META ANALYSIS

Caesarean section is associated with an increased risk of childhood-onset type 1 diabetes mellitus: a meta-analysis of observational studies

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Abstract

Aims/hypothesis The aim of this study was to investigate the evidence of an increased risk of childhood-onset type 1 diabetes in children born by Caesarean section by systematically reviewing the published literature and performing a meta-analysis with adjustment for recognised confounders. *Methods* After MEDLINE, Web of Science and EMBASE searches, crude ORs and 95% CIs for type 1 diabetes in children born by Caesarean section were calculated from the data reported in each study. Authors were contacted to

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facilitate adjustments for potential confounders, either by supplying raw data or calculating adjusted estimates. Meta-analysis techniques were then used to derive combined ORs and to investigate heterogeneity between studies.

Results Twenty studies were identified. Overall, there was a significant increase in the risk of type 1 diabetes in children born by Caesarean section (OR 1.23, 95% CI 1.15–1.32, $p<0.001$). There was little evidence of heterogeneity between studies ($p=0.54$). Seventeen authors provided raw data or adjusted estimates to facilitate adjustments for potential confounders. In these studies, there was evidence of an increase in diabetes risk with greater birthweight, shorter gestation and greater maternal age. The increased risk of type 1 diabetes after Caesarean section was little altered after adjustment for gestational age, birth weight, maternal age, birth order, breast-feeding and maternal diabetes (adjusted OR 1.19, 95% CI 1.04–1.36, $p=0.01$).

Conclusions/interpretation This analysis demonstrates a 20% increase in the risk of childhood-onset type 1 diabetes after Caesarean section delivery that cannot be explained by known confounders.

Keywords Caesarean section · Cesarean section · Diabetes mellitus · Epidemiology · Type 1

Introduction

Although type 1 diabetes has an important genetic component [1], the marked increases in incidence rate observed among the under 15 age group in recent decades [2, 3] strongly suggest the role of environmental influences. Various observations have lead to speculation that Caesarean section delivery could be involved. Rapid increases in Caesarean section rates [4] have occurred in parallel with increasing diabetes rates. For example, rates of Caesarean

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section in England, Sweden and the USA have risen from 6%, 8% and 10% in 1975 [5] to 19%, 12% and 22% in 1999 [4], respectively. Animal models suggest a higher risk of diabetes after Caesarean section [6, 7]. Also, children delivered by Caesarean section have been shown to have altered gut microbiotic composition and immune function [8–11], which could increase their risk of type 1 diabetes. Numerous studies have investigated Caesarean section and type 1 diabetes, but findings have been inconsistent, possibly as a result of inadequate size and limited power in some studies. In such a situation, meta-analysis is valuable in synthesising the available evidence [12].

The first aim of this study was to assess the evidence of an association between type 1 diabetes and Caesarean section by performing a meta-analysis. Previous studies have shown that various perinatal and early life factors are associated with type 1 diabetes, such as maternal age, birthweight and breastfeeding [13–15]. As such factors may differ in children born by Caesarean section, the second aim was to adjust the pooled estimate of the association between Caesarean section and type 1 diabetes for the influence of these potential confounders.

Methods

Literature search The main literature search was conducted using MEDLINE, through OVID ONLINE, with the following strategy: ('Cesarean Section' or 'Delivery, Obstetric' or cesarean or caesarean or mode of delivery) and ('Diabetes Mellitus, Type 1' or (diabetes and Type 1) or IDDM), using the terms in inverted commas as MEDLINE subject heading key words. Similar searches were conducted on Web of Science and EMBASE. To identify studies that investigated Caesarean section along with other risk factors, a more general search was conducted on MEDLINE using: ('Diabetes Mellitus, Type 1' and ('Case–Control Studies' or 'Cohort Studies')). The searches were limited to studies on humans, published before September 2007. Abstracts were screened independently by two investigators (C. R. Cardwell and C. C. Patterson) to establish if the studies were likely to provide relevant data based on the following inclusion criteria: (1) they identified a group with type 1 diabetes (containing more than 15 cases) and a group without type 1 diabetes, and (2) they determined the prevalence of delivery by Caesarean section in these groups. Citations generated from the more general MEDLINE search were initially screened to remove obviously irrelevant articles. Finally, the reference lists of all pertinent articles were examined.

