.03)	
≥4	175	2.6	4951	3.9	0.70	(0.59, 0.81)	0.65	(0.55, 0.76)	
Missing information	35	0.5	648	0.5					
Number of maternal previous pregnancies not ending to a live birth									0.019
0	4801	70.0	86883	68.3	1.00		1.00		
1	1480	21.6	27678	21.8	0.96	(0.91, 1.02)	0.96	(0.91, 1.02)	
2	401	5.8	8346	6.6	0.89	(0.80, 0.99)	0.90	(0.81, 1.00)	
3	94	1.4	2432	1.9	0.74	(0.60, 0.92)	0.74	(0.60, 0.92)	
≥4	51	0.7	1218	1.0	0.84	(0.63, 1.11)	0.85	(0.63, 1.13)	
Missing information	35	0.5	659	0.5					

† Adjusted for maternal age, smoking, diabetes, and asthma as well as child's birth decade.

‡ overall *P* value in the adjusted model

Table 2 Pregnancy factors and the risk of type 1 diabetes in children born 1987-2008 in Finland

Pregnancy factor	Children with type 1 diabetes (*n*= 6862)		Children without type 1 diabetes (n= 127216)		Unadjusted model		Adjusted model†		*P* value‡
	No	%	No	%	HR	(95% CI)	HR	(95% CI)	
Gestational age (weeks)									<0.001
<33	34	0.5	922	0.7	0.79	(0.56, 1.11)	0.87	(0.59, 1.27)	
33-36	303	4.4	4538	3.6	1.29	(1.14, 1.45)	1.21	(1.05, 1.39)	
37-38	1358	19.8	21552	16.9	1.19	(1.12, 1.27)	1.17	(1.09, 1.26)	
39-40	3695	53.9	69221	54.4	1.00		1.00		
41	1154	16.8	24061	18.9	0.91	(0.85, 0.97)	0.89	(0.83, 0.96)	
>41	276	4.0	6087	4.8	0.88	(0.78, 1.00)	0.87	(0.77, 0.99)	
Missing information	42	0.6	835	0.7					
Mode of delivery §									0.193
Normal vaginal delivery	5 299	77.2	100049	78.6	1.00		1.00		
Assisted vaginal delivery	403	5.9	7701	6.1	1.12	(1.01, 1.24)	1.07	(0.96, 1.19)	
Planned Caesarean section	487	7.1	7367	5.8	1.39	(1.26, 1.53)	1.10	(0.99, 1.22)	
Other Caesarean section	475	6.9	9232	7.3	1.10	(1.00, 1.21)	0.99	(0.90, 1.10)	
Missing information	198	2.9	2867	2.3					

† Adjusted for maternal age, smoking during pregnancy, diabetes, asthma, number of previous live births, mode of delivery, gestational age, child's sex, birth weight, birth length, and birth decade

‡ overall *P* value in the adjusted model

§ Information on separate type of Caesarean section available since 1990 [information on Caesarean section (type unknown) from years 1987-1989 is coded as missing information]

Table 3 Newborn characteristics and the risk of type 1 diabetes in children born 1987-2008 in Finland

Newborn characteristic	Children with type 1 diabetes (n= 6862)		Children without type 1 diabetes (n= 127216)		Unadjusted model		Adjusted model†		*P* value‡
	No	%	No	%	HR		HR	(95% CI)	
Sex						<0.001			<0.001
Girl	3149	45.9	62203	48.9	1.00		1.00		
Boy	3713	54.1	65013	51.1	1.13	(1.08, 1.19)	1.10	(1.05, 1.16)	
Birth decade									<0.001
1980s	1258	18.3	17944	14.1	1.00		1.00		
1990s	4348	63.4	59580	46.8	1.14	(1.07, 1.22)	1.15	(1.07, 1.22)	
2000s	1256	18.3	49692	39.1	1.22	(1.12, 1.32)	1.21	(1.11, 1.32)	
Season of birth									0.103
Winter (Dec, Jan, Feb)	1593	23.3	30183	23.7	1.00		1.00		
Spring (Mar, Apr, May)	1870	27.3	33127	26.0	1.05	(0.98, 1.12)	1.07	(0.99, 1.14)	
Summer (Jun, Jul, Aug)	1742	25.4	33156	26.1	1.00	(0.94, 1.08)	1.02	(0.95, 1.09)	
Autumn (Sep, Oct, Nov)	1657	24.2	30750	24.2	1.05	(0.98, 1.13)	1.08	(1.01, 1.16)	
Fetal asphyxia									0.727
No	6729	98.1	124362	97.8	1.00		1.00		
Yes	133	1.9	2854	2.2	1.14	(0.96, 1.37)	1.03	(0.86, 1.25)	

