Risk of Asthma from Cesarean Delivery Depends on Membrane Rupture

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Objective To assess our prospective mother-child cohort and the national registry data to analyze the risk of asthma by delivery mode and whether cesarean delivery before or after membrane rupture affects this risk differently.

Study design The Copenhagen Prospective Studies on Asthma in Childhood$_{2000}$ is a high-risk birth cohort of 411 Danish children. Asthma was diagnosed prospectively by physicians at the research site, and associations with cesarean delivery were investigated using Cox proportional hazard models. From the Danish national prospective registry we included data from 1997-2010. Childhood asthma was defined from recurrent use of inhaled corticosteroids filled at pharmacies. Cesarean delivery was classified as either before or after rupture of membranes, and the risk of asthma was compared with vaginal delivery. Results were adjusted stepwise for age and calendar year, sex, birth weight, gestational age, multiple births, parity, and maternal factors (age, smoking/antibiotics during pregnancy, employment status, and asthma).

Results In the Copenhagen Prospective Studies on Asthma in Childhood$_{2000}$ cohort, the adjusted hazard ratio for asthma was increased by cesarean delivery relative to vaginal birth 2.18 (1.27-3.73). Registry data replicated these findings. Cesarean delivery performed before rupture of membranes carried significantly higher risk of asthma, (incidence rate ratio to vaginal delivery 1.20 [1.16-1.23]) than cesarean delivery after rupture of membranes (incidence rate ratio to vaginal delivery 1.12 [1.09-1.16]).

Conclusions We confirmed cesarean delivery to be a risk factor for childhood asthma. This effect was more pronounced for cesarean delivery performed before rupture of membranes. *(J Pediatr 2016;171:38-42)*.

Birth by cesarean delivery seems to be a risk factor for childhood asthma.[1,2] However, the mechanisms leading to this increased risk remain unknown. Population-based studies have previously investigated the risk for asthma after delivery by emergency or planned cesarean delivery reporting conflicting results.[3-5] Emergency cesarean delivery may be performed for different reasons most commonly during labor because of delivery complications. However, emergency cesarean delivery may also be performed before onset of labor because of pregnancy complications.

We speculate that cesarean delivery could mediate the asthma risk through alterations of the newborn's microbiome.[6] Hence, the rupture of membranes and thereby possible microbial transmission may cause different effects of cesarean delivery. We analyzed the association between cesarean delivery and asthma in our prospective clinical birth cohort Copenhagen Prospective Studies on Asthma in Childhood$_{2000}$ (COPSAC$_{2000}$) with stringent asthma criteria. To further investigate the potential mechanisms leading to an increased asthma risk after cesarean delivery, we used registry data on the entire Danish pediatric population between 1997-2010.

Methods

The COPSAC$_{2000}$ cohort study was conducted in accordance with the guiding principles of the Declaration of Helsinki and was approved by the Local Ethics Committee (KF 01-289/96) and the Danish Data Protection Agency (2008-41-1754). Both parents gave written informed consent before enrollment. The registry study was based on existing data in national registries and was approved by the Danish Data Protection Agency (J.no. 2012-41-0388). Because subjects were not contacted in the registry study, written informed consent was not required.

COPSAC$_{2000}$ Birth Cohort

The COPSAC$_{2000}$ birth cohort consists of 411 children born 1998-2001 to mothers with a history of asthma, excluding children born before 36 weeks of gestation and anyone suspected of chronic diseases or lung symptoms prior to inclusion, as previously described in detail.[7]

COPSAC$_{2000}$	Copenhagen Prospective Studies on Asthma in Childhood$_{2000}$
HR	Hazard ratio
IRR	Incidence rate ratio