Eligible studies were assessed independently by two reviewers (C. R. Cardwell and C. C. Patterson) to abstract information about the study (country, design and year of publication), participants with type 1 diabetes (source, age at

onset), control participants (source) and mode of delivery (methods of ascertainment).

Attempts were made to contact the corresponding author of all eligible studies to facilitate adjustment for maternal age, birthweight, gestational age, birth order, breast-feeding and maternal diabetes. Authors were requested to provide raw data or to provide adjusted estimates of the association between Caesarean section and type 1 diabetes after conducting specified additional analyses.

Statistical analysis ORs and SEs were calculated for the association between diabetes and Caesarean section for each study. Conditional logistic regression was used to calculate the ORs and SEs for the matched case–control studies. In cohort studies with varying duration of participant follow-up, rate ratios and their SEs were used instead of ORs, which were not directly calculable. As type 1 diabetes is a rare disease, these measures should be approximately equal [16]. Poisson regression was used to adjust these rate ratios for differences in the year of birth between cases and controls, a consequence of this study design [17, 18], by adding a year of birth and age term to the regression model in addition to Caesarean section. Tests for heterogeneity between studies were conducted, and random effects models used to calculate pooled ORs [19]. Random effects models were deemed more appropriate than fixed effects models because it was anticipated that there would be between study heterogeneity due to their observational nature. The I^2 statistic was calculated to quantify the degree of heterogeneity between studies [20]. This statistic measures the percentage of the total variation across studies that is due to heterogeneity. Study-specific weights in the random effects model were calculated and scaled to percentages. Publication/selection bias was investigated by checking for asymmetry in funnel plots of the study ORs against the SE of the logarithm of the ORs [21]. In the absence of publication/selection bias this graph should conform to a funnel shape, as the OR estimates from smaller studies (with larger SEs) show greater variation around the overall estimate than the OR estimates from larger studies (with smaller SEs). An identical approach was adopted to combine ORs for the association between type 1 diabetes and available confounders. To investigate the trend across categories for maternal age and birthweight, an OR (and SE) was calculated per increase in category using regression models appropriate to the design of the study, and then meta-analysis techniques were applied.

A two-stage technique was used to calculate pooled estimates of the association between Caesarean section and diabetes after adjustment for potential confounders [22]. First, adjusted estimates and SEs were calculated within each study using regression models appropriate to the study design (logistic regression for case–control studies, conditional logistic regression for matched case–control studies and Poisson regression for cohort studies) including diabetes as the outcome variable and Caesarean section and the potential confounder(s) of interest as explanatory variables. As explained previously, Poisson regression models additionally included terms to adjust for differences in year of birth between cases and controls in the cohort studies with varying participant follow-up. Meta-analysis techniques were then applied to these adjusted estimates.

Sensitivity analyses were conducted by subdividing studies by quality (whether population-based randomly selected controls were used) and using the Trim and Fill method to calculate pooled estimates after adjustment for any potential publication bias [23]. This method identifies funnel plot asymmetry and imputes study results, which are considered to have been conducted but not published, to create funnel plot symmetry. The overall combined estimate of the association is then based on the observed and imputed study results.

All statistical analyses were performed using STATA 9.0 software (STATA, College Station, TX, USA).

Results

The searches identified nine eligible articles using MEDLINE [15, 17, 24–30]; a further article was identified from Web of Science [31] and another from EMBASE [32]. The more general MEDLINE search identified a further eight articles [33–40], and review of reference lists revealed another two articles [41, 42].

