Original Investigation

Planned Cesarean Delivery at Term and Adverse Outcomes in Childhood Health

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IMPORTANCE Planned cesarean delivery comprises a significant proportion of births globally, with combined rates of planned and unscheduled cesarean delivery in a number of regions approaching 50%. Observational studies have shown that offspring born by cesarean delivery are at increased risk of ill health in childhood, but these studies have been unable to adjust for some key confounding variables. Additionally, risk of death beyond the neonatal period has not yet been reported for offspring born by planned cesarean delivery.

OBJECTIVE To investigate the relationship between planned cesarean delivery and offspring health problems or death in childhood.

DESIGN, SETTING, AND PARTICIPANTS Population-based data-linkage study of 321 287 term singleton first-born offspring born in Scotland, United Kingdom, between 1993 and 2007, with follow-up until February 2015.

EXPOSURES Offspring born by planned cesarean delivery in a first pregnancy were compared with offspring born by unscheduled cesarean delivery and with offspring delivered vaginally.

MAIN OUTCOMES AND MEASURES The primary outcome was asthma requiring hospital admission; secondary outcomes were salbutamol inhaler prescription at age 5 years, obesity at age 5 years, inflammatory bowel disease, type 1 diabetes, cancer, and death.

RESULTS Compared with offspring born by unscheduled cesarean delivery (n = 56 015 [17.4%]), those born by planned cesarean delivery (12 355 [3.8%]) were at no significantly different risk of asthma requiring hospital admission, salbutamol inhaler prescription at age 5 years, obesity at age 5 years, inflammatory bowel disease, cancer, or death but were at increased risk of type 1 diabetes (0.66% vs 0.44%; difference, 0.22% [95% CI, 0.13%-0.31%]; adjusted hazard ratio [HR], 1.35 [95% CI, 1.05-1.75]). In comparison with children born vaginally (n = 252 917 [78.7%]), offspring born by planned cesarean delivery were at increased risk of asthma requiring hospital admission (3.73% vs 3.41%; difference, 0.32% [95% CI, 0.21%-0.42%]; adjusted HR, 1.22 [95% CI, 1.11-1.34]), salbutamol inhaler prescription at age 5 years (10.34% vs 9.62%; difference, 0.72% [95% CI, 0.36%-1.07%]; adjusted HR, 1.13 [95% CI, 1.01-1.26]), and death (0.40% vs 0.32%; difference, 0.08% [95% CI, 0.02%-1.00%]; adjusted HR, 1.41 [95% CI, 1.05-1.90]), whereas there were no significant differences in risk of obesity at age 5 years, inflammatory bowel disease, type 1 diabetes, or cancer.

CONCLUSIONS AND RELEVANCE Among offspring of women with first births in Scotland between 1993 and 2007, planned cesarean delivery compared with vaginal delivery (but not compared with unscheduled cesarean delivery) was associated with a small absolute increased risk of asthma requiring hospital admission, salbutamol inhaler prescription at age 5 years, and all-cause death by age 21 years. Further investigation is needed to understand whether the observed associations are causal.

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Rates of cesarean delivery in the United Kingdom and Brazil were 26% and 52%, respectively, between 2005 and 2011.[1] Such high rates demand an understanding of the longer-term consequences. Cesarean delivery offers safety advantages in obstructed labor and breech presentation and in the presence of a cesarean scar, but the World Health Organization (WHO) reports that 10% of births involve prelabor cesarean delivery without medical indication.[2,3] Although nonmedically indicated cesarean delivery could potentially offer safety advantages, such as reduced risk of offspring cerebral palsy attributable to birth-related hypoxia, recent evidence does not support this.[4]

A favorable safety profile, with low maternal mortality of 0.001%, has facilitated societal acceptance of cesarean delivery.[5] In the United Kingdom, women and health professionals are encouraged to consider short- and medium-term consequences of cesarean delivery during preoperative discussions, including the likelihood of postsurgical wound infection (9%-10%) and future placental problems.[2] Discussion of short-term offspring risks, including respiratory compromise, is advised, but consequences beyond the neonatal period are not routinely considered.

Planned cesarean delivery means offspring circumvent the normal labor-induced activation of the hypothalamic-pituitary-adrenal axis, and lack of exposure to maternal bowel flora, in addition to perioperative antibiotic use, alters neonatal microbiome development.[6,7] Experimental data have linked avoidance of labor to altered offspring stress response, immune function, and epigenetic changes.[8-11] This may explain why asthma-related illness, obesity, and type 1 diabetes are more common following cesarean delivery.[12-15] There is a recognized need for robust assessment of the relationship between cesarean delivery and offspring health, because previous studies have been unable to adjust for key confounders or to separate planned from unscheduled (emergency or intrapartum) cesarean delivery.[2,13-15]

Our aim was to explore the association between planned cesarean delivery and chronic illness and death in offspring using a national birth cohort.

Methods

Study approvals were obtained from the Privacy Advisory Committee of Information Services Division Scotland, the Caldicott Guardians for NHS Scotland Health Boards and the North of Scotland Research Ethics Committee. The latter approved use of anonymized data without specific consent from study participants.

Study Population

This retrospective cohort study identified all term (≥37 completed weeks of gestation) singleton live births in first-time mothers between January 1, 1993, and December 31, 2007, in Scotland, United Kingdom. Offspring were followed up until January 2015. Offspring with missing or implausible data on date and mode of delivery, gestation, birth weight, or sex (less than 0.1% of cases for each variable) were excluded.