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Registry Study Population

In the prospective registry based cohort study, we identified a cohort of live born children in Denmark in the period 1997-2010 and used their unique identification number to link information on maternal age, sex, parity, maternal smoking during pregnancy, mode of delivery, and maternal identification number from the Danish Medical Birth Registry; information on prescribed antibiotics and anti-asthmatic steroids from the National Prescription Registry; information on hospital admissions (inpatient and outpatient attendance) with asthma as primary diagnosis from the Danish National Patient Registry; information on maternal employment status from Statistics Denmark; and information on date of migration from the Danish Person Registry. The diagnoses are based on the International Statistical Classification of Diseases and Related Health Problems version 10.[8]

Cesarean Delivery Classification

In the $COPSAC_{2000}$ cohort, we defined delivery by cesarean delivery as a dichotomous variable. The National Registry classified cesarean delivery as: (1) elective cesarean performed before delivery; (2) emergency cesarean because of delivery complications performed during delivery; (3) emergency cesarean because of pregnancy complications performed during delivery; and (4) emergency cesarean performed before onset of labor. Children with no registration of cesarean delivery were coded as vaginal delivery. We combined the different classifications to comprise either cesarean delivery performed before rupture of membranes (1 and 4) or cesarean delivery performed after rupture of membranes (2 and 3).

Asthma Definitions

In the $COPSAC_{2000}$ cohort, asthma was diagnosed by trained physicians at the research unit in accordance with strict, standardized criteria based on daily diary cards since birth. The burden of recurrent symptoms was quantified from an algorithm of 5 episodes of at least 3 consecutive days of troublesome lower lung symptoms within 6 months and need of short-acting ß2-agonists as previously described in detail.[9] Furthermore, the diagnosis required symptom improvement during a 3-month trial of inhaled corticosteroids and relapse when this medication was stopped. Asthma exacerbations were defined by need for oral prednisolone, high-dose inhaled corticosteroids, or acute hospitalization with asthmatic symptoms.

In the registry, we defined asthma as long-term recurrent use of inhaled corticosteroids: at least 200 defined daily doses (World Health Organization index) filled at a pharmacy (R03BA01; R03BA02; R03BA05; R03BA07). The child becomes a case at first collection of medication. In the sensitivity analyses, we investigated 2 alternative definitions of childhood asthma based on asthma hospitalizations as described earlier[10]: (1) recurrent hospital admissions for asthma: at least 2 inpatient admissions (primary diagnosis of asthma ICD10: J45.x; J46.x) separated by at least 1 month (child is considered case at first admission); or (2) long-term outpatient attendance related to asthma: child followed in outpatient care (primary diagnosis of asthma ICD10: J45.x; J46.x) for minimum 1 year (child becomes case at date of outpatient treatment initiation). For each definition, cases were compared with noncases where noncases were all children not fulfilling case definitions.

Confounders

Confounders were chosen a priori as sex, parity, birth weight, gestational age, maternal age, mother smoking during pregnancy, maternal disease, multiple births, mother's use of antibiotics during pregnancy, and maternal employment/education. All confounders were included in the regression models as categorical variables in registry analyses: parity (first child, second child, third child or more), birth weight (2.5-3.0 kg, 3.0-3.5 kg, 3.5-4.0 kg, >4.0 kg), gestational age (<37 weeks, 37-39 weeks, 40-41 weeks, 42 or more weeks), maternal age (4 categories), maternal disease (mothers ever hospital admission for asthma or mothers prescription of inhaled steroid ever), multiple births (singleton, twins, triplets or more), mothers use of antibiotics during pregnancy (ever prescription of antibiotics 14 days before last menstruation until offspring's birthdate), mothers smoking during pregnancy (yes/no), and maternal employment status in the year of child birth or the previous year if child is born during the first 8 months (7 categories).

Statistical Analyses

Time to first asthma diagnosis before the age of 7 years was illustrated with Kaplan Meier plots. For clinical cohort data, confounder adjusted hazard ratios (HRs) were calculated with Cox regression. All confounders were investigated for proportionality, and nonproportional variables (sex and parity) were added as stratifying variables to get adjusted estimates of cesarean delivery.