Seven of the identified articles were excluded from further consideration. An earlier study [41] was excluded in favour of a larger study [42] that included all the participants enrolled in the former. Three articles [25, 26, 28] reported the same data. A study [33] was excluded because no raw data were presented in the paper or available from the authors. Another study was excluded as it contained fewer than 15 cases [29]. A meeting abstract [31] was replaced with the subsequently published article [43] and, after contact with authors, an earlier report from a cohort [35] was replaced with a later report [18].

The 16 remaining articles corresponded to 20 independent studies, because one study [15] provided data from eight centres, three of which were reported elsewhere [25, 27, 32], and another provided data from two centres [24], one of which was subsequently reported in a larger study [32]. Finally, to ensure two studies [17, 30] provided independent information, authors removed cases from one study [30] that were included in the other [17]. Study characteristics are summarised in Table 1.

The unadjusted association between Caesarean section and childhood-onset type 1 diabetes for all 20 studies, including 9,938 cases, is shown in Fig. 1. Overall, there was a significant increase ($p<0.001$) in the risk of type 1

Table 1 Characteristics of studies investigating the association between Caesarean section and type 1 diabetes, ordered by publication date

First author, year[a] [reference]	Design	Country	Type 1 diabetes Ascertainment method	Age at diagnosis	n	Controls n	Controls Source (matching criteria)	Ascertainment of Caesarean section	GA	MA	BW	BO	BF	MD
Dahlquist, 1992 [42]	C–C	Sweden	Swedish Childhood Diabetes Registry	0–14 years	2,757	8,271	Swedish Medical Birth Registry (year of birth, delivery unit)	Maternity record	✓					
Patterson, 1994 [24]	C–C	Scotland	Hospital admission / childhood diabetes register	0–14 years	271	1,355	Scottish maternal discharge records (age, sex and area)	Maternity record	✓	✓	✓			✓
McKinney, 1997 [25]	C–C	England	Yorkshire Childhood Diabetes Register	0–15 years	220	433	General practitioner's records (age and sex)	Questionnaire	✓	✓	✓			✓
Tai, 1998 [34]	C–C	China	Taipei type 1 Diabetes Registry	0–29 years (mean = 8 years)	117	193	Classmates or colleagues[c] (age, sex, parental and individual education)	Questionnaire						
Rami, 1999 [27]	C–C	Austria	Vienna type 1 diabetes register	0–14 years	114	495	Schools (age and sex)	Maternity record	✓	✓	✓	✓	✓	✓[d]
Bache, 1999 [36]	C–C	Denmark	Hospital admission	0–14 years	839	1,687	Medical birth register (age, sex and district)	Maternity record	✓	✓	✓			
	C–C	Bulgaria	West Bulgaria type 1 diabetes register	0–14 years	176	562	Schools and policlinics (age)	Maternity record	✓	✓	✓	✓	✓	✓[d]
	C–C	Latvia	Latvian type 1 diabetes register	0–14 years	143	410	Population register (age)	Maternity record	✓	✓	✓	✓	✓	✓[d]
EURODIAB, 1999 [15]	C–C	Lithuania	Lithuanian type 1 diabetes register	0–14 years	124	369	Policlinics (age)	Maternity record	✓	✓	✓	✓	✓	✓[d]
	C–C	Luxembourg	Luxembourg type 1 diabetes register	0–14 years	59	188	Pre-schools and schools (age)	Maternity record	✓	✓	✓	✓	✓	✓[d]
	C–C	Romania	Bucharest type 1 diabetes register	0–14 years	111	342	Pre-schools and schools (age)	Maternity record	✓	✓	✓	✓	✓	✓[d]
Visalli, 2003 [43]	C–C	Italy	Lazio type 1 diabetes register	0–14 years	150	750	Schools (age)	Questionnaire	✓	✓	✓	✓	✓	✓
Stene, 2003 [17]	Cohort	Norway	Norwegian Childhood Diabetes Registry	0–14 years	1,824	1,380,778	Norwegian medical birth registry	Maternity record	✓	✓	✓	✓	✓	✓
Stene, 2004 [30]	C–C	Norway	Norwegian Childhood Diabetes Registry	0–14 years	545	1,668	Norwegian population registry	Maternity record	✓	✓	✓	✓	✓	✓[d]
Cardwell, 2005 [32]	Cohort	Northern Ireland	Northern Ireland type 1 diabetes register	0–14 years	991	447,633	Northern Ireland Child Health Register	Maternity record	✓	✓	✓	✓	✓	✓
Šipetić, 2005 [38]	C–C	Serbia	Belgrade Hospital admission	0–16 years	105	210	Hospital outpatients with skin disease[c] (age, sex and area)	Questionnaire	✓	✓	✓	✓	✓	✓[d]