† Adjusted for maternal age, smoking during pregnancy, diabetes, asthma, number of previous live births, mode of delivery, gestational age, child's sex, birth weight, birth length and birth decade

‡ overall *P* value in the adjusted model

Table 4 Maternal previous live births, child's birth weight for gestational age and sex and the risk of type 1 diabetes by age

Perinatal factor	Type 1 diabetes											
	0.0-3.9 years			4.0-6.9 years			7.0-9.9 years			10.0-15.9 years		
	No	HR[†]	(95% CI)	No	HR[†]	(95% CI)	No	HR[†]	(95% CI)	No	HR[†]	(95% CI)
Number of maternal previous live births												
0	808	1.00		703	1.00		600	1.00		695	1.00	
1	630	0.93	(0.83, 1.04)	524	0.86	(0.76, 0.97)	571	1.06	(0.94, 1.20)	692	1.14	(1.02, 1.27)
2	256	0.79	(0.68, 0.91)	283	0.96	(0.83, 1.11)	250	0.96	(0.82, 1.12)	295	1.00	(0.87, 1.16)
3	93	0.88	(0.70, 1.10)	96	1.01	(0.81, 1.26)	71	0.84	(0.64, 1.09)	84	0.92	(0.72, 1.17)
≥4	44	0.56	(0.41, 0.76)	44	0.62	(0.45, 0.86)	45	0.78	(0.57, 1.09)	42	0.67	(0.48, 0.93)
Birth weight for gestational age[‡]												
Small for gestational age	29	0.55	(0.37, 0.81)	40	0.84	(0.60, 1.18)	27	0.64	(0.43, 0.96)	53	1.24	(0.92, 1.67)
Average for gestational age	1716	1.00		1524	1.00		1430	1.00		1673	1.00	
Large for gestational age	81	1.05	(0.81, 1.36)	84	1.24	(0.96, 1.59)	78	1.15	(0.89, 1.49)	82	1.04	(0.82, 1.32)
Sex												
Girl	846	1.00		826	1.00		730	1.00		747	1.00	
Boy	992	1.09	(0.99, 1.20)	833	0.95	(0.86, 1.05)	814	1.03	(0.92, 1.14)	1074	1.36	(1.24, 1.50)

[†] Adjusted hazard ratios. Number of maternal previous live births was adjusted for maternal age, smoking during pregnancy, diabetes, and asthma as well as child's birth decade. Child's birth weight for gestational age was adjusted for maternal age, smoking during pregnancy, diabetes, asthma, previous live births, mode of delivery, child's birth length, and birth decade. Child's sex was adjusted for maternal age, smoking during pregnancy, diabetes, asthma, previous live births, mode of delivery, gestational age, child's sex, birth weight, birth length and birth decade

[‡] Categories for birth weight for gestational age were based on Finnish sex-, plurality- and parity-specific population-based growth curves (Sankilampi et al. Ann Med 2013): Small for gestational age ≤ -2 SD of the mean birth weight for gestational age, appropriate for gestational age = within mean ± 2 SD, large for gestational age ≥ mean + 2 SD

