Birth by cesarean section, allergic rhinitis, and allergic sensitization among children with a parental history of atopy

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Background: Cesarean delivery can alter neonatal immune responses and increase the risk of atopy. Studies of the relation between cesarean delivery and allergic diseases in children not selected on the basis of a family history of atopy have yielded inconsistent findings.

Objective: We sought to examine the relation between birth by cesarean delivery and atopy and allergic diseases in children at risk for atopy.

Methods: We examined the relation between mode of delivery and the development of atopy and allergic diseases among 432 children with a parental history of atopy followed from birth to age 9 years. Asthma was defined as physician-diagnosed asthma and wheeze in the previous year, and allergic rhinitis was defined as physician-diagnosed allergic rhinitis and naso-ocular symptoms apart from colds in the previous year. Atopy was considered present at school age if there was 1 or more positive skin test response or specific IgE to common allergens. Stepwise logistic regression was used to study the relation between cesarean delivery and the outcomes of interest.

Results: After adjustment for other covariates, children born by cesarean section had 2-fold higher odds of atopy than those born by vaginal delivery (odds ratio, 2.1; 95% CI, 1.1-3.9). In multivariate analyses birth by cesarean section was significantly associated with increased odds of allergic rhinitis (odds ratio, 1.8; 95% CI, 1.0-3.1) but not with asthma.

Conclusions: Our findings suggest that cesarean delivery is associated with allergic rhinitis and atopy among children with a parental history of asthma or allergies. This could be explained by lack of contact with the maternal vaginal/fecal flora or reduced/absent labor during cesarean delivery.
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Key words: *Cesarean delivery, allergic rhinitis, atopy, childhood*

Atopic diseases, such as atopic asthma, allergic rhinitis, and eczema, are a major public health problem worldwide.[1] Perinatal exposures might have a role in the pathogenesis of atopic diseases, such as asthma and allergic rhinitis, which often begin in early childhood.[2]

In the United States the percentage of children born by cesarean delivery increased from 23% in 1990 to 28% in 2003.[3] Compared with vaginal delivery, birth by cesarean section leads to long-lasting changes in the neonatal intestinal flora,[4,5] which have been associated with atopy, allergic diseases, or both in some studies[6] but not in others.[5] Among children unselected for a parental history of atopy, birth by cesarean section has been associated with an increased risk of asthma, atopic diseases, or both in some studies[7-13] but not in others.[14-17]

To date, there has been no longitudinal study of the relation between birth by cesarean section and atopy and allergic diseases at school age among children at high risk for atopy. We examined the relation between birth by cesarean section and atopy and atopic diseases (asthma and allergic rhinitis) among children with a parental history of atopy followed from birth to age 9 years.

METHODS

Study population

Subject recruitment for the Epidemiology of Home Allergens and Asthma Study has been previously described in detail.[18] In brief, subjects were recruited between September 1994 and August 1996. Eligibility criteria included living inside route 128 (which encircles the Boston Metropolitan Area), maternal age of 18 years or older, parental ability to speak either English or Spanish, and a history of asthma or allergies in either parent. Exclusion criteria included gestational age of less than 36 weeks, hospitalization in the neonatal intensive care unit, or the presence of a congenital anomaly.

After obtaining written informed consent, a home visit was conducted at age 2 to 3 months, and a questionnaire concerning demographics, home characteristics, environmental exposures, tobacco use, and health outcomes was given by trained research assistants. Starting at age 2 months, a telephone questionnaire (modified from the American Thoracic Society-Division of Lung Disease Questionnaire)[19] was administered by trained research assistants to the child's primary caregiver until the age of 2 years. Afterward, interviews were conducted every 6 months. Seven of the 505 children enrolled in the study were excluded because they were followed for less than 5 months during their first year of life. The study was approved by the Institutional Review Board of Brigham and Women's Hospital.