Svensson, 2005 [37]	C–C	Denmark	Danish register of childhood diabetes	490	Danish population register (age and sex)	696	Questionnaire	✓	✓	✓	✓	✓		✓
Malcova, 2006 [39]	C–C	Czech Republic	Czech Childhood Diabetes Register	868	School friends[c]	1,466	Questionnaire	✓	✓	✓	✓	✓		✓
Tenconi, 2007 [40]	C–C	Italy	Pavia type 1 Diabetes Registry	159	Hospital patients[c] (age and sex)	318	Questionnaire		✓	✓	✓	✓	✓	
Ievins, 2007 [18]	Cohort	England	Hospital admission (ICD code for diabetes)	411	Oxfordshire and West Berkshire maternity records	292,845	Maternity record	✓	✓	✓	✓	✓		✓

[a] Year of publication

[b] Tick denotes data recorded in study and available for analysis

[c] Not randomly selected or not population-based

[d] Maternal type 1 diabetes used in analyses

BF, Breast-feeding; BO, birth order; BW, birthweight; C–C, case–control; GA, gestational age; MA, maternal age; MD, maternal diabetes
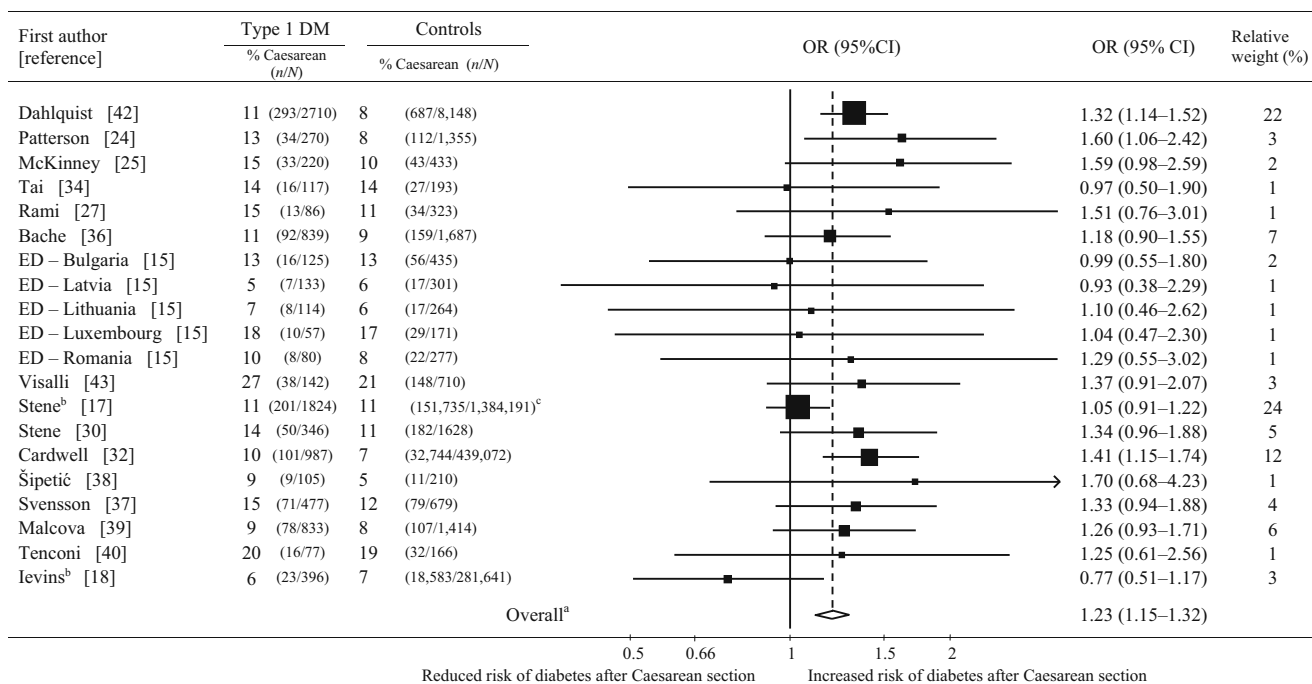
First author [reference]	Type 1 DM % Caesarean (n/N)	Controls % Caesarean (n/N)	OR (95%CI)	OR (95% CI)	Relative weight (%)
Dahlquist [42]	11 (293/2710)	8 (687/8,148)		1.32 (1.14–1.52)	22
Patterson [24]	13 (34/270)	8 (112/1,355)		1.60 (1.06–2.42)	3