In the registry analyses, children contributed to person time of observation from date of birth to becoming asthmatic, death, migration, or December 31, 2010. The number of asthma cases by cesarean delivery was investigated with log-linear Poisson regression models offset by the log-transformed person years of observation adjusted for attained age (1-year group) and attained calendar year (1-year group) (Model 1). In 2 additional models, we included stepwise the a priori chosen confounders. Model 2: adding sex, parity, multiple birth, maternal factors (age, smoking during pregnancy, usage of antibiotics during pregnancy, employment status, asthma [ever prescription of steroid or ever admission for asthma]); and model 3: adding birth weight and gestational age. The offset of log-transformed person-years models the rate of diseases, and with the categorical adjustment for timing variable (attained age and calendar year), the resulting incidence rate ratios (IRRs) with 95% CIs can be interpreted as HRs from Cox regression.

Term children (birth weight >2.5 kg) were investigated in a separate sensitivity analysis. In another sensitivity analysis for children above 6 years of age, only children born from 1997-2005 were included and contribute only from the date of the 6-year birthday to case definition, death, migration, or December 31, 2010.

Registry data were summarized with the Pyrsstep macro.[11] A significance level of .05 was used in all analyses. The data processing was performed using R v 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria) and SAS v 9.3 for Windows (SAS Institute Inc, Cary, North Carolina).

Results

During 1998-2001, 411 children from the greater Copenhagen area were included in the $COPSAC_{2000}$ cohort. The cohort has been extensively described earlier.[12-14] In Denmark, 864 049 (95%) of 910 301 children born had data on all confounders. These children were followed in the registries from birth to death/emigration or final follow-up date of December 31, 2010 covering 5 987 664 person years in the age range 0-15 years with declining observation time with child age. Distributions of all confounders in the population are presented in **Table I** (available at www.jpeds.com).

Prevalence of Cesarean Delivery

Eighty-seven of 411 children (22%) in the $COPSAC_{2000}$ cohort were delivered by cesarean delivery. In the registry cohort, 19% (163 462) of the Danish children were born by cesarean delivery during the period 1997-2010. Ten percent (87 559) of the children were born by cesarean delivery performed before rupture of membranes (71% elective and 29% emergency before delivery), 9% (75 863) of the children were born by cesarean delivery performed after rupture of membranes (88% emergency because of delivery complications, 12% emergency because of pregnancy complications).

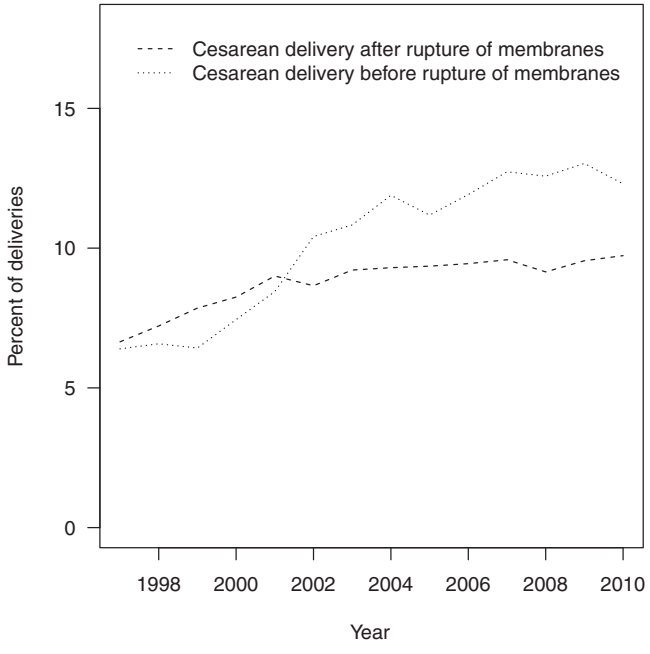

Figure 1. Prevalence of cesarean delivery.

