



Mode of Delivery Is Associated With Asthma and Allergy Occurrences in Children

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PURPOSE: A growing body of evidence indicates that perinatal factors modulate immune development and thereby may affect childhood asthma risk. In this study, we examined the associations between birth by cesarean section (C-section) and atopic disease occurrence in childhood.

METHODS: Subjects were born in California between 1975 and 1987 and were 8 to 17 years old during their enrollment in the Children's Health Study. Our analysis was restricted to 3464 children born at or after 37 weeks of gestation with a birth weight of 2500 g or greater based on birth certificate data. Information about sociodemographic factors, reported physician-diagnosed asthma, and other atopic diseases was obtained by using a self-administered structured questionnaire. Logistic regression models were fitted to compute odds ratios (ORs) and 95% confidence intervals (CIs).

RESULTS: Children born by C-section were at increased risk for asthma (OR, 1.33; 95% CI, 1.01–1.75), hay fever (OR, 1.57; 95% CI, 1.24–1.99), and allergy (OR, 1.26; 95% CI, 1.03–1.53) compared with those born vaginally. Risk associated with C-section was the same for children regardless of family history of asthma or allergy.

CONCLUSION: We conclude that birth by C-section or processes associated with it may increase the risk for atopic disease in childhood.

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INTRODUCTION

Asthma is the most common chronic childhood disease, and understanding its cause is a major research goal (1). Studies have suggested that in utero and early infancy are critical windows during which events and exposures may affect risk for atopic diseases in childhood (2, 3). A parallel increase in prevalences of atopic diseases and cesarean section (C-section) delivery in developed nations has prompted several epidemiologic studies to examine the role of C-section in the cause of atopic diseases.

Limited evidence indicates that mode of delivery may affect asthma and allergy outcomes in children. Although

some researchers observed positive associations between C-section delivery and asthma and allergy risk in children (4–8), Nafstad et al. (9) did not observe an association. These investigators (9) excluded children who required oxygen during the first 6 hours of life. Pregnancy or labor complications may lead to C-section. By excluding children requiring oxygen in the first few hours of life, the investigators may have excluded more children who were born by C-section than by vaginal delivery. This may have resulted in attenuation of risk estimates. In addition, follow-up time for these children was less (e.g., 4 years), and it may not have adequately covered the at-risk period for developing atopic disease. To further investigate the role of mode of delivery on asthma and allergic outcomes during childhood, we examined the association of delivery by C-section on the development of childhood atopic diseases within the uniquely large and diverse population of children born in California and who participated in the Children's Health Study (CHS).

METHODS

The study population and methods for the CHS have been described previously (10, 11), and a number of respiratory health associations with outdoor air pollution have been

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Selected Abbreviations and Acronyms

C-section = cesarean section
 OR = odds ratio
 CI = confidence interval
 CHS = Children's Health Study
 SES = socioeconomic status
 BHR = bronchial hyperresponsiveness

reported (12–17). In brief, 6259 subjects were enrolled in 1993 and 1996 from 12 southern California communities and tracked annually by lung-function testing, self-administered medical history and residential characteristics questionnaires, and monitoring of school absences to assess respiratory health development and its potential association with a number of ambient air pollutants (which were monitored continuously in all communities for the 10-year study duration). Of children recruited into the CHS cohort, 5013 children (80.1%) were born between 1975 and 1987 in the state of California, 702 children were born outside California (11.2%), and the remaining 544 children (8.7%) did not provide sufficient information to reliably determine place of birth. For participants born in California, 4842 birth certificates (96.6%) were obtained from the California Department of Health Services' Birth Statistical Master Files and Birth Cohort Files. Because low birth weight and preterm birth may influence associations between C-section and atopic diseases, we excluded 688 children who were born before 37 weeks of gestation and/or who weighed less than 2500 g at birth, documented by birth certificate data. Subjects with missing covariate information also were excluded from analysis, resulting in a study sample size of 3464 children. The University of Southern California Institutional Review Board approved the study. At study entry, the child's parent or legal guardian provided informed consent.