McKinney [25]	15 (33/220)	10 (43/433)		1.59 (0.98–2.59)	2
Tai [34]	14 (16/117)	14 (27/193)		0.97 (0.50–1.90)	1
Rami [27]	15 (13/86)	11 (34/323)		1.51 (0.76–3.01)	1
Bache [36]	11 (92/839)	9 (159/1,687)		1.18 (0.90–1.55)	7
ED – Bulgaria [15]	13 (16/125)	13 (56/435)		0.99 (0.55–1.80)	2
ED – Latvia [15]	5 (7/133)	6 (17/301)		0.93 (0.38–2.29)	1
ED – Lithuania [15]	7 (8/114)	6 (17/264)		1.10 (0.46–2.62)	1
ED – Luxembourg [15]	18 (10/57)	17 (29/171)		1.04 (0.47–2.30)	1
ED – Romania [15]	10 (8/80)	8 (22/277)		1.29 (0.55–3.02)	1
Visalli [43]	27 (38/142)	21 (148/710)		1.37 (0.91–2.07)	3
Stene[b] [17]	11 (201/1824)	11 (151,735/1,384,191)[c]		1.05 (0.91–1.22)	24
Stene [30]	14 (50/346)	11 (182/1628)		1.34 (0.96–1.88)	5
Cardwell [32]	10 (101/987)	7 (32,744/439,072)		1.41 (1.15–1.74)	12
Šipetić [38]	9 (9/105)	5 (11/210)		1.70 (0.68–4.23)	1
Svensson [37]	15 (71/477)	12 (79/679)		1.33 (0.94–1.88)	4
Malcova [39]	9 (78/833)	8 (107/1,414)		1.26 (0.93–1.71)	6
Tenconi [40]	20 (16/77)	19 (32/166)		1.25 (0.61–2.56)	1
Ievins[b] [18]	6 (23/396)	7 (18,583/281,641)		0.77 (0.51–1.17)	3
Overall[a]				1.23 (1.15–1.32)	

0.5   0.66   1   1.5   2
Reduced risk of diabetes after Caesarean section   Increased risk of diabetes after Caesarean section