The prevalence of birth by cesarean delivery increased during the study period, primarily because of increasing numbers of cesarean deliveries before rupture of membranes (**Figure 1** and **Table I**). Cesarean deliveries performed before rupture of membranes included more preterm children with a lower birth weight (**Table I**).

Prevalence of Asthma

In the high-risk $COPSAC_{2000}$ birth cohort, 18% (72 children) developed asthma before the age of 7 years. In the registry cohort 4.4% (38 085) had filled at least 200 defined daily doses of anti-asthmatic steroids.

Cesarean Delivery and Asthma

We found significant association between delivery by cesarean delivery and development of asthma in the $COPSAC_{2000}$ cohort with a confounder adjusted HR of 2.18 (1.27-3.73); $P = .005$ (**Figure 2**). Similarly, we found significant association with asthma exacerbations with adjusted HR of 2.48 (1.37-4.49); $P = .003$ (**Figure 3**; available at www.jpeds.com). This overall association between cesarean delivery and increased asthma risk was confirmed in the population cohort, where we found a smaller effect of cesarean delivery with IRR 1.16 (1.13-1.19). The main confounder appeared to be prematurity because the biggest drop in risk occurs from model 2 (all confounders except birth weight and gestational age) to model 3 including those (**Table II**).

When separating cesarean delivery by rupture of membranes in the population cohort, we found differences in the risk of asthma. Cesarean deliveries performed before rupture of membranes carried a significant larger risk of asthma, IRR to vaginal delivery (1.20 [1.16-1.23]) compared with IRR to vaginal delivery (1.12 [1.09-1.16]) after rupture of membranes (**Table II**). For cesarean deliveries performed after rupture of membranes, we found increased risk of asthma in all adjustment models with the biggest decrease in effect size from model 1 to model 2. For cesarean deliveries performed before rupture of membranes, we observed overall larger effect sizes and mainly a decrease when including birth weight and gestational age as confounders in model 3 (**Table II**). When restricting the population cohort to term children only (birth weight >2.5 kg), the results are similar (**Table III**; available at www.jpeds.com). In sensitivity analyses on the population cohort, we investigated asthma among children above 6 years of age. We found similar results with cesarean deliveries performed before rupture of membranes being a stronger risk factor for later asthma (**Table IV**; available at www.jpeds.com).

In another sensitivity analysis on the population cohort, we investigated 2 alternative asthma definitions: recurrent inpatient hospitalizations and long-term outpatient treatment for asthma. The results are shown in **Tables V** and **VI** (available at www.jpeds.com). There were fewer cases by these definitions of asthma, but the associations to cesarean delivery were in fact stronger, indicating more strict asthma

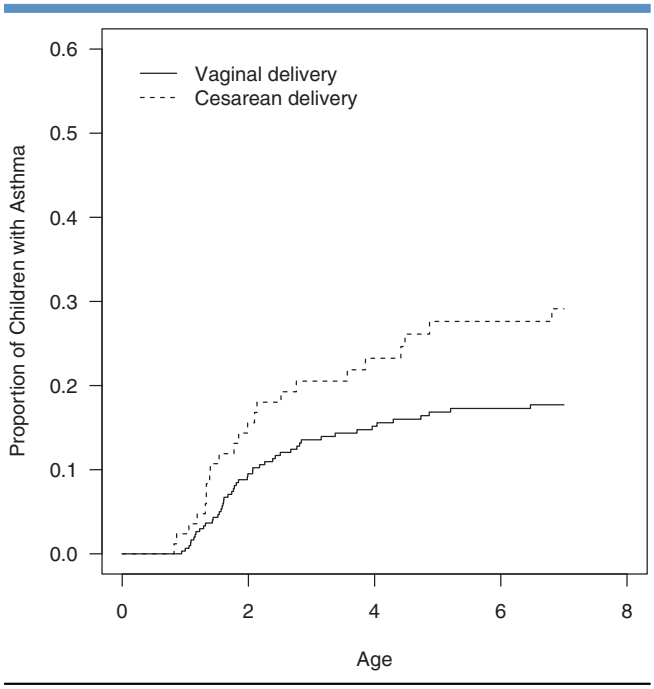

Figure 2. Kaplan Meier curves for asthma by delivery method in the $COPSAC_{2000}$ cohort. Confounder adjusted HR 2.18 (1.27-3.73); $P = .005$.

definitions. Cesarean deliveries performed before rupture of membranes remained a stronger risk factor for asthma regardless of asthma definition.