Detailed information on demographic characteristics and socioeconomic status (SES) was obtained at the time of CHS enrollment. Information on mode of delivery, maternal age at childbirth, birth weight, and birth order of the index child was obtained from birth certificates. Parents or guardians also provided information regarding subjects' history of hay fever, allergy, pneumonia, bronchitis, bronchiolitis, and croup. To assess subject's allergic status, we asked each parent or guardian whether his or her child was allergic to foods or drugs, any inhalant, or dermal allergens other than poison ivy or poison oak. Asthma status was determined based on parental report of physician-diagnosed asthma. Based on the age of asthma onset and persistence patterns, we divided subjects with asthma histories into three categories: early-onset transient, early-onset persistent, and late-onset persistent asthma. Children with early-onset asthma were diagnosed by the age of 3 years, and those with late-onset asthma were diagnosed after the age of 3 years. Children with persistent asthma had wheeze

and/or used asthma medications (i.e., inhaled medications and/or corticosteroid pills or injections) in the 12 months before study entry. Those with transient asthma had no wheeze and had not used asthma medications in the 12 months before study entry.

We computed odds ratios (ORs) and 95% confidence intervals (95% CIs) for associations between mode of delivery and various respiratory outcomes by using logistic regression. Children with missing data for a specific disease outcome were excluded from analyses for that particular outcome. Potential confounding covariates were included in multivariate models. We considered that calendar period of birth may capture changes in indications and management of C-section and examined whether the association between C-section and atopic diseases was modified by calendar period of birth. We also tested for effect modification by maternal, paternal, and parental history of asthma and allergy; maternal smoking during pregnancy; birth weight; and birth order of the index child by using likelihood ratio tests. Pairwise logistic regression was used to assess the role of mode of delivery among the three different asthma subgroups and reported allergies (i.e., to food, drug, inhalants, or dermal exposure). Inference of statistical significance was based on two-sided distributions using a 5% significance level. A commercially available statistical software package (SAS; version 8.2; SAS Institute, Inc., Cary, NC) was used for all analyses.

RESULTS

Most of the children were middle-class non-Hispanic or Hispanic white, based on annual family income, parent or guardian education level, and health insurance coverage at the time of CHS enrollment (Table 1). The majority of mothers were older than 20 years at the time of delivery of the index child, and 18.8% smoked during pregnancy. Prevalence of C-section was 20.7%. Mean birth weights in children born by C-section and vaginally were 3545 g (SD, 500.5 g) and 3509 g (SD, 458.0 g), respectively. The difference in mean birth weights attained borderline statistical significance ($p = 0.08$, independent t -test). Mean age of participants at the time of enrollment in the CHS was 10.5 years (SD, 2.2 years; range, 8 to 17 years). The proportion of children born by C-section increased over time. Between the calendar periods 1975 to 1977, 1978 to 1980, 1981 to 1983, and 1983 to 1987, proportions of children born by C-section were 12.9%, 17.7%, 20.2%, and 25.1%, respectively ($p < 0.0001$).

Children born by C-section were at increased risk for physician-diagnosed asthma (OR, 1.33; 95% CI, 1.01–1.75), hay fever (OR, 1.57; 95% CI, 1.24–1.99), and allergy (OR, 1.26; 95% CI, 1.03–1.53; Table 2). Although the OR

TABLE 1. Selected characteristics of the study participants from the Children's Health Study born at term in California between 1975 and 1987