Fig. 1 Meta-analysis of studies of Caesarean section and type 1 diabetes (including 9,938 cases) using the random effects model, studies ordered by publication date. Reference numbers are provided in Table 1. [a]Test for heterogeneity χ^2=17.70, df 19, p=0.54; I^2=0% (95% CI 0–48%); test for overall effect Z=5.70, p≤0.001; [b]adjusted for year of birth and age group, as explained in Statistical analysis; [c]approximated from person years. DM, diabetes mellitus; ED, EURODIAB

diabetes after Caesarean section delivery, with an OR of 1.23 (95% CI 1.15–1.32). There was little evidence of heterogeneity between the study estimates (I^2=0%, 95% CI 0–48%; χ^2=17.70, df 19, p=0.54). A funnel plot, shown in Fig. 2, roughly conformed to the expected funnel shape, providing little evidence of asymmetry and therefore little evidence of publication bias. Similarly, the Trim and Fill method, which attempts to adjust for any publication bias by imputing possible unpublished studies, produced estimates that were unaltered (OR 1.23), suggesting that any effect of publication bias was negligible. Further analysis in the subgroup of 16 studies judged to have used randomly

Fig. 2 Funnel plot of studies of Caesarean section and type 1 diabetes, labelled by reference number

selected population-based controls produced a similar pooled estimate (OR 1.24, 95% CI 1.13–1.35).

Adjustment for potential confounders was possible in 17 studies. Fifteen authors provided raw data, and two calculated adjusted estimates. Raw data from two studies were not available [36, 42] and one author could not be contacted [34].

Table 2 summarises the crude association between childhood-onset type 1 diabetes and potential confounders. Overall, there was an increase in the risk of diabetes with increasing birthweight (combined OR per category increase 1.05, p=0.006) and little heterogeneity between studies (I^2= 25, p=0.17). There was evidence (p=0.02) of a reduction in risk of diabetes with longer gestation. The pooled risk of diabetes in children born later than 42 weeks was 0.84 times that of children born 38–41 weeks, and was similar across studies (I^2=10, p=0.34). There was evidence of an increase in diabetes risk with maternal age (combined OR per category increase 1.08, p=0.001) but there was considerable heterogeneity between studies (I^2=50, p=0.01). Overall, there was some evidence that children second born (OR 1.12, p=0.03) or third or later born (OR 1.08, p=0.17) had a slightly higher risk of type 1 diabetes than first born children, but these associations were also subject to considerable heterogeneity (I^2=45, p=0.03 and I^2=25, p=0.17, respectively). Children whose mother had diabetes (OR 4.92, p<0.001) or, specifically, type 1 diabetes (OR 4.03, p=0.001) had a higher risk of type 1 diabetes, and these associations
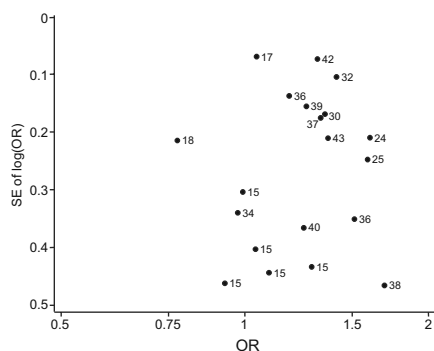
were fairly consistent across studies (I^2=0, p=0.49 and I^2=0, p=0.88, respectively). Finally, there was some indication that children who were breastfed, or breastfed for a longer duration, had a slightly lower risk of diabetes than children who were not breastfed, or breastfed for a shorter duration, (OR 0.84, p=0.02). This association was subject to marked heterogeneity (I^2=61, p=0.001)—perhaps due in part to the different categorisations used in each study—and should therefore be carefully interpreted.

Table 3 shows the association between Caesarean section and type 1 diabetes after adjustment for confounders. The crude association between Caesarean section delivery and type 1 diabetes was little altered after adjustment for birthweight (OR 1.24, p<0.001), gestational age (OR 1.19,

p<0.001), maternal age (OR 1.19, p<0.001), birth order (OR 1.21, p<0.001), maternal diabetes (OR 1.17, p=0.003), breast-feeding (OR 1.26, p<0.001) or all of these confounders (OR 1.19, p=0.01).