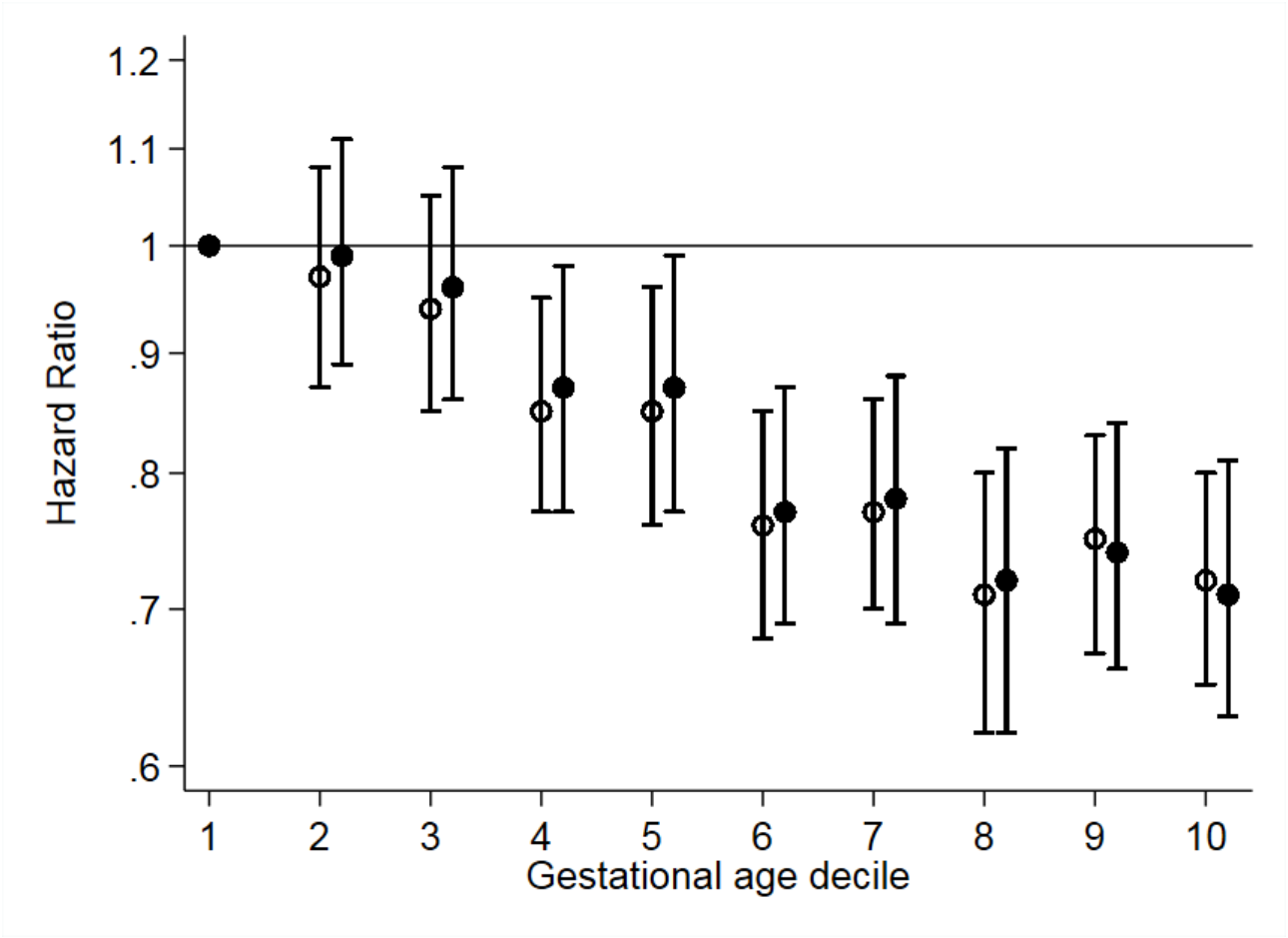

Figure 1. The association between gestational age (in days, deciles) and the risk of type 1 diabetes in children born in 1987–2008 in Finland (overall *P*<0.001). Data points are unadjusted (open circles) and adjusted (full circles) hazard ratios with 95% confidence intervals (bars).Variables in the adjusted model were maternal age, smoking during pregnancy, maternal diabetes, maternal asthma, previous live births, mode of delivery, child's sex, birth weight, birth length and birth decade. Deciles of gestational age were based on the distribution among the non-cases: 1 <265 days (reference), 2 = 265-270 days, 3 = 271-273 days, 4 = 274-276 days, 5 =277-279 days, 6= 280-281 days, 7=282-284 days, 8= 285-286 days, 9= 287-290 days, 10 ≥291 days