	N ^a	(%)
Age (years)		
8–9	2131	(51.3)
10–11	864	(20.8)
12–13	645	(15.5)
≥ 14	514	(12.4)
Race		
Non-Hispanic White	2450	(59.3)
Hispanic White	1168	(28.3)
African-American	198	(4.8)
Asian	110	(2.7)
Other	204	(4.9)
Sex (boys)	2015	(48.5)
Maternal asthma	476	(11.8)
Maternal allergy	1317	(32.9)
Paternal asthma	343	(8.8)
Paternal allergy	1056	(27.9)
Maternal smoking during pregnancy	764	(18.8)
Secondhand smoke exposure	1641	(40.1)
Covered by health insurance	3511	(86.2)
Birth by cesarean section	717	(20.7)
Child kept in special care unit after birth		
Maternal age at childbirth (years)		
<20	282	(6.9)
21–25	577	(13.9)
26–30	1382	(33.3)
31–35	1350	(32.5)
> 35	845	(20.3)
Birth order		
1	1740	(42.0)
2	1399	(33.8)
3	636	(15.3)
> 3	368	(8.9)
Birth weight (g)		
2500–2999	467	(13.5)
3000–3250	547	(15.8)
3251–3500	782	(22.6)
3501–3750	657	(19.0)
3751–4000	504	(14.5)
> 4000	507	(14.6)
Season of birth		
Winter (Jan-Mar)	1003	(24.2)
Spring (Apr-Jun)	1092	(26.3)
Summer (Jul-Sep)	1061	(25.5)
Fall (Oct-Dec)	998	(24.0)
Informant's education		
<12th grade	510	(12.6)
12th grade	849	(20.9)
Some college	1825	(45.1)
College	396	(9.8)
Some graduate	470	(11.6)
Annual family income (\$)		
<15,000	584	(16.6)
15,000–49,999	1480	(41.9)
≥50,000	1466	(41.5)

^aTotals differ due to missing values.

for late-onset persistent asthma was stronger (OR, 1.48; 95% CI, 1.05–2.09), ORs for different subgroups of asthma (early-onset transient, early-onset persistent, and late-onset persistent) were not statistically significantly different from one another. In multivariate analysis, the OR for inhalant allergy was 1.19 (95% CI, 0.94–1.50). Birth by C-section was associated with other infectious respiratory diseases (e.g., pneumonia, bronchitis, bronchiolitis, and croup) in univariate analysis (OR, 1.21; 95% CI, 1.02–1.45); however, ORs were not statistically significant in multivariate analysis.

Because there was overlap between asthma and allergy outcomes, we compared children with asthma alone, allergy alone, or both asthma and allergy with those who had neither asthma nor allergies. We found no substantial differences in ORs among the three groups with asthma and/or allergy (Table 3).

In mothers with and without a history of asthma, C-section rates were 20.3% (i.e., 619 of 3056 mothers) and 24.0% (98 of 408 mothers), respectively ($p = 0.08$, chi-square test). However, maternal history of asthma did not modify the associations between birth by C-section and any of the outcomes of interest (all $p \geq 0.10$). Maternal allergy, paternal history of asthma or allergy, maternal smoking during pregnancy, birth weight, calendar period of birth, and birth order of the index child also did not modify any of these associations.

DISCUSSION

In the present study, we observed that mode of delivery was associated with early childhood asthma and allergy occurrences, and children born by C-section were at increased risk for asthma, hay fever, and allergy compared with those who had a vaginal birth. Although the mechanisms by which C-section may affect asthma, allergy, and hay fever occurrences are not completely understood, there are several biologically plausible mechanisms by which C-section may affect asthma, allergy, and hay fever occurrences in children.

First, differences in immune development in early life between children born vaginally and by C-section may be important. Intestinal bacterial flora are important in immune development (18), and children with atopic diseases have been found to have lower gut levels of *Bacteroides* and *Bifidobacterium* species than children without atopic disease (19, 20). Bifidobacteria have probiotic properties and are associated with reduced risk for atopic disease in children (21). C-Section has been shown to delay and alter the development of intestinal bacterial flora in infants (22). This may, in turn, alter immune development and subsequently increase the risk for atopic disease in children.