Discussion

The major strengths of the $COPSAC_{2000}$ clinical cohort is the thorough prospective clinical monitoring and diagnosing based on highly standardized operating procedures. The birth cohort was followed prospectively with diary cards and 6 monthly routine visits, strengthening the asthma diagnosis. However, the size of the cohort does not allow for investigation of different types of cesarean deliveries. For this purpose, we used 14 years of nationwide population follow-up in national registries. The content and validity of the Danish National Registries have been well documented previously.[8,15,16]

The Danish National Prescription Registry has nationwide information on steroids prescribed and filled at the pharmacies. The registry is highly accurate and in Denmark all anti-asthmatic steroid inhalants can be prescribed only by authorized physicians and purchased from authorized pharmacies. Medication was collected on the children's own unique identification number. Unlike the clinical cohort, asthma must be defined based on registered events (there are no registrations of diagnoses from general practitioners). Previous studies have used parental reporting, hospital records, and prescription medication as outcomes. This study is strengthened by defining asthma from both hospitalizations and medication filled. The Danish National Patient Registry covers all hospital admissions nationwide as well as children attending outpatient clinics. Asthma diagnosis in the National Patient Registry has previously been validated,[17] and we recently demonstrated the phenotypic specificity of asthma hospitalization in our discovery of a novel genetics risk variants.[18]

A wide range of potential confounders were included as categorical variables, and no assumptions were made on directions of associations. To ensure that associations were not confounded by prematurity, we excluded children born before week 36 in our mother-child cohort and children with birth weight below 2.5 kg in the registry based cohort, which did not affect the conclusions (**Table III**). However, we cannot exclude residual confounding in our results.

Diagnosis of asthma in a young child may be inaccurate. We, therefore, did a sensitivity analysis in the registry-based cohort excluding children below 6 years of age (**Table IV**). We studied only children born after 1997, and, therefore, the number of observation years was inversely reduced with age in the study-base. This limits our study power for asthmatics with a late onset. Despite this, we still found cesarean delivery to have a significant risk for asthma, and we were still able to differentiate types of cesarean deliveries.

A potential study limitation is that we defined rupture of membranes based solely on the obstetrician's diagnoses of being in active labor or not. The obstetric classification may furthermore be inaccurate and affected by changing medical practice in the long follow-up period. Any misclassification of the types of cesarean delivery could increase noise but would not lead to systematic bias in the results.

Table II. Confounder adjusted IRR for asthma (200 defined daily dose collected anti-asthmatic steroids) by type of cesarean delivery vs vaginal birth in 3 models with increasing confounder adjustments

	N (person y)	Model 1	Model 2	Model 3
Population	864 049 (5 987 664)	N = 41 633	N = 41 633	N = 38 085
Vaginal delivery	700 587 (4 963 792)	Ref	Ref	Ref
Cesarean delivery	163 462 (1 023 872)	1.31 (1.28-1.34); $P < .001$	1.25 (1.22-1.28); $P < .001$	1.16 (1.13-1.19); $P < .001$
Type of cesarean vs vaginal delivery				
Cesarean delivery after rupture of membranes	75 863 (496 772)	1.24 (1.20-1.28); $P < .001$	1.15 (1.11-1.19); $P < .001$	1.12 (1.09-1.16); $P < .001$
Cesarean delivery before rupture of membranes	87 599 (527 100)	1.38 (1.34-1.42); $P < .001$	1.34 (1.30-1.39); $P < .001$	1.20 (1.16-1.23); $P < .001$

Ref, reference group.
Children are investigated from birth to asthma/censoring.