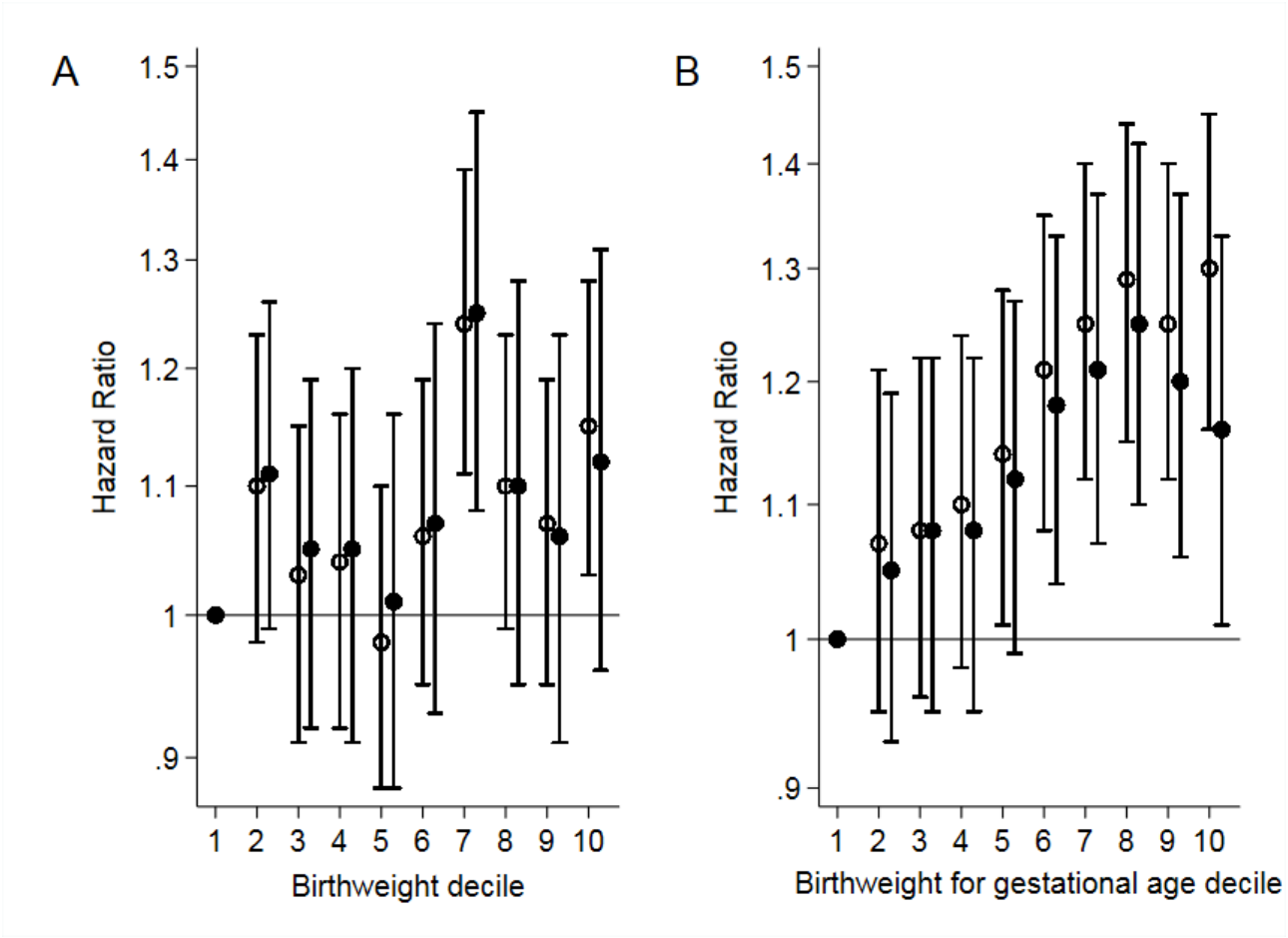

Figure 2. The association between birth weight, actual (A) and for gestational age (B) (in deciles), and the risk of type 1 diabetes in children born in 1987–2008 in Finland (overall *P*=0.009 and 0.021, respectively). Data points are unadjusted (open circles) and adjusted (full circles) hazard ratios with 95% confidence intervals (bars). Variables in the adjusted model were maternal age, smoking during pregnancy, maternal diabetes, maternal asthma, previous live births, mode of delivery, gestational age (when applicable), child's sex (when applicable), birth length, and birth decade. Deciles of actual birth weight were based on the distribution among the non-cases: 1 <2930 g (reference), 2 2930-3164 g, 3 = 3165-3319 g, 4 = 3320-3449 g, 5 =3450-3579 g, 6= 3580-3699 g, 7=3700-3829 g, 8= 3830-3989 g, 9= 3990-4209 g, 10 ≥4210 g. A composite variable birth weight for gestational age was constructed according to Goldacre (Diabetologia 2018) (see methods): 1=lightest (reference), ... 10= heaviest.