Databases

The study population was identified from the Scottish Morbidity Record (SMR02) database, which contains social demographic and clinical data on all deliveries in women discharged from Scottish maternity hospitals since 1980. SMR02 quality assurance assessment demonstrates accuracy of 98% for offspring sex, date of delivery, and birth weight; 90% to 94% for smoking status, estimated gestation, and pregnancy number; and 97% for cesarean delivery as mode of birth.[16] Using SMR02 as the base population, 6 further national databases were record-linked to the SMR02 by Information Services Division Scotland:

- SMR01: Records the main condition diagnosed at discharge from all acute admissions to Scottish hospitals, with validity checks suggesting 87% accuracy.[17] This provided diagnoses of asthma and inflammatory bowel disease.
- Prescribing Information System: Contains all filled prescriptions issued in the community from NHS Scotland starting in 2009.[18] Data were extracted on prescriptions for offspring salbutamol inhalers during the period 2009-2013.
- Scottish Care Information Diabetes Collaboration: Records all registered diagnoses of diabetes in NHS Scotland, with validity checks suggesting 98% accuracy.[19] Offspring type 1 diabetes diagnoses were extracted.
- Child Health Surveillance System: Includes body mass index (BMI) centile (adjusted for age) based on height and weight measured routinely in the first year of compulsory UK full-time education, when pupils' ages range from 4.5 to 6.25 years. Valid BMI records from 2009-2012 were obtained, providing childhood obesity (BMI greater than the 95th centile) data.[20]
- National Register for Scotland: A mandatory data set compiled from all birth and death certificates in Scotland. Details of offspring death were extracted.
- Scottish Cancer Registry: Records details of every primary diagnosis of cancer (including neonatal cancers) in Scotland using sources including hospital administrative data systems, screening data sets, death records and community prescribing records.[21] Data quality checks demonstrate 64% to 100% completeness.

Exposure Status

Births were defined as "planned cesarean delivery" if cesarean delivery was recorded in the SMR02 as "scheduled," whereas all remaining cesarean deliveries recorded in the SMR02 were considered "unscheduled." A cesarean delivery is defined by the Information Services Division as scheduled when performed during the day, with both staff and patient fully prepared.[22]

Covariates

The following covariates were obtained from the SMR02: maternal age at delivery in years, maternal BMI in pregnancy (calculated as weight in kilograms divided by height in meters squared); gestation at delivery (weeks); Carstairs decile (ordinal measure from 1 [most affluent] to 10 [most deprived] derived from 1981 and 2001 census data on social class, car ownership, male unemployment, and overcrowding)[23]; maternal smoking status during pregnancy; year of delivery; offspring sex; and birth weight (g). Further data were obtained on maternal salbutamol inhaler prescription from the Prescribing Information

System, maternal type 1 diabetes diagnoses from the Scottish Care Information Diabetes Collaboration, and breastfeeding status at age 6 weeks from the Child Health Surveillance System.

Comparisons

The risk of chronic childhood illness or death following planned cesarean delivery among term first-born singleton infants was compared with risk among offspring born by unscheduled cesarean delivery, who are likely to have been exposed to labor for varying periods of time, and with risk among offspring delivered vaginally.

Outcomes

Primary Outcome

Risk of asthma requiring hospital admission was assessed using the full 1993-2007 cohort.

Secondary Outcomes

The following outcomes were analyzed using the full cohort, providing up to 21 years of follow-up: inflammatory bowel disease, type 1 diabetes, cancer, and death. Additional analyses assessed risk of death up to, and beyond, age 1 year to allow assessment of potential confounding by indication for cesarean delivery. A 2004-2007 birth cohort was used to assess risk of obesity at age 5 years, in which 80% of births (those with complete outcome data) were included. Salbutamol inhaler prescription at age 5 years was assessed using a complete 2004-2007 birth cohort.

The study was designed to provide 95% power to detect a clinically and statistically significant difference of 1% in incidence of asthma requiring hospital admission (population incidence, 3.5%) following planned cesarean delivery, compared with vaginal birth at a significance level of 5%.

Statistical Analysis

Continuous variables were summarized by exposure group using mean and standard deviation for normally distributed data or median and interquartile range for skewed data. Comparisons between the groups were made using *t* test or the Mann-Whitney U test, respectively. The *P* values for all hypothesis tests were 2-sided at a 5% significance level.

To study the associations with planned cesarean delivery over time, hazard ratios (HRs) were calculated for each outcome using Cox proportional hazards models. The time origin was taken as the date of delivery, and the end point was either the end of follow-up (censored) or the event of interest. For outcomes for which time at risk was the same for all offspring, and for consistent estimation purposes, the relevant duration was included in the Cox model. The proportional hazards assumption of the Cox model was tested using plots of the log of the negative log of the survival function against log of time for each comparison group.

Hazard ratios were adjusted for prespecified confounding factors based on expert knowledge and published literature. For all outcomes, the following potential confounding factors were included as covariates: maternal age; maternal Carstairs decile; maternal smoking status; estimated gestation at delivery; offspring birth weight; offspring sex; year of delivery; and breastfeeding status at age 6 weeks. Maternal salbutamol inhaler prescription was included in the models assessing risk of asthma requiring hospital admission and salbutamol inhaler prescription at age 5 years. The model assessing risk of type 1 diabetes was also adjusted for maternal type 1 diabetes. Risk of obesity at age 5 years was additionally adjusted for maternal BMI. Because maternal BMI was only available for a minimum of 50% of cases from 2004 onward, it was not included in the models assessing risk of the other outcomes.