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Abbreviation used
OR: Odds ratio

Perinatal variables

Information on mode of delivery and other perinatal variables was extracted from the maternal and neonatal medical records shortly after delivery. For data analysis, mode of delivery was considered as a binary (cesarean vs vaginal) variable. Birth weight and gestational age were used as continuous and categorical variables.[20] Head circumference data were missing for 21% of the participating children and were thus not included in the analysis.

Definition of other variables

Additional variables considered for inclusion in the multivariate analysis included sex, annual household income,[21] child's ethnicity,[21] number of older siblings, maternal age at delivery, gestational age,[20] maternal asthma (ever and current), paternal asthma (ever and current), *in utero* smoke exposure, average number of cigarettes smoked by adults in the household per day, breastfeeding,[22] day care attendance in the first year of life,[23] antibiotic use in the first year of life,[24] bottle feeding in the crib or bed before sleep,[22] physician-diagnosed illnesses of the upper (sinusitis and recurrent [$\geq$3 episodes] of nasal catarrh) and lower (pneumonia, bronchiolitis, bronchitis, and croup) respiratory tract in the first year of life,[25] and levels of dust mite allergen and endotoxin in house dust at age 2 to 3 months.[26] The methods used to collect house dust samples and quantify levels of dust mite allergen (in the child's bed) and endotoxin (in the family/living room) have been previously described.[26-29]

Assessment of allergic sensitization

At a mean age of 7.4 years (range, 6.5-10.1 years), allergy skin testing was performed in 248 children, and IgEs specific to common allergens were measured in an additional 23 children. Skin prick testing was performed on the volar aspect of the lower arms by using extracts for cat dander, dog dander, mouse epithelia, cockroach *(Blatella germanica)*, dust mite (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), ragweed, mixed trees, mixed grasses, and molds (*Alternaria*, *Aspergillus*, *Cladosporium*, and *Penicillium* species; Hollister-Stier Labs, Spokane, Wash). Histamine was used as a positive control, and glycerinated saline was used as a negative control. Skin test results were read as positive if the mean diameter of the wheal was 3 mm or larger after subtraction of the saline control wheal.

UniCAP 250 (Pharmacia & Upjohn, Kalamazoo, Mich) was used to assay for specific IgE to the above allergens in the 23 children who refused skin prick testing. IgE values to specific allergens were considered positive at 0.35 IU/mL or greater.

Definition of outcomes

At age 9 years, asthma was defined as physician-diagnosed asthma and at least 1 episode of wheezing in the previous year, and allergic rhinitis was defined as physician-diagnosed allergic rhinitis and a history of nasal discharge or sneezing apart from colds in the previous year.

Atopy (sensitization to $\geq$1 allergens) was primarily defined as at least 1 positive skin test result or specific IgE to the tested allergens at school age.[26] In exploratory analyses we subdivided atopy into 2 categories (ie, sensitization to 1 or more perennial allergens and sensitization to 1 or more seasonal allergens) and considered the degree of atopy (different categories for the number of positive skin tests or specific IgEs [eg, 0, 1-2, or $\geq$3) to the allergens tested.

For the longitudinal analysis of repeated measures of wheeze, wheeze was considered present at any time point between ages 12 and 108 months if the child's caretaker reported "wheezing or whistling in the chest" since the previous visit.

Statistical analysis

Bivariate analyses were performed by using χ^2 or Fisher exact tests for categorical variables and 2-sided *t* tests or Wilcoxon tests for pairs of categorical and continuous variables, as appropriate. Stepwise logistic regression was used to study the relation between mode of delivery and the outcomes of interest (asthma, allergic rhinitis, and atopy) while adjusting for potential confounders. The final models included variables that were significant at a *P* value of less than .05 or that caused a change in the estimated measure of effect (odds ratio [OR]) of 10% or greater. Selected interactions were examined after the final models were chosen.