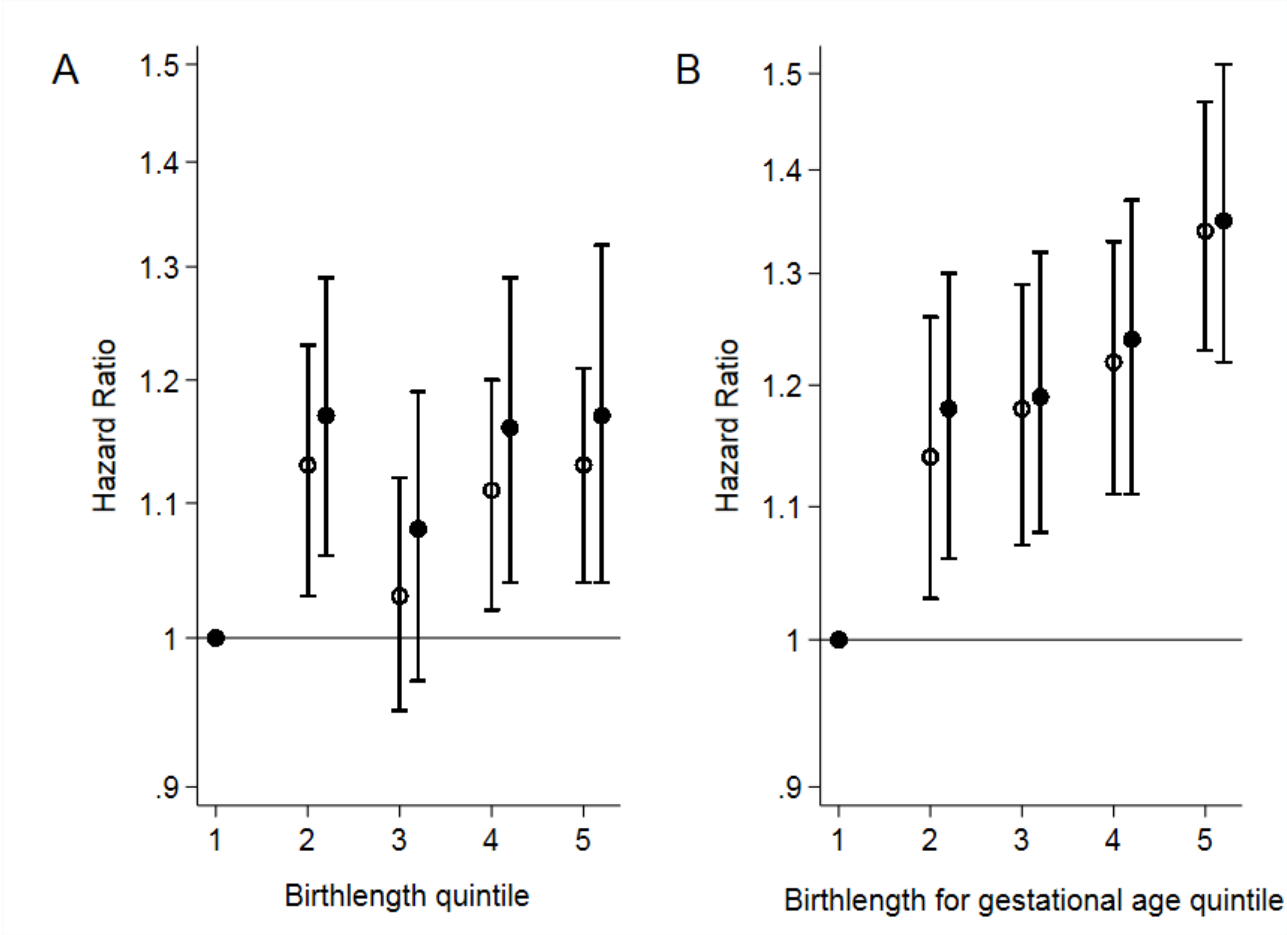

Figure 3. The association between birth length, actual (A) and for gestational age (B) (in quintiles), and the risk of type 1 diabetes in children born in 1987–2008 in Finland (overall *P*=0.009 and <0.001, respectively). Data points are unadjusted (open circles) and adjusted (full circles) hazard ratios with 95% confidence intervals (bars). Variables in the adjusted model were maternal age, smoking during pregnancy, maternal diabetes, maternal asthma, previous live births, mode of delivery, gestational age (when applicable), child's sex (when applicable), birth weight, and birth decade. Quintiles of actual birth length were based on the distribution among the non-cases: 1 <49.0 cm (reference), 2 = 49.0-49.9 cm, 3 = 50.0-50.9 cm, 4 = 51.0-51.9 cm, 5 ≥52 cm. A composite variable birth length for gestational age was constructed according to Goldacre (Diabetologia 2018) (see methods): 1= shortest (reference), ... 5=tallest