Missing values relating to Carstairs index, smoking status, breastfeeding, and maternal BMI were imputed using multiple imputation. Observed characteristics of women with missing data differed from those with complete data, supporting the missing-at-random assumption (as opposed to missing completely at random) required for multiple imputation (eTables 1-4 in the Supplement).[24] Ten imputed data sets were generated using the Markov Chain Monte Carlo method, because the efficiency of an estimate obtained from 10 imputations relative to one obtained from an infinite number of imputations has been shown to be 95%, even when 50% of data are missing.[25] All available demographic and clinical variables were used to inform the imputation process, as reported in eTables 5-8 in the Supplement. Continuous variables were log transformed to ensure normal distribution, a requirement for multiple imputation. The Cox models were fitted to each imputed data set, and a pooled result was obtained for estimates of effect.

Sensitivity Analyses

To assess the effects of multiple imputation on the main study findings, a sensitivity analysis was performed that involved complete case analyses for each outcome studied.

All statistical analyses were conducted using IBM SPSS version 22 (IBM SPSS).

Results

Of the 323 145 records obtained on liveborn singleton deliveries at or beyond 37 weeks' gestation to primiparous women, 321 287 were eligible for inclusion in the analysis. The process involved in deriving the study cohorts is outlined in the **Figure**. Data were missing on deprivation level (0.3%), maternal smoking (11.0%), breastfeeding (37.5%), and maternal BMI (49.9% in the cohort that used maternal BMI).

Between 1993 and 2007, 12 355 offspring (3.8%) were born by planned cesarean delivery, 56 015 (17.4%) by unscheduled cesarean delivery, and 252 917 (78.7%) by vaginal delivery. The rate of planned cesarean delivery increased across this period from 3.3% to 4.1%. Mean duration of follow-up of the full cohort was 14.8 years (SD, 4.4). Demographic and clinical characteristics of the planned cesarean delivery group and both comparison groups are reported in **Table 1**.

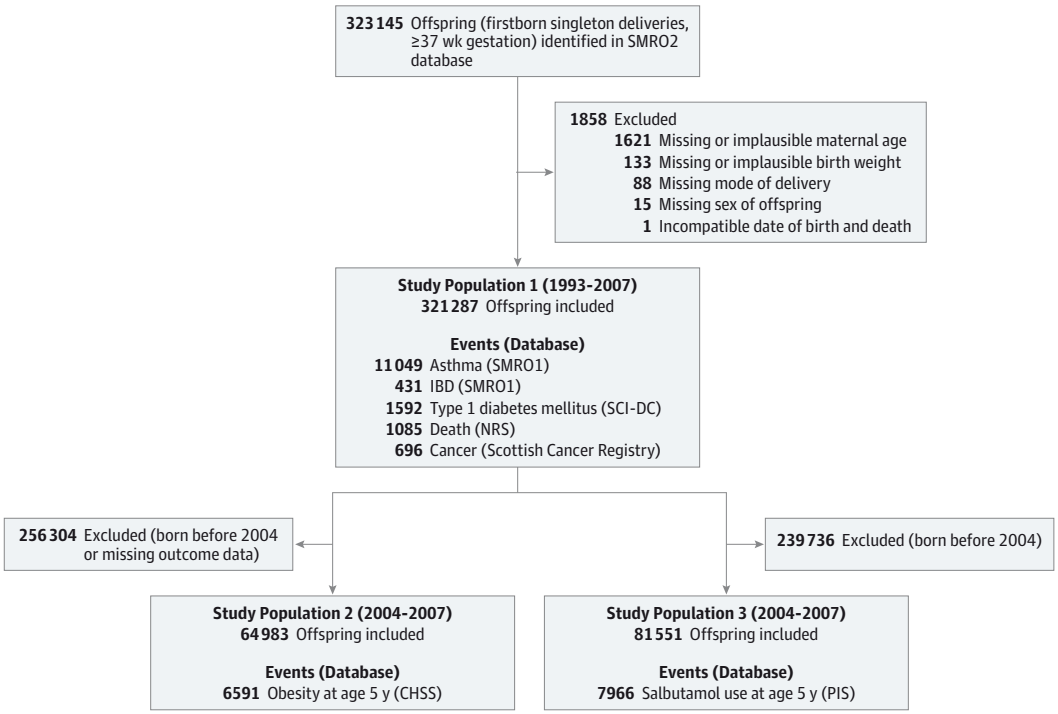
Planned vs Unscheduled Cesarean Delivery

Outcomes of planned cesarean delivery compared with unscheduled cesarean delivery are reported in **Table 2**.

Primary Outcome

There was no significant difference in the risk of asthma requiring hospital admission when comparing offspring born by

Figure. Derivation of Study Cohort



Derivation of study populations for the different outcomes. SMRO2 indicates Scottish Morbidity Record 02; SMRO1, Scottish Morbidity Record 01; PIS, Prescribing Information System; CHSS, Child Health Surveillance System; SCI-DC, Scottish Care Information Diabetes Collaboration; NRS, National Register for Scotland.

Table 1. Characteristics of Planned Cesarean Delivery Group Compared With Unscheduled Cesarean Delivery Group and Vaginal Delivery Group (Full Birth Cohort 1993-2007, Pregnancies Involving Firstborn Singleton Infants)