We found an increased risk of asthma and asthma exacerbations in the longitudinally followed $COPSAC_{2000}$ birth cohort among children born by cesarean delivery. The diagnosis and treatment of this cohort are very stringent based on symptom load and clinical appearance ruling out the possibility that treatment-seeking behavior in the mother may lead to both cesarean delivery in pregnancy and asthma diagnosis in the child. This observation is replicated in the national registries by different asthma categories strengthening the confidence in the findings.

The birth setting around cesarean delivery is different from vaginal birth with respect to several factors including anesthetic agents and antibiotics administered during birth, physiological effects of the newborn, and the hospital environment after birth.[19] We speculate that the effect from cesarean delivery may be mediated by changes in the microbiome of the newborn.[6] Cesarean delivery performed before rupture of membranes could exaggerate the differences in microbiota, as the child in this setting is born without vertical microbial transmission from the mother.[20] This could explain the higher risk of asthmatic outcomes following this type of cesarean delivery. Our findings are in line with other studies differentiating between cesarean delivery by rupture of membranes, where the electively born children likewise had increased risk of asthma.[21] One previous study found the opposite, but this could be confounded by not accounting for types of emergency cesarean delivery and no exclusion of premature children.[5]

It cannot be determined whether long-term effects observed after delivery by cesarean delivery is caused by the procedure itself or by the obstetric indication for the procedure. Because a randomized controlled trial on cesarean delivery cannot be performed, we can only attempt to settle this issue by optimizing observational studies such as the present one based on both strong disease phenotypes from clinical cohort data and national registry data with the power for stratification.

Cesarean delivery was a risk factor for childhood asthma in several different disease phenotypes. We found a higher asthma risk among children born by cesarean performed before rupture of membranes compared with cesarean after rupture of membranes, which could imply microbiome mediated effect on later disease development. ■

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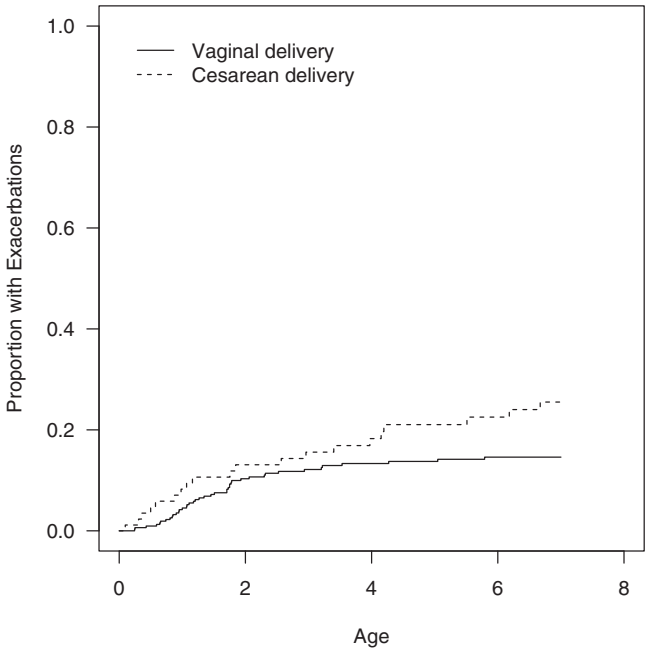

Figure 3. Kaplan Meier curves for asthma exacerbations by delivery method in the $COPSAC_{2000}$ cohort. Confounder adjusted HR 2.48 (1.37-4.49); $P = .003$.