Supplemental material

Supplemental Table 1. Full list of variables used in the adjusted models

Exposure	Adjusted for
Maternal background factors	Maternal age, smoking during pregnancy, diabetes, asthma and child's birth decade
Maternal age	-"-
Maternal smoking during pregnancy	-"-
Maternal diabetes	-"-
Maternal asthma	-"-
Maternal previous pregnancies (all)	-"-
Maternal previous live births	-"-
Maternal previous pregnancies not terminated to live birth	-"-
Pregnancy factors	Maternal age, smoking during pregnancy, diabetes, asthma, previous live births, gestational age, mode of delivery, child's sex, birth weight, birth length, and birth decade
Gestational age	-"-
Mode of delivery	-"-
Newborn characteristics	Maternal age, smoking during pregnancy, diabetes, asthma, previous live births, mode of delivery, gestational age, child's sex, birth weight, birth length and birth decade
Birth weight (actual)	-"-
Birth length (actual)	-"-
Sex	-"-
Birth decade	-"-
Season of birth	-"-
Apgar scores	-"-
Fetal asphyxia	-"-
Birth weight (for gestational age)	Maternal age, smoking during pregnancy, diabetes, asthma, previous live births, mode of delivery, birth length, and birth decade
Birth length (for gestational age)	Maternal age, smoking during pregnancy, diabetes, asthma, previous live births, mode of delivery, birth weight, and birth decade

Supplemental Table 2. Description of the sensitivity analysis conducted for selected exposures

Exposure	Separate analysis by excluding
Maternal asthma	1) children who were born before gestational age 37 weeks 2) children who were born small for gestational age
Gestational age	1) children born small for gestational age 2) children born large for gestational age 3) children of mothers with diabetes 4) children of mothers with asthma 5) children born by Caesarean section
Mode of delivery	1) children born before gestational age 37 weeks 2) children born with low birth weight (<2500 g) or small for gestational age 3) children born large for gestational age 4) children of mothers with diabetes 5) children of mothers with asthma
Birth weight (actual) Birth weight for gestational age Birth length (actual) Birth length for gestational age	1) children born before gestational age 37 weeks 2) children born before gestational age 39 weeks 3) children of mothers with diabetes 4) children of mothers with asthma 5) children of mothers who smoked during pregnancy 6) children born by Caesarean section or assisted vaginal delivery

Supplemental Table 3. Sensitivity analyses on the association between gestational age and the risk of type 1 diabetes

Gestational age (weeks)	Whole population (n=129549)		SGA (n=3986) excluded		LGA (n=4518) excluded		Maternal diabetes (n=684) excluded		Maternal asthma (n=3844) excluded		Caesarean section (n=20239) excluded	
	HR[†]	(95% CI)	HR[†]	(95% CI)	HR[†]	(95% CI)	HR[†]	(95% CI)	HR[†]	(95% CI)	HR[†]	(95% CI)
<33	1.02	(0.75, 1.37)	0.82	(0.55, 1.20)	0.94	(0.63, 1.40)	0.88	(0.59, 1.30)	0.89	(0.61, 1.30)	1.00	(0.59, 1.70)
33-36	1.20	(1.04, 1.38)	1.21	(1.05, 1.40)	1.21	(1.04, 1.40)	1.20	(1.04, 1.39)	1.22	(1.06, 1.40)	1.27	(1.07, 1.49)
37-38	1.17	(1.09, 1.26)	1.16	(1.08, 1.25)	1.16	(1.08, 1.25)	1.18	(1.10, 1.27)	1.16	(1.08, 1.24)	1.22	(1.13, 1.32)
39-40	1.00		1.00		1.00		1.00		1.00		1.00	
41	0.89	(0.83, 0.96)	0.89	(0.83, 0.96)	0.89	(0.83, 0.95)	0.89	(0.83, 0.96)	0.89	(0.83, 0.96)	0.90	(0.84, 0.97)
≥42	0.87	(0.77, 0.99)	0.88	(0.76, 1.00)	0.86	(0.76, 0.98)	0.87	(0.77, 0.99)	0.88	(0.77, 1.00)	0.88	(0.77, 1.02)

SGA=small for gestational age, LGA= large for gestational age

[†] Variables in the adjusted model were maternal age, maternal smoking, number of maternal previous live births, maternal diabetes (when applicable), maternal asthma (when applicable), mode of delivery, child's sex, birth decade, birth weight, and birth length

Supplemental Table 4. Sensitivity analyses on the association between mode of delivery and the risk of type 1 diabetes

Mode of delivery	Whole population (n=129549)		Gestational age <37 weeks (n=5797) excluded		LBW/SGA (n=6044) excluded		LGA (n=4518) excluded		Maternal diabetes (n=684) excluded		Maternal asthma (n=3844) excluded	
	HR[†]	(95% CI)	HR[†]	(95% CI)	HR[†]	(95% CI)	HR[†]	(95% CI)	HR[†]	(95% CI)	HR[†]	(95% CI)
Normal vaginal delivery	1.00		1.00		1.00		1.00		1.00		1.00	
Assisted vaginal delivery	1.07	(0.96, 1.19)	1.03	(0.92, 1.16)	1.05	(0.94, 1.17)	1.06	(0.95, 1.18)	1.06	(0.95, 1.18)	1.06	(0.94, 1.18)
Planned Caesarean section	1.10	(0.99, 1.22)	1.15	(1.03, 1.28)	1.12	(1.00, 1.24)	1.08	(0.97, 1.21)	1.11	(1.00, 1.24)	1.11	(0.99, 1.23)
Other Caesarean section	0.99	(0.90, 1.10)	0.97	(0.87, 1.09)	1.00	(0.89, 1.11)	1.00	(0.91, 1.12)	1.00	(0.90, 1.11)	1.00	(0.90, 1.11)