Characteristic	Cesarean Delivery				
	Planned (n = 12 355)[a]	Unscheduled (n = 56 015)[a]	*P* Value	Vaginal Birth (n = 252 917)[a]	*P* Value
Maternal age, median (IQR), y	29 (25-33)	29 (24-32)	<.001[b]	26 (21-30)	<.001[b]
Maternal BMI, median (IQR)[c]	24.8 (21.9-28.9)	25.8 (23.0-30.1)	<.001[b]	23.9 (21.5-27.3)	<.001[b]
Gestation, mean (SD), wk	38.66 (1.00)	39.99 (1.29)	<.001[d]	39.8 (1.21)	<.001[d]
Carstairs decile, median (IQR)[e]	6 (3-8)	6 (3-8)	<.001[b]	6 (3-8)	<.001[b]
Maternal smoker, No. (%)[f]	2261 (20.5)	10 529 (21.0)	.22[g]	59 058 (26.3)	<.001[g]
Maternal salbutamol prescription, No. (%)	2073 (16.8)	9413 (16.8)	.96[g]	39 757 (15.7)	.002[g]
Maternal type 1 diabetes, No. (%)	177 (1.4)	501 (0.9)	<.001[g]	733 (0.3)	<.001[g]
Birth weight, mean (SD), g	3301 (494.1)	3531.9 (556.3)	<.001[d]	3379.4 (454.6)	<.001[d]
Year of delivery, median (IQR)	2000 (1996-2004)	2001 (1997-2004)	<.001[b]	1999 (1996-2003)	<.001[b]
Male offspring, No. (%)	5963 (48.3)	31 439 (56.1)	<.001[g]	126 991 (50.2)	<.001[g]
Breastfeeding at age 6 wk, No. (%)[h]	3055 (37.8)	13 056 (35.7)	.001[g]	54 006 (34.6)	<.001[g]

Abbreviations: BMI, body mass index; IQR, interquartile range.

[a] Complete sample size unless specified below.

[b] Mann-Whitney U test.

[c] Calculated as weight in kilograms divided by height in meters squared. Complete case data from 2004-2007 cohort: n = 1294 for planned cesarean delivery; n = 6655 for unscheduled cesarean delivery; n = 24 620 for vaginal birth.

[d] From *t* test.

[e] Carstairs decile represents an ordinal measure from 1 (most affluent) to 10 (most deprived), derived from Census data (1981-2001) on social class, car ownership, male unemployment, and overcrowding. Complete case data: n = 12 323 for planned cesarean delivery; n = 55 862 for unscheduled cesarean delivery; n = 252 174 for vaginal birth.

[f] Complete case data: n = 11 041 for planned cesarean delivery; n = 50 125 for unscheduled cesarean delivery; n = 224 898 for vaginal birth.

[g] From χ^2 test.

[h] Complete case data: n = 8091 for planned cesarean delivery; n = 36 557 for unscheduled cesarean delivery; n = 156 014 for vaginal birth.

Table 2. Offspring Health Outcomes in Planned Cesarean Delivery Group Compared With Unscheduled Cesarean Delivery Group

	Cesarean Delivery, No. of Events/No. of Offspring (%)			HR (95% CI)	
Outcomes[a]	Planned	Unscheduled	% Difference (95% CI)	Unadjusted	Adjusted
Asthma	461/12 355 (3.73)	1964/56 015 (3.51)	0.23 (0.13 to 0.32)	1.05 (0.95 to 1.16)	1.00 (0.90 to 1.12)[b,c]
IBD	14/12 355 (0.11)	69/56 015 (0.12)	−0.01 (−0.03 to 0.01)	0.84 (0.48 to 1.50)	1.01 (0.97 to 1.05)[b]
Type 1 diabetes	82/12 355 (0.66)	250/56 015 (0.44)	0.22 (0.13 to 0.31)	1.42 (1.10 to 1.82)	1.35 (1.05 to 1.75)[c,d]
Cancer	29/12 355 (0.23)	124/56 015 (0.22)	0.01 (−0.01 to 0.04)	1.03 (0.69 to 1.54)	1.02 (0.98 to 1.05)[c]
Death	49/12 355 (0.40)	235/56 015 (0.42)	−0.02 (−0.05 to 0.01)	0.93 (0.68 to 1.26)	0.98 (0.96 to 1.00)[c]
Death up to age 1 y	26/12 355 (0.21)	136/56 015 (0.24)	−0.03 (−0.07 to 0.003)	0.87 (0.57 to 1.32)	0.63 (0.51 to 0.79)[c]
Death beyond age 1 y[e]	23/12 329 (0.19)	99/55 879 (0.18)	0.01 (−0.01 to 0.03)	1.01 (0.64 to 1.59)	0.87 (0.59 to 1.28)[c]
Obesity at age 5 y	302/2682 (11.26)	1697/13 415 (12.65)	−1.39 (−1.80 to −0.90)	0.89 (0.79 to 1.01)	0.93 (0.82 to 1.06)[c,f]
Salbutamol at age 5 y	350/3386 (10.34)	1725/16 928 (10.19)	0.15 (0.01 to 0.29)	1.01 (0.90 to 1.14)	1.01 (0.90 to 1.15)[b,c]

Abbreviations: HR, hazard ratio; IBD, inflammatory bowel disease.

[a] Asthma indicates the primary diagnosis made during an admission to hospital; IBD indicates the primary diagnosis made during an admission to hospital; type 1 diabetes indicates a formal diagnosis made prior to registration on a national clinical database; cancer indicates a validated diagnosis (at any age) recorded on a hospital administrative data system, screening data set, death record, or community prescribing record and subsequently recorded on a national cancer registry; death indicates a death recorded through mandatory national reporting system; obesity at age 5 years reflects a body mass index exceeding the 95th centile for age; salbutamol at age 5 years indicates that a prescription for salbutamol inhaler has been issued for the offspring during the calendar year in which they turned 5 years old.

[b] Adjusted for maternal salbutamol prescription.

[c] Adjusted for maternal age, gestation at birth, maternal Carstairs decile, maternal smoking status, birth weight, year of delivery, male infant, and breastfeeding at 6 weeks.

[d] Adjusted for maternal type 1 diabetes mellitus.

[e] Sample size excludes those offspring that died in the first year.

[f] Adjusted for maternal body mass index.

planned cesarean delivery with those born by unscheduled cesarean delivery (3.73% vs 3.51%; difference, 0.23% [95% CI, 0.13% to 0.32%]; adjusted HR, 1.00 [95% CI, 0.90 to 1.12]).