To assess the relation between mode of delivery and childhood wheeze, we performed a longitudinal analysis of the relation between birth by cesarean section and repeated measures of any wheeze between ages 1 and 9 years. For that analysis, we used proportional hazard models, with repeated events on the same child handled by using the method of Andersen and Gill[30] and adjustment for correlations between these repeated events handled by using methods described by Therneau and Grambsch.[31] To examine age-dependent associations, we calculated interaction terms between the age of the children at each survey and the variables in the model.

RESULTS

The characteristics of the 498 study subjects have been described in detail elsewhere.[24,32] Of the 498 participating children, 432 (87%) were followed up to age 9 years, and 271 (54%) had an assessment of allergic sensitization. Children who did not have an assessment of allergic sensitization or who were not followed up to age 9 years were more likely to be of nonwhite ethnicity, to live in households with an annual income of less than $30,000, and to have more than 1 sibling than children who had an assessment of allergic sensitization or who were followed up to age 9 years (Table I).

There were no significant differences in mode of delivery, birth weight, or gestational age between children who did and did not have an assessment of allergic sensitization. There were no significant differences in mode of delivery, birth weight, or gestational age between children who were and were not followed up to age 9 years.

Table II summarizes the main results of the analysis of the relation between mode of delivery and allergic rhinitis at age 9 years. In bivariate analyses cesarean section, a birth weight in the highest quartile (3.8-4.9 kg), and recurrent nasal catarrh in the first year of life were all associated with increased odds of allergic rhinitis at age 9 years. In contrast, exposure to an endotoxin level greater than the lowest quartile at age 2 to 3 months was associated with reduced odds of allergic rhinitis at age 9 years. After adjustment for relevant covariates, there was slight attenuation of the magnitude and statistical significance of the association between cesarean section and increased odds of allergic rhinitis. In this multivariate analysis recurrent nasal catarrh in the first year of life and birth weight in the highest quartile were significantly associated with increased odds and endotoxin exposure in early life was associated with decreased odds of allergic rhinitis at age 9 years.

Table III shows the results of the bivariate and multivariate analyses of the relation between birth by cesarean section and atopy at school age. In both bivariate and multivariate analyses, cesarean section was significantly associated with a 2-fold increase in the odds of atopy at school age. In the multivariate analysis early exposure to endotoxin levels of greater than the lowest quartile and physician-diagnosed croup in the first year of life were each associated with reduced odds of atopy at school age.