Table I. Baseline characteristics by mode of delivery

	Vaginal delivery	Cesarean delivery after rupture of membranes	Cesarean delivery before rupture of membranes	Total
N (%)	700 587	75 863	87 599	864 049
Birth y				
1997-1999	86.29	7.24	6.47	184 387 (21.34%)
2000-2002	82.61	8.63	8.75	188 567 (21.82%)
2003-2005	79.41	9.29	11.30	187 198 (21.67%)
2006-2008	78.20	9.39	12.41	183 584 (21.25%)
2009-2011	77.70	9.64	12.66	120 313 (13.92%)
Sex				
Male	50.91	55.32	50.58	442 967 (51.27%)
Female	49.09	44.68	49.42	421 082 (48.73%)
Birth weight				
<2.5 kg	2.93	10.42	15.40	41 911 (4.85%)
2.5-3.0 kg	10.49	12.68	16.53	97 619 (11.3%)
3.0-3.5 kg	31.74	24.06	30.69	267 513 (30.96%)
3.5-4.0 kg	35.64	28.70	24.53	292 951 (33.9%)
>4.0 kg	19.20	24.14	12.86	164 055 (18.99%)
Gestational age				
<36 wk	4.16	12.10	17.31	53 476 (6.19%)
37-39 wk	15.33	18.95	47.53	163 391 (18.91%)
40-41 wk	53.25	36.88	29.23	426 623 (49.37%)
>42 wk	27.27	32.06	5.94	220 559 (25.53%)
Parity				
First child	42.45	64.21	36.89	378 445 (43.8%)
Second child	37.74	26.17	40.07	319 335 (36.96%)
Third (or more) child	19.81	9.62	23.05	166 269 (19.24%)
Multiple birth				
Singleton	97.89	89.43	87.09	829 929 (96.05%)
Multiple	2.11	10.57	12.91	34 120 (3.95%)
Maternal age				
..-25	13.83	11.38	7.31	111 918 (12.95%)
26-30	34.95	33.79	26.27	293 494 (33.97%)
31-35	35.47	36.00	39.61	310 492 (35.93%)
36-..	15.75	18.82	26.81	148 145 (17.15%)
Maternal use of antibiotics during pregnancy				
No	67.73	67.14	64.38	581 807 (67.33%)
Yes	32.27	32.86	35.62	282 242 (32.67%)
Maternal asthma (hospitalization or steroid prescription)				
No	88.13	86.54	85.81	758 230 (87.75%)
Yes	11.87	13.46	14.19	105 819 (12.25%)
Smoking during pregnancy				
Yes	18.67	18.38	17.92	160 469 (18.57%)
No	81.33	81.62	82.08	703 580 (81.43%)
Maternal employment status in y or previous y of childbirth				
Unemployed	10.21	9.41	12.14	89 273 (10.33%)
Entrepreneur/leader	1.14	1.31	1.44	10 259 (1.19%)
Employee, unknown status	9.69	10.36	9.92	84 455 (9.77%)
Employee, basic skilled	29.83	30.98	29.65	258 464 (29.91%)
Employee, medium skilled	20.50	21.54	22.10	179 337 (20.76%)
Employee, highly skilled	12.38	12.17	12.92	107 266 (12.41%)
Entrepreneur, no employees	1.89	1.89	2.07	16 484 (1.91%)
Education	4.98	4.56	3.17	41 111 (4.76%)
Other	9.38	7.79	6.59	77 400 (8.96%)

For overall N and birth year, numbers represent row-percentages. For all other confounders, numbers represent column percentages.

Table III. Population: term children only (birth weight >2.5 kg)

	N (person y)	Model 1	Model 2	Model 3
Population	822 138 (5 707 421)	N = 38 085	N = 38 085	N = 38 085
Vaginal delivery	680 066 (4 822 345)	Ref	Ref	Ref
Cesarean delivery	142 072 (885 075)	1.26 (1.23-1.29); $P < .001$	1.21 (1.17-1.24); $P < .001$	1.16 (1.13-1.19); $P < .001$
Type of cesarean vs vaginal delivery				
Cesarean delivery after rupture of membranes	67 960 (443 453)	1.20 (1.16-1.25); $P < .001$	1.13 (1.09-1.17); $P < .001$	1.13 (1.09-1.17); $P < .001$
Cesarean delivery before rupture of membranes	74 112 (441 621)	1.31 (1.27-1.35); $P < .001$	1.29 (1.24-1.33); $P < .001$	1.20 (1.16-1.24); $P < .001$

Ref, reference group.