Secondary Outcomes

Offspring born by planned cesarean delivery were more likely to develop type 1 diabetes than those born by unscheduled cesarean delivery, despite adjustment for potential confounders including maternal type 1 diabetes (0.66% vs 0.44%; difference, 0.22% [95% CI, 0.13% to 0.31%]; adjusted HR, 1.35 [95% CI, 1.05 to 1.75]). There was no significant difference in risk of salbutamol inhaler prescription at age 5 years (10.34% vs 10.19%; difference, 0.15% [95% CI, 0.01% to 0.29%]), adjusted HR, 1.01 [95% CI, 0.90 to 1.15]); obesity at age 5 years (11.26% vs 12.65%; difference, −1.39% [95% CI, −1.80% to −0.90%]; adjusted HR, 0.93 [95% CI, 0.82 to 1.06]); inflammatory bowel disease (0.11% vs 0.12%; difference, −0.01% [95% CI, −0.03% to 0.01%]; adjusted HR, 1.01 [95% CI, 0.97 to 1.05]); cancer (0.23% vs 0.22%; difference, 0.01% [95% CI, 0.01% to 0.04%]; adjusted HR, 1.02 [95% CI, 0.98 to 1.05]); or death (0.40% vs 0.42%; difference, −0.02% [95% CI, −0.05% to 0.01%]; adjusted HR, 0.98 [95% CI, 0.96 to 1.00]). Risk of death up to age 1 year was lower following planned cesarean delivery compared with unscheduled cesarean delivery (0.21% vs 0.24%; difference, −0.03% [95% CI, −0.07% to 0.003%]; adjusted HR, 0.63 [95% CI, 0.51 to 0.79]), whereas there was no difference when comparing risk of death beyond age 1 year between these 2 groups (0.19% vs 0.18%; difference, 0.01% [95% CI, −0.01% to 0.03%]; adjusted HR, 0.87 [95% CI, 0.59 to 1.28]).

Planned Cesarean Delivery vs Vaginal Delivery

Table 3 reports the comparison of outcomes between offspring born by planned cesarean delivery and those delivered vaginally.

Primary Outcome

Offspring born by planned cesarean delivery were significantly more likely to have asthma requiring hospital admission (3.73% vs 3.41%; difference, 0.32% [95% CI, 0.21% to 0.42%] adjusted HR, 1.22 [95% CI, 1.11 to 1.34]) compared with those delivered vaginally; this was evident in both univariable and multivariable analyses.

Secondary Outcomes

Salbutamol inhaler prescription at age 5 years (10.34% vs 9.62%; difference, 0.72% [95% CI, 0.42% to 1.01%]; adjusted HR, 1.13 [95% CI, 1.01 to 1.26]), and death before age 21 years (0.40% vs 0.32%; difference, 0.08% [95% CI, 0.02% to 1.00%]; adjusted HR, 1.41 [95% CI, 1.05 to 1.90]) were more likely following planned cesarean delivery compared with vaginal birth, contrary to the univariable analyses, which suggested nonsignificant differences in risk of each outcome. There was no significant difference in risk of inflammatory bowel disease (0.11% vs 0.13%; difference, −0.02% [95% CI, −0.05% to 0.004%]; adjusted HR, 0.86 [95% CI, 0.50 to 1.49]) or cancer (0.23% vs 0.21%; difference, 0.02% [95% CI, −0.01% to 0.05%]; adjusted HR, 1.05 [95% CI, 0.72 to 1.55]) following planned cesarean delivery compared with vaginal birth. Type 1 diabetes (0.66% vs 0.49%; difference, 0.17% [95% CI, 0.09% to 0.24%]; adjusted HR, 1.20 [95% CI, 0.95 to 1.52]) and obesity at age 5 years (11.26% vs 9.39%; difference, 1.87% [95% CI, 1.34% to 2.39%]; adjusted HR, 1.12 [95% CI, 0.99 to 1.26]) appeared more likely following planned cesarean delivery in univariate analysis, but this was not significant after adjustment. Breakdown of risk of death up to and beyond 1 year of life demonstrated no statistically significant differences between planned cesarean delivery and vaginal birth (0.21% vs 0.15%; difference, 0.06% [95% CI, 0.01% to 0.10%]; adjusted HR, 1.43 [95% CI, 0.95 to 2.16]) for death up to age 1 year, and 0.19% vs 0.17%;

Table 3. Offspring Health Outcomes in Planned Cesarean Delivery Group Compared With Vaginal Birth Group

Outcomes[a]	Delivery, No. of Events/No. of Offspring (%)			HR (95% CI)	
	Planned Cesarean	Vaginal	% Difference (95% CI)	Unadjusted	Adjusted
Asthma requiring hospital admission	461/12 355 (3.73)	8624/252 917 (3.41)	0.32 (0.21 to 0.42)	1.12 (1.02 to 1.23)	1.22 (1.11 to 1.34)[b,c]
IBD	14/12 355 (0.11)	348/252 917 (0.13)	−0.02 (−0.05 to 0.004)	0.91 (0.53 to 1.55)	0.86 (0.50 to 1.49)[c]
Type 1 diabetes	82/12 355 (0.66)	1260/252 917 (0.49)	0.17 (0.09 to 0.24)	1.37 (1.09 to 1.71)	1.20 (0.95 to 1.52)[c,d]
Cancer	29/12 355 (0.23)	543/252 917 (0.21)	0.02 (−0.01 to 0.05)	1.13 (0.78 to 1.64)	1.05 (0.72 to 1.55)[c]
Death	49/12 355 (0.40)	801/252 917 (0.32)	0.08 (0.02 to 1.0)	1.23 (0.96 to 1.72)	1.41 (1.05 to 1.90)[c]
Death up to age 1 y	26/12 355 (0.21)	384/252 917 (0.15)	0.06 (0.01 to 0.1)	1.39 (0.93 to 2.06)	1.43 (0.95 to 2.16)[c]
Death beyond age 1 y[e]	23/12 329 (0.19)	417/252 533 (0.17)	0.02 (−0.01 to 0.05)	1.19 (0.78 to 1.8)	1.39 (0.90 to 2.14)[c]
Obesity at age 5 y	302/2682 (11.26)	4592/48 886 (9.39)	1.87 (1.34 to 2.39)	1.20 (1.07 to 1.35)	1.12 (0.99 to 1.26)[c,f]
Salbutamol at age 5 y	350/3386 (10.34)	5891/61 237 (9.62)	0.72 (0.42 to 1.01)	1.08 (0.97 to 1.20_	1.13 (1.01 to 1.26)[b,c]