TABLE I. Characteristics of participating children

Variable	At baseline* (n = 498), no. (%)	At 9 y follow-up* (n = 432), no. (%)	Children with assessment of allergen sensitization* (n = 271), no. (%)
Female sex	230 (46.2)	195 (45)	116 (43)
Household income <$30,000	45 (9.3)	24 (5.7)†	13 (5)†
Ethnicity			
White	375 (75.3)	344 (79.6)†	219 (81)†
Black	60 (12.1)	37 (8.6)†	23 (9)†
Hispanic	28 (5.6)	19 (4.4)	11 (4)
Asian and "other"	35 (7.0)	32 (7.4)	18 (7)
Cesarean delivery	114 (22.9)	102 (23.6)	65 (24.0)
Scheduled	27 (5.4)	24 (5.6)	16 (5.9)
Nonscheduled	86 (17.3)	77 (17.9)	48 (17.8)
Quartiles of birth weight (kg)			
1.84 to <3.18	125 (25.2)	106 (24.6)	67 (24.7)
3.18 to <3.46	126 (25.4)	108 (25.1)	65 (24.0))
3.46 to <3.79	122 (24.6)	108 (25.1)	68 (25.1)
3.79 to <4.91	124 (25.0)	109 (25.3)	71 (26.2)
Season of birth			
Spring	144 (28.9)	127 (29.4)	86 (31.7)†
Summer	110 (22.1)	94 (21.8)	58 (21.4))
Fall	120 (24.1)	106 (24.5)	68 (25.1)
Winter	124 (24.9)	105 (24.3)	59 (21.8)
Gestational age <38.5 wk	104 (20.9)	87 (20.1)	60 (22.14)
Maternal history of asthma	152 (30.5)	125 (28.9)†	76 (28.0)
No. of siblings in the child's home			
0	228 (45.8)	215 (49.8)†	136 (50.2)†
1	176 (35.4)	147 (34.0)	93 (34.3)
≥2	94 (18.9)	70 (16.2)†	42 (15.5)†
≥3 Episodes of nasal catarrh in the first year of life	421 (84.5)	365 (84.5)	229 (84.5)
Physician-diagnosed bronchiolitis in the first year of life	65 (13.1)	52 (12.0)	35 (12.9)
Physician-diagnosed croup in the first year of life	57 (11.5)	47 (10.9)	30 (11.1)
Quartiles of endotoxin (EU/mg)			
2.14-52.5	100 (24.9)	84 (24.1)	50 (22.6)
52.5-79.9	100 (24.9)	90 (25.8)	53 (24.0)
80.48-125.59	101 (25.2)	88 (25.2)	60 (27.2)
125.6-713.2	100 (24.9)	87 (24.9)	58 (26.2)
Dust mite allergen (μg/g; tertiles of detectable levels)			
<0.0523 (nondetectable)	192 (44.4)	192 (44.4)	124 (46.1)
≥0.0523 to <0.685	80 (18.5)	80 (18.5)	49 (18.2)
≥0.685 to <2.725	80 (19)	80 (19)	44 (16.4)
≥2.725	80 (19)	80 (19)	52 (19.3)

*Numbers and percentages reflect missing information on some variables.
†$P < .05$ for comparison with children at baseline.

Although we had limited statistical power to conduct a stratified analysis, we also examined whether the observed association between cesarean delivery and atopy differed by type of sensitization (to perennial vs seasonal allergens). In a bivariate analysis there were similar non–statistically significant trends for an association between cesarean section and either sensitization to at least 1 perennial allergen (OR, 1.7; 95% CI, 1.0-2.9; $P = .07$) or sensitization to at least 1 seasonal allergen (OR, 1.5; 95% CI, 0.8-2.6; $P = .18$).

We found no significant association between cesarean section and asthma in bivariate or multivariate analyses (Table IV). In addition, we found no association between birth by cesarean section and a major asthma symptom (wheeze) from ages 1 to 9 years (unadjusted hazard ratio, 1.0; 95% CI, 0.997-1.007; $P = .50$).

With the exception of birth weight (see Table II), there was no significant association between other prenatal and perinatal exposures (eg, gestational age and breast-feeding) and any of the outcomes of interest.

DISCUSSION

To our knowledge, this is the first prospective birth cohort study of the relation between birth by cesarean section and atopy and allergic diseases at school age among children at high risk for atopy. In our study birth by cesarean section was associated with increased risks of allergic rhinitis and atopy but not with asthma.

Table V[7-17,33] summarizes the results of 12 previous epidemiologic studies of birth by cesarean section and atopy, atopic diseases, or both, all of which were conducted among subjects not selected on the basis of a familial or parental history of atopy. Of these 12 studies, 7 were retrospective, assessed mode of delivery and other covariates using data from existing databases, or both[7,8,10,12,13,15,16]; 9 had limited,[10,11,13,15-17,33] variable,[8,10,15,16] or both duration of follow-up during childhood; 6 reported losing 20% or more of the study participants at entry or during follow-up[8,9,13,14,17,33]; and only 5 assessed allergic sensitization by means of objective methods.[7,9,11,14,33] Thus the seemingly conflicting findings of these studies can be due to selection bias

TABLE II. Analysis of the relation between birth by cesarean section and allergic rhinitis at age 9 years