Discussion

This meta-analysis demonstrates a consistent increase, of around 20%, in the risk of type 1 diabetes in children delivered by Caesarean section. This observed increase in diabetes risk after Caesarean section delivery could not be explained by the confounding influence of birthweight, gestational age, maternal age, birth order, maternal diabetes or breastfeeding.

Table 2 Pooled analysis of the association between potential confounders and type 1 diabetes

Potential confounder	Number of studies	Heterogeneity			Combined OR (95% CI)	p value
		χ^2	p value	I^2 (95%CI)		
Birthweight (g)	16					
<2,500		21.05	0.14	29 (0–61)	0.87 (0.71–1.07)	0.18
2,500–2,999		11.15	0.74	0 (0–52)	0.93 (0.86–1.02)	0.14
3,000–3,499					1.00 (Ref. cat.)	–
3,500–3,999		10.77	0.77	0 (0–52)	1.03 (0.97–1.10)	0.33
≥4,000		11.24	0.74	0 (0–52)	1.12 (1.02–1.21)	0.01
Trend across categories		20.10	0.17	25 (0–59)	1.05 (1.02–1.09)	0.006
Gestational age (weeks)	16					
≤37		8.56	0.86	0 (0–54)	1.01 (0.91–1.11)	0.87
38–41					1.00 (Ref. cat.)	–
≥42		16.67	0.34	10 (0–47)	0.84 (0.73–0.97)	0.02
Maternal age (years)	17					
<20		29.54	0.02	46 (4–69)	0.84 (0.68–1.04)	0.10
20–24		19.11	0.26	16 (0–52)	0.90 (0.83–0.98)	0.01
25–29					1.00 (Ref. cat.)	–
30–34		17.94	0.32	11 (0–48)	1.03 (0.95–1.13)	0.47
≥35		14.01	0.59	0 (0–51)	1.11 (1.01–1.23)	0.04
Trend across categories		32.22	0.01	50 (13–72)	1.08 (1.03–1.13)	0.001
Birth order	16					
First born					1.00 (Ref. cat.)	–
Second born		27.29	0.03	45 (1–69)	1.12 (1.02–1.24)	0.03
Third or later born		20.05	0.17	25 (0–59)	1.08 (0.97–1.19)	0.17
Maternal diabetes[a]						
No	8				1.00 (Ref. cat.)	–
Yes		6.42	0.49	0 (0–68)	4.92 (3.93–6.16)	<0.001
Maternal type 1 diabetes[a]						
No	8				1.00 (Ref. cat.)	–
Yes		3.05	0.88	0 (0–68)	4.03 (1.76–9.20)	0.001
Breast-feeding[b]						
No or short period	15				1.00 (Ref. cat.)	–
Yes or long period		36.25	0.001	61 (32–78)	0.84 (0.72–0.98)	0.02

[a] Studies recording maternal diabetes and maternal type 1 diabetes are shown in Table 1
[b] Breast-feeding was categorised as breast-feeding at discharge from hospital [18, 32], any breast-feeding [15, 25, 27], breast-feeding for approximately 3 months or more [30, 40, 43] and breast-feeding for approximately 4 months or more [37–39]
Ref. cat., reference category

The main finding was observed consistently across studies, conferring a level of robustness to this result. Importantly, using individual patient data, or adjusted estimates, we were able to demonstrate that the increased risk of diabetes after Caesarean section delivery could not be explained by known confounding factors. However, as this meta-analysis was based upon observational studies, it is impossible to rule out the influence of unrecorded confounders, although any such confounder would have to operate similarly across all studies. Social class is a possibility, as it may be associated with the likelihood of delivery by Caesarean section, but as the association between social class and type 1 diabetes is inconsistent [24, 44–46] it seems unlikely that it could exert the necessary confounding influence. Gestational diabetes is another possibility, but the proportion of mothers with gestational diabetes in these European populations is likely to be small [47], reducing the likelihood of marked confounding, and adjustment for gestational diabetes in seven of the studies [15, 25, 27] revealed little evidence of confounding. A further weakness of this study was that the reason for Caesarean section could not be investigated, as this was not available in the majority of studies, and therefore we were unable to confirm a report suggesting that any increased risk of type 1 diabetes after Caesarean section was most marked after elective procedures [24].