LBW=low birth weight (<2500g), SGA=small for gestational age, LGA= large for gestational age

[†] Variables in the adjusted model were maternal age, maternal smoking, number of maternal previous live births, maternal diabetes (when applicable), maternal asthma (when applicable), gestational age, child's sex, birth decade, birth weight, and birth length

Supplemental Table 5. Sensitivity analyses on the association between birth weight and the risk of type 1 diabetes

	Whole population (n=129549)		Gestational age <37 weeks (n=5797) excluded		Gestational age <39 weeks (n= 28707) excluded		Maternal diabetes (n=684) excluded		Maternal asthma (n=3844) excluded		Caesarean section and assisted vaginal delivery (n=28730) excluded		Maternal smoking during pregnancy (n=20378) excluded	
Birth weight variable	HR†,‡	(95% CI)	HR†,‡	(95% CI)	HR†,‡	(95% CI)	HR†,‡	(95% CI)	HR†,‡	(95% CI)	HR†,‡	(95% CI)	HR†,‡	(95% CI)
Actual birth weight (g)														
<2500	0.79	(0.65, 0.95)	0.71	(0.51, 0.97)	0.63	(0.35, 1.14)	0.76	(0.63, 0.92)	0.76	(0.62, 0.92)	0.71	(0.54, 0.92)	0.77	(0.62, 0.95)
2500-2999	0.94	(0.85, 1.05)	0.90	(0.80, 1.01)	0.93	(0.80, 1.08)	0.94	(0.84, 1.04)	0.93	(0.83, 1.04)	0.90	(0.79, 1.02)	0.91	(0.81, 1.03)
3000-3499	1.00		1.00		1.00		1.00		1.00		1.00		1.00	
3500-3999	1.04	(0.97, 1.11)	1.03	(0.96, 1.10)	1.02	(0.94, 1.10)	1.04	(0.97, 1.12)	1.04	(0.97, 1.11)	1.04	(0.96, 1.13)	1.02	(0.95, 1.10)
≥4000	1.01	(0.92, 1.11)	1.01	(0.92, 1.10)	1.00	(0.90, 1.10)	1.01	(0.92, 1.11)	1.01	(0.92, 1.11)	0.98	(0.88, 1.09)	0.99	(0.90, 1.09)
Birth weight for gestational age														
Small for gestational age	0.80	(0.67, 0.96)	0.83	(0.69, 1.00)	0.77	(0.61, 0.97)	0.80	(0.67, 0.95)	0.78	(0.65, 0.93)	0.75	(0.60, 0.94)	0.78	(0.64, 0.95)
Average for gestational age	1.00		1.00		1.00		1.00		1.00		1.00		1.00	
Large for gestational age	1.12	(0.98, 1.27)	1.13	(0.99, 1.30)	1.11	(0.94, 1.30)	1.14	(1.00, 1.31)	1.14	(1.00, 1.30)	1.13	(0.96, 1.32)	1.10	(0.96, 1.27)

†Variables in the adjusted model for actual birth weight were maternal age, maternal smoking (when applicable), number of maternal previous live births, maternal diabetes (when applicable), maternal asthma (when applicable), mode of delivery (when applicable), gestational age, child's sex, birth decade, and birth length

‡Variables in the adjusted model for birth weight for gestational age were maternal age, maternal smoking (when applicable), number of maternal previous live births, maternal diabetes (when applicable), maternal asthma (when applicable), mode of delivery (when applicable), child's birth decade, and birth length

Supplemental Table 6. Sensitivity analyses on the association between birth length and the risk of type 1 diabetes