Variables	Allergic rhinitis		OR (95% CI), *P* value	
	Yes	No	Unadjusted	Adjusted*
Mode of delivery				
Vaginal	53	277	1	1
Cesarean section	27	75	1.9 (1.1-3.2), .02	1.8 (1.0-3.1), .047
Quartiles of birth weight				
1st	15	91	1	1
2nd	21	87	1.5 (0.7-3.0), .3	1.7 (0.8-3.5), .2
3rd	17	91	1.1 (0.5-2.4), .7	1.3 (0.6-2.8), .5
4th	27	82	2.0 (1.0-4.0), .05	2.0 (1.0-4.1), .05
Endotoxin levels†				
1st Quartile	22	62	1	1
2nd-4th Quartiles	43	222	0.6 (0.3-1.0), .04	0.5 (0.3-0.9), .03
≥3 Episodes of nasal catarrh in the first year of life				
No	7	60	1	1
Yes	73	292	2.1 (0.9-4.9), .06	2.4 (1.0-5.6), .04
Day care attendance in the first year of life				
No	48	181	1	1
Yes	32	171	0.7 (0.4-1.2), .17	0.6 (0.4-1.1), .08

*Adjusted for age and sex in addition to all of the variables listed in the column.
†Of the 432 participating children, 349 had data on indoor endotoxin levels at age 2 to 3 months.

TABLE III. Analysis of the relation between mode of delivery and atopy at school age

Variables	Atopy		OR (95% CI), *P* value	
	Yes	No	Unadjusted	Adjusted*
Mode of delivery				
Vaginal	105	101	1	1
Cesarean section	44	21	2.0 (1.1-3.6), .02	2.1 (1.1-3.9), .02
Endotoxin levels†				
1st Quartile	34	16	1	1
2nd-4th Quartile	90	81	0.5 (0.3-1.0), .04	0.5 (0.2-0.9), .03
Croup				
No	140	101	1	1
Yes	9	21	0.3 (0.1-0.7), .004	0.3 (0.1-0.6), .003

*Adjusted for mode of delivery, sex, household income, endotoxin level, and croup.
†Of the 271 children who had an assessment of allergic sensitization, 221 had data on indoor endotoxin levels at age 2 to 3 months.

TABLE IV. Analysis of the relation between mode of delivery and asthma at age 9 years

Variables	Asthma		OR (95% CI), *P* value	
	Yes	No	Unadjusted	Adjusted*
Mode of delivery				
Vaginal	35	295	1	
Cesarean section	12	90	1.1 (0.6-2.3), .7	
Bronchiolitis in the first year of life				
No	37	343	1	1
Yes	10	42	2.2 (1.0-4.8), .04	2.3 (1.0-5.2), .04
Highest tertile of dust mite allergen levels (≥2.73 μg/g)				
No	33	319	1	1
Yes	14	66	2.1 (1.0-4.0), .04	2.2 (1.1-4.5), .03
Current maternal asthma				
No	28	279	1	
Yes	18	106	2.3 (1.0-5.2), .05	2.1 (0.8-5.0), .1

*Adjusted for sex, household income, bronchiolitis, highest tertile of bedroom dust mite levels, and current maternal asthma.

caused by differential loss of follow-up in some studies and to differences in design (eg, retrospective vs prospective), characteristics of the populations studied (eg, adults vs children), sample size and statistical power, duration of follow-up, and definition of the outcomes of interest.