Table IV. Population: only children above 6 years of age

	N (person y)	Model 1	Model 2	Model 3
Population	498 371 (1 937 919)	N = 12 189	N = 12 189	N = 12 189
Vaginal delivery	414 452 (1 644 591)	Ref	Ref	Ref
Cesarean delivery	83 919 (293 327)	1.26 (1.20-1.31); $P < .001$	1.18 (1.13-1.24); $P < .001$	1.12 (1.06-1.17); $P < .001$
Type of cesarean vs vaginal delivery				
Cesarean delivery after rupture of membranes	41 249 (149 996)	1.21 (1.13-1.28); $P < .001$	1.10 (1.04-1.18); $P = .002$	1.08 (1.01-1.15); $P = .021$
Cesarean delivery before rupture of membranes	42 670 (143 331)	1.31 (1.23-1.39); $P < .001$	1.27 (1.19-1.35); $P < .001$	1.16 (1.09-1.24); $P < .001$

Confounder adjusted IRRs for asthma by type of cesarean vs vaginal delivery birth in term children in 3 models with increasing confounder adjustments. Children are followed from birth to asthma/censoring.

Table V. Population: all children. Asthma defined by recurrent inpatient hospitalizations

	N (person y)	Model 1	Model 2	Model 3
Population	864 049 (5 987 664)	N = 7166	N = 7166	N = 6466
Vaginal delivery	700 587 (4 963 792)	Ref	Ref	Ref
Cesarean delivery	163 462 (1 023 872)	1.38 (1.30-1.45); $P < .001$	1.35 (1.28-1.43); $P < .001$	1.20 (1.13-1.27); $P < .001$
Type of cesarean vs vaginal delivery				
Cesarean delivery after rupture of membranes	75 863 (496 772)	1.26 (1.17-1.36); $P < .001$	1.23 (1.13-1.33); $P < .001$	1.17 (1.08-1.27); $P < .001$
Cesarean delivery before rupture of membranes	87 599 (527 100)	1.48 (1.38-1.59); $P < .001$	1.46 (1.36-1.57); $P < .001$	1.22 (1.14-1.32); $P < .001$

Confounder adjusted IRRs for asthma by type of cesarean vs vaginal delivery in 3 models with increasing confounder adjustments. Children are followed from birth to asthma/censoring. Asthma defined by recurrent inpatient hospitalizations.

Table VI. Population: all children. Asthma defined by long term outpatient treatment

	N (person y)	Model 1	Model 2	Model 3
Population	864 049 (5 987 664)	N = 12 711	N = 12 711	N = 11 711
Vaginal delivery	700 587 (4 963 792)	Ref	Ref	Ref
Cesarean delivery	163 462 (1 023 872)	1.31 (1.26-1.37); $P < .001$	1.27 (1.21-1.33); $P < .001$	1.17 (1.12-1.23); $P < .001$
Type of cesarean vs vaginal delivery				
Cesarean delivery after rupture of membranes	75 863 (496 772)	1.20 (1.13-1.27); $P < .001$	1.15 (1.09-1.23); $P < .001$	1.12 (1.05-1.19); $P < .001$
Cesarean delivery before rupture of membranes	87 599 (527 100)	1.42 (1.34-1.50); $P < .001$	1.38 (1.30-1.46); $P < .001$	1.22 (1.15-1.30); $P < .001$

Confounder adjusted IRRs for asthma by type of cesarean vs vaginal delivery birth in 3 models with increasing confounder adjustments. Children are followed from birth to asthma/censoring. Asthma defined by long-term outpatient treatment.