Abbreviations: HR, hazard ratio; IBD, inflammatory bowel disease.

[a] Asthma indicates the primary diagnosis made during an admission to hospital; IBD indicates the primary diagnosis made during an admission to hospital; type 1 diabetes indicates a formal diagnosis made prior to registration on a national clinical database; cancer indicates a validated diagnosis (at any age) recorded on a hospital administrative data system, screening data set, death record, or community prescribing record and subsequently recorded on a national cancer registry; death indicates a death recorded through mandatory national reporting system; obesity at age 5 years reflects a body mass index exceeding the 95th centile for age; salbutamol at age 5 years indicates that a prescription for salbutamol inhaler has been issued for the offspring during the calendar year in which they turned 5 years old.

[b] Adjusted for maternal salbutamol prescription.

[c] Adjusted for maternal age, gestation at birth, maternal Carstairs decile, maternal smoking status, birth weight, year of delivery, male infant, and breastfeeding at 6 weeks.

[d] Adjusted for maternal type 1 diabetes mellitus.

[e] Sample size excludes those offspring that died in the first year.

[f] Adjusted for maternal body mass index.

Table 4. Complete-Cases Analyses of Offspring Health Outcomes in Planned Cesarean Delivery Group Compared With Unscheduled Cesarean Delivery Group

Outcomes[a]	Cesarean Delivery, No. of Events/No. of Offspring (%)			HR (95%CI)	
	Planned	Unscheduled	% Difference (95% CI)	Unadjusted	Adjusted[b]
Asthma	205/7325 (2.80)	993/32 926 (3.02)	−0.22 (−0.34 to −0.10)	0.91 (0.79 to 1.06)	0.92 (0.78 to 1.08)[c,d]
IBD	8/7325 (0.11)	31/32 926 (0.09)	0.02 (−0.02 to 0.05)	1.07 (0.49 to 2.32)	
Type 1 diabetes	40/7325 (0.54)	136/32 926 (0.41)	0.13 (0.04 to 0.23)	1.25 (0.88 to 1.79)	1.21 (0.82 to 1.78)[d,e]
Cancer	15/7325 (0.20)	63/32 926 (0.19)	0.01 (−0.02 to 0.04)	1.05 (0.60 to 1.84)	
Death	14/7325 (0.19)	57/32 926 (0.17)	0.02 (−0.02 to 0.05)	1.08 (0.60 to 1.93)	
Obesity at age 5 y	122/1015 (12.02)	686/5355 (12.81)	−0.79 (−1.38 to −0.20)	0.94 (0.77 to 1.14)	0.95 (0.78 to 1.17)[d,f]
Salbutamol at age 5 y	242/2303 (10.51)	1195/11 412 (10.47)	0.04 (−0.05 to 0.12)	1.00 (0.87 to 1.15)	1.00 (0.86 to 1.15)[c,d]

Abbreviations: HR, hazard ratio; IBD, inflammatory bowel disease.

[a] Asthma indicates the primary diagnosis made during an admission to hospital; IBD indicates the primary diagnosis made during an admission to hospital; type 1 diabetes indicates a formal diagnosis made prior to registration on a national clinical database; cancer indicates a validated diagnosis (at any age) recorded on a hospital administrative data system, screening data set, death record, or community prescribing record and subsequently recorded on a national cancer registry; death indicates a death recorded through mandatory national reporting system; obesity at age 5 years reflects a body mass index exceeding the 95th centile for age; salbutamol at age 5 years indicates that a prescription for salbutamol inhaler has been issued for the offspring during the calendar year in which they turned 5 years old.

[b] Blank cells indicate that no multivariable model was conducted, because risk of overfitting was high owing to low number of outcome events.

[c] Adjusted for maternal salbutamol prescription.

[d] Adjusted for maternal age, gestation at birth, maternal Carstairs decile, maternal smoking status, birth weight, year of delivery, male infant, and breastfeeding at 6 weeks.

[e] Adjusted for maternal type 1 diabetes mellitus.

[f] Adjusted for maternal body mass index.

difference, 0.02% [95% CI, −0.01% to 0.05%]; adjusted HR, 1.39 [95% CI, 0.90 to 2.14] for death beyond age 1 year).