Seven studies[8-12,15,17] have examined birth by cesarean section and allergic rhinitis among subjects not selected on the basis of familial history of atopy (see Table V). Of the 5 studies that found no association between cesarean section and allergic rhinitis among unselected subjects, 3 included children younger than 5 years of age (in whom a diagnosis of allergic rhinitis might be difficult),[11,15,17] 2 included adults ages 20 to 31 years,[9,12] and 3 included data from fewer than 81% of eligible participants in their data analysis.[9,11,17] Our finding of an increased risk of allergic rhinitis among children with a parental history of atopy is consistent with the results of 2 studies of children not selected on the basis of a parental history.[8,10]

Five studies have examined birth by cesarean section and atopy (defined as sensitization to at least 1 allergen, as assessed by skin prick testing or IgE measurements) among children not selected on the basis of familial history (see Table V).[7,9,11,14,33] Limitations of the 3 studies that found no association between cesarean delivery and atopy include limited statistical power because of small sample size,[7] potential selection bias,[9,14] and small number of inhalant allergens tested.[9] Two studies of children followed only to the age of 2 years reported a positive association between cesarean delivery and sensitization to at least 1 aeroallergen.[11,33] Eggesbo et al[33] reported that cesarean delivery was associated with a 3-fold increase in the odds of parental report of food allergy (to egg, fish, or nuts) among 2803 Norwegian children followed to age 2 years (95% CI for OR, 1.4-7.3). Of relevance to our findings, the observed association between cesarean delivery and food allergy among Norwegian infants became much stronger after the analysis was stratified by maternal history of allergy. Norwegian children who were born by cesarean section and had a maternal history of allergy had 9-fold higher odds of food allergy than those who were born by vaginal delivery and had no maternal history of allergy (95% CI for OR, 3.1-28). Similar results were reported for birth by cesarean section and allergy or intolerance to cow's milk at age 2 years in a subsequent study of this Norwegian cohort.[34]

Although 7 of 10 previous studies in children not selected on the basis of familial history showed that birth by cesarean section was significantly associated with increased odds of asthma in childhood or adulthood,[7-10,12,13] 5 of these studies estimated only a modest increase in the odds of asthma caused by cesarean delivery (OR range, 1.1-1.3; reviewed in a recent meta-analysis[35]). Thus our negative finding might be due to limited statistical power to detect a weak association between cesarean delivery and asthma. However, we did not detect an association between birth by cesarean section and a major asthma symptom (wheeze) in our longitudinal analyses, for which we had adequate statistical power.

TABLE V. Summary of the results of previous studies of birth by cesarean section and atopy or atopic diseases

Reference	Study design	Duration of follow-up	Sample size at follow-up/baseline	OR (95% CI) for association between cesarean delivery and: Asthma	Hay fever or allergic rhinitis	Sensitization to ≥1 allergen
Kero et al[7]	Retrospective/DB	7 y	59,927	1.2 (1.1-1.4)	NA	1.3 (0.7-2.7)*
Salam et al[8]	Retrospective	8-17 y	2928/6259	1.3 (1.0-1.8)	1.6 (1.2-2.0)	NA
McKeever et al[15]	Retrospective/DB	0-11 y	24,690/29,238	1.1 (1.0-1.1)	1.0 (0.9-1.2)	NA
Xu et al[9]	Prospective†	31 y	1953/11,635	3.2 (1.5-6.8)	1.3 (0.7-2.2)	1.0 (0.6-1.6)
Nafstad et al[17]	Prospective	4 y	2531/3754	1.1 (0.7-1.8)	1.2 (0.7-2.1)	NA
Annesi-Maesano et al[16]‡	Retrospective	1-18 y	4065/4153	1.2 (0.7-2.0)	NA	NA
Maitra et al[14]§	Prospective	7 y	7495/14,062	1.2 (0.9-1.5)	NA	1.1 (0.9-1.5)
Renz-Polster et al[10]	Retrospective/DB	3-10 y	7872/8953	1.2 (1.0-1.5)	1.4 (1.1-1.6)	NA
Negele et al[11]	Prospective	2 y	2500/3097	NA	1.4 (0.8-2.4)	1.7 (1.0-2.9)
Bager et al[12]	Retrospective/DB	20-28 y	9722/10,482	1.3 (1.0-1.7)	1.2 (0.9-1.5)	NA
Eggesbo et al[33]	Prospective	2 y	2803/3621	NA	NA	3.2 (1.4-7.3)
Hakansson and Kallen[13]	Retrospective case-control/DB	1 y	650,959/916,131	1.1 (1.1-1.2)‖	NA	NA

DB, Database; *NA*, not available.