	Whole population (n=129549)		Gestational age <37 weeks (n=5797) excluded		Gestational age <39 weeks (n= 28707) excluded		Maternal diabetes (n=684) excluded		Maternal asthma (n=3844) excluded		Caesarean section and assisted vaginal delivery (n=28730) excluded		Maternal smoking during pregnancy (n=20378) excluded	
Birth length variable	HR†,‡	(95% CI)	HR†,‡	(95% CI)	HR†,‡	(95% CI)	HR†,‡	(95% CI)	HR†,‡	(95% CI)	HR†,‡	(95% CI)	HR†,‡	(95% CI)
Actual birth length (cm, quintiles)														
<49	1.00		1.00		1.00		1.00		1.00		1.00		1.00	
49	1.17	(1.06, 1.29)	1.17	(1.06, 1.30)	1.10	(0.97-1.25)	1.17	(1.06-1.29)	1.15	(1.04-1.27)	1.14	(1.02-1.28)	1.14	(1.02-1.27)
50	1.08	(0.97, 1.19)	1.08	(0.97, 1.20)	1.02	(0.90-1.16)	1.07	(0.97-1.19)	1.07	(0.96-1.18)	1.06	(0.94-1.19)	1.08	(0.96-1.20)
51	1.16	(1.04, 1.29)	1.17	(1.04, 1.31)	1.08	(0.94-1.24)	1.15	(1.02-1.28)	1.14	(1.02-1.27)	1.15	(1.01-1.30)	1.18	(1.04-1.33)
≥52	1.17	(1.04, 1.32)	1.19	(1.05, 1.34)	1.12	(0.97-1.29)	1.17	(1.04-1.32)	1.15	(1.03-1.30)	1.15	(1.00-1.31)	1.19	(1.04-1.34)
Birth length for gestational age (quintiles)														
1 (shortest)	1.00		1.00		1.00		1.00		1.00		1.00		1.00	
2	1.18	(1.06, 1.30)	1.16	(1.04, 1.29)	1.13	(1.00-1.28)	1.17	(1.06-1.30)	1.18	(1.06-1.31)	1.17	(1.04-1.32)	1.17	(1.04-1.31)
3	1.19	(1.08, 1.32)	1.19	(1.07, 1.33)	1.11	(0.99-1.26)	1.19	(1.07-1.32)	1.19	(1.07-1.32)	1.20	(1.06-1.34)	1.22	(1.08-1.36)
4	1.24	(1.11, 1.37)	1.23	(1.10, 1.37)	1.15	(1.01-1.30)	1.23	(1.11-1.37)	1.24	(1.11-1.38)	1.24	(1.10-1.40)	1.26	(1.12-1.41)
5 (tallest)	1.35	(1.22, 1.51)	1.35	(1.20, 1.51)	1.21	(1.07-1.38)	1.35	(1.21-1.50)	1.36	(1.22-1.52)	1.33	(1.17-1.50)	1.38	(1.22-1.55)

†Variables in the adjusted model for actual birth length were maternal age, maternal smoking (when applicable), number of maternal previous live births, maternal diabetes (when applicable), maternal asthma (when applicable), mode of delivery (when applicable), gestational age, child's sex, birth decade, and birth weight

‡Variables in the adjusted model for birth length for gestational age were maternal age, maternal smoking (when applicable), number of maternal previous live births, maternal diabetes (when applicable), maternal asthma (when applicable), mode of delivery (when applicable), child's birth decade, and birth weight

Supplemental Table 7. Multiple testing correction for the main adjusted results

Perinatal factor (original result presented in)	p value	FDR[a]
Maternal age (Table 1)	0.327	0.344
Maternal smoking during pregnancy (Table 1)	<0.001	<0.001
Maternal diabetes (Table 1)	<0.001	<0.001
Maternal asthma (Table 1)	0.006	0.010
Number of maternal previous pregnancies, any (Table 1)	<0.001	<0.001
Number of maternal previous live births (Table 1)	<0.001	<0.001
Number of maternal previous pregnancies not ending to a live birth (Table 1)	0.019	0.026
Gestational age (weeks, 6 categories) (Table 2)	<0.001	<0.001
Mode of delivery (Table 2)	0.193	0.217
Child's sex (Table 3)	<0.001	<0.001
Birth decade (Table 3)	<0.001	<0.001
Season of birth (Table 3)	0.103	0.124
Fetal asphyxia (Table 3)	0.727	0.727
Gestational age (days, deciles) (Figure 1)	<0.001	<0.001
Birth weight (Figure 2A)	0.009	0.014
Birth weight for gestational age (Figure 2B)	0.021	0.028
Birth lenght (Figure 3A)	0.009	0.014
Birth lenght for gestational age (Figure 3B)	<0.001	<0.001

[a] Multiple testing was addressed by using a p value adjustment method that controls the false discovery rate (FDR) (Benjamini and Hochberg 1995) (a step-up procedure using 0.05 level as the criterion, 18 tests)