Sensitivity Analyses

Complete case analyses comparing outcomes following planned cesarean delivery with unscheduled cesarean delivery demonstrated no significant differences in risk of any outcomes studied, as reported in **Table 4.** Complete-cases analysis revealed a significantly increased risk of offspring obesity at age 5 years following planned cesarean delivery compared with vaginal birth, but no significant differences in risk of salbutamol inhaler prescription at age 5 years, asthma requiring hospital admission, inflammatory bowel disease, cancer, or death up to age 21 years. These results are reported in **Table 5.**

Discussion

Summary of Main Findings

In this national cohort of 321 287 offspring, planned cesarean delivery in a first pregnancy was associated with a small increase in risk of offspring asthma and death in childhood when

Table 5. Complete-Cases Analyses of Offspring Health Outcomes in Planned Cesarean Delivery Group Compared With Vaginal Birth Group

	Delivery, No. of Events/No. of Offspring (%)			HR (95% CI)	
Outcomes[a]	Planned Cesarean	Vaginal	% Difference (95% CI)	Unadjusted	Adjusted
Asthma	205/7325 (2.80)	4155/141 169 (2.94)	−0.14 (−0.23 to −0.06)	0.96 (0.83 to 1.11)	1.05 (0.91 to 1.22)[b,c]
IBD	8/7325 (0.11)	130/141 169 (0.09)	0.02 (−0.01 to 0.05)	1.27 (0.62 to 2.58)	1.30 (0.62 to 2.73)[c]
Type 1 diabetes	40/7325 (0.54)	654/141 169 (0.46)	0.08 (0.02 to 0.15)	1.18 (0.86 to 1.63)	1.07 (0.77 to 1.50)[c,d]
Cancer	15/7325 (0.20)	262/141 169 (0.2)	0.03 (−0.01 to 0.07)	1.12 (0.67 to 1.88)	1.05 (0.62 to 1.81)[c]
Death	14/7325 (0.19)	230/141 169 (0.16)	0.03 (−0.01 to 0.07)	1.19 (0.70 to 2.05)	1.32 (0.76 to 2.31)[c]
Obesity at age 5 y	122/1015 (12.02)	1759/19 718 (8.92)	3.10 (2.01 to 4.19)	1.35 (1.12 to 1.62)	1.22 (1.01 to 1.48)[c,e]
Salbutamol at age 5 y	242/2303 (10.51)	4093/41 806 (9.79)	0.72 (0.36 to 1.07)	1.07 (0.94 to 1.22)	1.11 (0.97 to 1.27)[b,c]

Abbreviations: HR, hazard ratio; IBD, inflammatory bowel disease.

[a] Asthma indicates the primary diagnosis made during an admission to hospital; IBD indicates the primary diagnosis made during an admission to hospital; type 1 diabetes indicates a formal diagnosis made prior to registration on a national clinical database; cancer indicates a validated diagnosis (at any age) recorded on a hospital administrative data system, screening data set, death record, or community prescribing record and subsequently recorded on a national cancer registry; death indicates a death recorded through mandatory national reporting system; obesity at age 5 years reflects a body mass index exceeding the 95th centile for age; salbutamol at age 5 years indicates that a prescription for salbutamol inhaler has been issued for the offspring during the calendar year in which they turned 5 years old.

[b] Adjusted for maternal salbutamol prescription.

[c] Adjusted for maternal age, gestation at birth, maternal Carstairs decile, maternal smoking status, birth weight, year of delivery, male infant, and breastfeeding at 6 weeks.

[d] Adjusted for maternal type 1 diabetes mellitus.

[e] Adjusted for maternal body mass index.

compared with vaginal birth but not when compared with unscheduled cesarean delivery. Offspring born by planned cesarean delivery were at a small but significantly increased risk of type 1 diabetes compared with those born by unscheduled cesarean delivery. No significant difference in risk of obesity at age 5 years, inflammatory bowel disease, or cancer was demonstrated following planned cesarean delivery compared with either unscheduled cesarean delivery or vaginal birth.

Interpretation

The increased risk of offspring asthma following planned cesarean delivery when compared with vaginal birth, but not with unscheduled cesarean delivery, suggests that vaginal birth rather than exposure to labor may offer some protection from asthma. An increased adjusted risk of both salbutamol inhaler prescription and asthma requiring hospital admission adds weight to the hypothesis that avoidance of exposure to maternal bowel flora may affect development of T-cell–mediated asthma.[26] Similar mechanisms have previously been hypothesized to explain increased incidence of type 1 diabetes, inflammatory bowel disease, and cancer following cesarean delivery.[15,27,28] Such associations were not demonstrated when compared with vaginal birth in this study, suggesting that, if causal, such an effect may have been too small to be detected in this cohort.

The increased risk of type 1 diabetes following planned vs unscheduled cesarean delivery was unexpected. There is a lack of evidence that circumstances specific to unscheduled cesarean delivery would be protective against type 1 diabetes; moreover, reports suggest that perinatal stress, commonly present prior to unscheduled cesarean delivery, may increase risk of offspring type 1 diabetes.[29] In the absence of a clinical explanation, the borderline statistical significance of the findings support that these may be attributable to type I error.

The increased risk of offspring death following planned cesarean delivery compared with vaginal birth (absolute risk, 0.7% vs 0.4%) is in keeping with previous reports on neonatal mortality.[30] Death of an infant born by planned cesarean delivery may reflect the increase in asthma-related illness or the avoidance of the physiological stress of labor, because cortisol-mediated organ maturation may facilitate response to future illness. However, the association with offspring death may be confounded by suspected fetal compromise leading to cesarean delivery. Because such deaths are likely to occur in the first year of life, our analysis of risk of death up to age 1 year allowed exploration of this possibility. No increased risk of death was identified up to age 1 year, which, although potentially attributable to the small number of events, does not support that our results are confounded by indication. Therefore, mode of birth as a risk factor for offspring death cannot be ruled out.