The explanation for the observed increase in the risk of type 1 diabetes in children born by Caesarean section is unknown, but various theories are plausible. The gut microbiota are thought to play an important role in stimulating the development of the immune system [48]. Recent studies have shown that the gut microbiotic composition differ in children born by Caesarean section compared with vaginally born children [8–11], perhaps because such children are first exposed postpartum to bacteria originating from the hospital environment rather than to maternal bacteria [11]. This difference in gut microbiotic composition could increase the risk of type 1 diabetes. Similarly, the hygiene hypothesis suggests that children with reduced or delayed exposure to infection in early life may have an increased risk of type 1 diabetes [49]. According to this hypothesis, as children born by Caesarean section may have a reduced exposure to infections compared with children born vaginally, this could increase their diabetes risk. Alternatively, a previous study [42] speculated that any increased risk of diabetes after Caesarean section could be caused by non-specific perinatal stress.

Our study also allowed the documentation of pooled estimates of the crude risk associated with various perinatal factors. Although not the result of a systematic review of the literature for each perinatal factor, there is no obvious reason why this selection of studies would not be representative. To our knowledge, this is the largest selection of studies that have been combined to investigate associations with birthweight, gestational age, maternal age, birth order and maternal diabetes. These analyses indicated that children who are heavier at birth, have a shorter gestation and whose mother has diabetes have a greater risk of type 1 diabetes. Although there was also evidence of an increased risk of type 1 diabetes with greater maternal age and later birth order, these associations varied considerably between studies and should be interpreted more cautiously. The findings for breast-feeding, of a slight reduction in type 1 diabetes risk, although broadly similar to that observed in two previous meta-analyses [50, 51], were subject to considerable heterogeneity, perhaps reflecting differences in the recording of breast-feeding in the individual studies.

Table 3 Pooled analysis of the association between Caesarean section and type 1 diabetes after adjustment for various potential confounders

Adjusted potential confounder(s)[a]	No. of studies	No. of cases	Heterogeneity			Adjusted combined OR (95% CI)	p value
			χ^2	p value	I^2 (95%CI)		
None	20	9,938	17.70	0.54	0 (0–48)	1.23 (1.15–1.32)	<0.001
Birthweight	16	6,138	13.55	0.56	0 (0–52)	1.24 (1.13–1.35)	<0.001
Gestational age	16	6,005	14.10	0.52	0 (0–52)	1.19 (1.09–1.31)	<0.001
Maternal age	17	6,246	16.04	0.45	0 (0–51)	1.19 (1.09–1.30)	<0.001
Birth order	16	6,029	16.19	0.37	7 (0–43)	1.21 (1.10–1.34)	<0.001
Maternal diabetes	16	6,150	16.79	0.33	11 (0–48)	1.17 (1.05–1.29)	0.003
Breastfeeding	15	3,874	9.00	0.83	0 (0–54)	1.26 (1.12–1.42)	<0.001
Birthweight, gestational age, maternal age and birth order	15	5,791	11.30	0.66	0 (0–54)	1.17 (1.06–1.28)	0.001
Birthweight, gestational age, maternal age, birth order and breastfeeding	13	3,444	7.86	0.80	0 (0–57)	1.21 (1.06–1.38)	0.005
Birthweight, gestational age, maternal age, birth order, breastfeeding and maternal diabetes	13	3,424	9.16	0.69	0 (0–57)	1.19 (1.04–1.36)	0.01

[a] Adjustments were made for potential confounders using broadly the categories shown in Table 2

In conclusion, our study detected a small but significant and consistent increase in the risk of type 1 diabetes after Caesarean section, which could reflect differences in exposure to bacteria in early life.

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