*Of the 59,927 members of the birth registry, 131 underwent allergy skin testing.

†One thousand nine hundred fifty-three of 11,635 subjects in the birth cohort were included in the study. Obstetric data were obtained in all nonnormal births but in only 10% of reportedly normal births.

‡Only emergency cesarean sections were included.

§Five thousand nine hundred sixteen of 14,062 participants underwent allergy skin testing.

‖Asthma was defined as at least 1 hospitalization for asthma.

Children born by cesarean section are not exposed to the maternal vaginal flora, gut flora, or both, which party explains changes in the neonatal microbial flora by mode of delivery.[4,5] Although results from cross-sectional[36-39] and birth cohort studies[6,40] and findings from small clinical trials of probiotics[41-43] suggest that the composition of the neonatal gut flora influences the development of atopy, atopic diseases, or both in childhood, this remains controversial.[5] A longitudinal study of 957 Dutch infants showed that the presence of *Clostridium difficile* in stool samples at age 1 month (assessed by means of quantitative real-time PCR) was associated with increased risk of atopic dermatitis, recurrent wheeze, and allergic sensitization at age 2 years.[6] In that study early colonization with *Escherichia coli* was associated with parental report of eczema but not with objectively diagnosed atopic dermatitis. In contrast to those findings, a smaller study of European infants (n = 324) followed from birth to age 18 months reported that neither time to gut colonization with 11 bacterial groups nor ratio of strict anaerobic to facultative anaerobic bacteria in cultures from neonatal stool samples was associated with eczema or food allergy.[5] We have no neonatal stool cultures and thus cannot assess whether the observed association between cesarean delivery and atopy is due to differences in the neonatal gut flora of study participants by mode of delivery.

We previously reported preliminary findings of an association between cesarean delivery and increased levels of IL-13 and IFN-γ in cord blood,[44] which have in turn been associated with an increased risk for the development of atopy or asthma in childhood.[45-48] Thus cesarean delivery might affect early neonatal immune responses through mechanisms other than alteration of the neonatal gut flora. Such mechanisms can include reduced or absent labor in children born by cesarean section and nonpassage through the birth canal during birth. Labor has been associated with alteration of neonatal immune responses (eg, reduced lymphocytes and $CD4^+$ T_H cells and increased IL-6 levels).[49,50] In rodents oral exposure to LPS during vaginal birth triggers activation of gut epithelial cells.[51] In contrast, activation of the gut epithelia is not found in mice born by cesarean section.

Our findings of an inverse association between each of 2 early-life exposures (indoor endotoxin levels at age 2-3 months and physician-diagnosed croup in the first year of life) and allergic rhinitis at age 9 years confirm and extend our previous findings in this cohort at age 7 years.[25,26]

Our study has 2 limitations in addition to those discussed above. First, allergy skin testing or measurement of IgE to common allergens could only be performed in a subgroup of study participants. Although there could be imbalances in the distribution of potential unmeasured confounders between children who did and did not undergo allergy skin testing or IgE measurements, selection bias is unlikely to be the main explanation for our results because there was no significant difference in the proportion of children born by cesarean section between the groups of children who did and did not undergo an assessment of allergic sensitization. In addition, our findings for atopy were consistent with those for allergic rhinitis, which were based on data for approximately 87% of children at baseline. Second, we could not separately examine the effects of scheduled and unscheduled cesarean deliveries because of limited statistical power.

In summary, our findings suggest that birth by cesarean section leads to an increased risk of allergic rhinitis and atopy among children at high risk of atopy in childhood.

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Clinical implications: Potential development of allergic diseases should be considered as a potential risk of cesarean delivery among children with a parental history of atopy.

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