Findings in Context of Existing Literature

The 22% increased risk of asthma identified following planned cesarean delivery compared with vaginal birth (3.8% vs 3.5%, respectively) is consistent with the magnitude of effect reported by others. However, previous retrospective studies have had limited confounder data, eg, on breastfeeding and maternal smoking, and prospective studies have lacked precision because of small sample size or have not differentiated between planned and unscheduled cesarean deliveries.[12,31-33]

To our knowledge, an increased risk of type 1 diabetes in offspring born by planned cesarean delivery compared with unscheduled cesarean delivery has not been reported. The lack of association between planned cesarean delivery and type 1 diabetes when compared with vaginal birth is consistent with findings of a large retrospective sibling analysis[34] but conflicts with previous studies, which were limited by risk of bias by study design or confounding by factors including breastfeeding.[15]

The lack of association between planned cesarean delivery and offspring obesity is in keeping with published studies that have separated planned from unscheduled cesarean delivery.[35] This likely reflects that data sets that discriminate between cesarean delivery types contain more extensive confounder data, allowing adjustment for these confounders.

In contrast to our results, a previous cohort study demonstrated an increased risk of inflammatory bowel disease following cesarean delivery,[36] whereas meta-analyses of unadjusted associations have each concluded that there is no increased risk; therefore, the literature remains conflicting.[27]

Our findings demonstrate no association between planned cesarean delivery and childhood cancer, supporting the findings of a Scandinavian registry study of more than 7 million offspring, in which risk of any childhood cancer following planned cesarean delivery was no different from that following vaginal birth.[28]

Increased risk of offspring death following planned cesarean delivery compared with vaginal birth (0.4% vs 0.3%) is consistent with findings of a prospective WHO study of neonatal mortality. The WHO reported an increased risk following planned cesarean delivery, which was robust to multivariate adjustment and sensitivity analyses testing associations with indication for cesarean delivery.[37]

Strengths and Limitations

The study has a number of strengths. The population-based cohort design minimized risk of selection bias, and use of routinely collected data avoided measurement bias. Data on multiple important covariates helped to control for confounding. Only first-born offspring were included, which avoided risk of confounding by either birth order or parity-related complications of pregnancy. The ability to discriminate between planned and unscheduled cesarean delivery allowed exploration of the potential for exposure to labor to offer protection against adverse outcomes, as some degree of labor frequently precedes unscheduled cesarean delivery. The large sample size helped to achieve sufficient power to assess risk of asthma-related illness and obesity, and the findings regarding risk of rarer outcomes, while less precise, may still be informative.

The study has some limitations, including potential bias and unmeasured confounding, risk of misclassification of cesarean delivery type, missing data, and risk of type 1 error. Maternal education, ethnicity, and indication for cesarean delivery may confound the relationships studied, although we are unaware of specific indications for planned cesarean delivery that affect risk of offspring asthma or type 1 diabetes.[38] Additional factors related to planned cesarean delivery, such as administration of intravenous antibiotics, also may have affected the outcomes measured. Potential ambiguity regarding "unspecified" cesarean delivery classified as "unscheduled" cesarean delivery was considered to pose minimal risk, because respective rates of planned and unscheduled cesarean delivery were comparable with those reported within individual Scottish hospitals.[39] Loss to follow-up attributable to emigration from Scotland was considered unlikely to affect study findings, because migration is not known to be linked to both mode of birth and the outcomes studied. A substantial proportion of missing data on covariates is acknowledged as a limitation but was largely overcome by using multiple imputation to facilitate inclusion of all valid cases in adjusted models, maximizing study power. Comparison of the multivariable analyses obtained using imputed data with data from complete cases demonstrated that the former detected more statistically significant associations, likely reflecting increased sample size.

Although all outcomes were determined a priori, the performance of multiple comparisons to assess secondary outcomes increased the risk of type 1 error. We recognize the potential for systematic bias from knowledge of mode of birth to influence surveillance of offspring health. Use of an unrelated outcome, such as radial fracture, may have been useful in excluding bias in this context. Such an analysis may have increased confidence in our findings but was not part of our analysis plan, so no suitable variable was present in our data set. A prespecified plan to include a similar control outcome, adjusting for relevant confounders, is recommended for future related studies.

Last, the risk of surveillance bias merits further discussion. Women undergoing planned cesarean delivery may be more likely to share information about their offspring with health professionals compared with women in the comparison groups, leading to greater recognition of chronic health conditions.

Clinical and Research Implications

Despite the study limitations, the findings suggest that avoidance of vaginal birth may be an important early-life factor in the growing global burden of asthma, although absolute increase in risk to individuals is low. Health professionals and women considering planned cesarean delivery should be made aware of this. However, the magnitude of risk is such that in the presence of a medical indication for cesarean delivery, the apparent risk to offspring health is unlikely to justify a plan for vaginal birth.

Until indications for cesarean delivery can be fully accounted for and cause of mortality measured, it would be premature to assume that planned cesarean delivery increases the risk of death in childhood—but given the consistency of findings from published studies, it is important to investigate this further.

Conclusions

Among offspring of women with first births in Scotland between 1993 and 2007, planned cesarean delivery compared with vaginal delivery (but not compared with unscheduled cesarean delivery) was associated with a small absolute increased risk of asthma requiring hospital admission, salbutamol inhaler prescription at age 5 years, and all-cause death by age 21 years. Further investigation is needed to understand whether the observed associations are causal.

ARTICLE INFORMATION

Author Contributions: Drs Black and McLernon had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Black, Bhattacharya, Norman, McLernon.
Acquisition, analysis, or interpretation of data: Bhattacharya, Philip, Norman, McLernon.
Drafting of the manuscript: Black.
Critical revision of the manuscript for important intellectual content: Bhattacharya, Philip, Norman, McLernon.
Statistical analysis: Black, McLernon.
Obtained funding: Black.
Administrative, technical, or material support: Philip.
Study supervision: Bhattacharya, Norman, McLernon.

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