TABLE 2. Associations between mode of delivery and different respiratory and allergic outcomes

	Ever asthma	Early transient asthma (diagnosed by 3 years of age)	Early persistent asthma (diagnosed by 3 years of age)	Late-onset persistent asthma (diagnosed > 3 years of age)	Hay fever
	Ca/Co ^a	Ca/Co ^a	Ca/Co ^a	Ca/Co ^a	Ca/Co ^a
Mode of delivery					
Vaginal	379/2344	39/2344	134/2344	182/2344	403/2143
Cesarean section	129/584	15/584	40/584	71/584	154/510
Unadjusted OR (95% CI)	1.37 (1.10–1.70)	1.54 (0.85–2.82)	1.20 (0.83–1.73)	1.57 (1.17–2.09)	1.61 (1.30–1.98)
Adjusted ^b OR (95% CI)	1.33 (1.01–1.75)	1.81 (0.92–3.59)	1.17 (0.74–1.84)	1.48 (1.05–2.09)	1.57 (1.24–1.99)
	Any allergy	Food or drug allergy	Inhalant allergy	Dermal allergy	Other respiratory diseases ^c
	Ca/Co ^a	Ca/Co ^a	Ca/Co ^a	Ca/Co ^a	Ca/Co ^a
Mode of delivery					
Vaginal	775/1884	232/1884	536/1884	118/1884	776/1903
Cesarean section	249/448	67/448	168/448	29/448	232/469
Unadjusted OR (95% CI)	1.35 (1.13–1.61)	1.22 (0.91–1.62)	1.32 (1.08–1.61)	1.03 (0.68–1.57)	1.21 (1.02–1.45)
Adjusted ^b OR (95% CI)	1.26 (1.03–1.53)	1.18 (0.85–1.62)	1.19 (0.94–1.50)	1.07 (0.67–1.70)	1.05 (0.87–1.27)

OR, odds ratio; CI, confidence interval.

^aNumber of subjects with/without the disease under study who were born at or after 37 weeks of gestation with birth weight of 2500 g or greater.^bAdjusted for age (as a continuous variable), sex, race, birth order, birth weight, community of residence, parental or guardian education, health insurance coverage, parental history of asthma and allergy, exposure to in utero smoking, exposure to secondhand smoke, maternal age at childbirth, requirement for special care after birth, calendar period of birth, and history of pneumonia, bronchitis, bronchiolitis, and croup.^cPneumonia, bronchitis, bronchiolitis, and croup.

Second, women and unborn children requiring C-section are more likely to have deliveries complicated by intrauterine infection or chorioamnionitis. Such intrauterine exposure to microbial antigens and the associated immunologic stimulation have been suggested to increase the risk for asthma (23). In addition, because women requiring C-section are less likely to breast-feed (24), their children lose the protection against childhood asthma offered by successful breast-feeding (25). Finally, children born by C-section do not experience the forcible removal of amniotic fluid from their lungs during passage through the birth canal. As a result, these children are much more likely to experience “wet lung” or transient tachypnea of the newborn (26). Such impaired fluid clearance may alter multiple aspects of pulmonary physiology and act as an asthma inducer in susceptible children (27). For the present study, we did

not have information on intrauterine infection and breast-feeding to adjust for these factors. Therefore, we did not have data to directly assess this potential bias. However, we conducted a sensitivity analysis to examine whether breast-feeding confounded the observed associations by using data from a nested case-control study (3) that included a subset of 569 subjects of this study. We observed little change in associations between C-section and atopic diseases when we adjusted for breast-feeding. Based on these results, it is unlikely that our results are explained by confounding by differences in breast-feeding by mode of delivery.

Early life exposures to allergens may vary by mode of delivery, and absence or avoidance of these factors may reduce the risk for atopic disease. Although we did not have information about dust mites, we had information collected at

TABLE 3. Mode of delivery on joint outcomes of asthma and allergy

Mode of delivery	No asthma or allergy	Only asthma	Only allergy	Both asthma and allergy
Vaginal	1735	134	534	235
Cesarean section	400	45	167	81
Unadjusted OR (95% CI)	1.0	1.46 (1.02–2.08)	1.36 (1.11–1.67)	1.50 (1.14–1.97)
Adjusted ^a OR (95% CI)	1.0	1.57 (1.03–2.41)	1.34 (1.07–1.67)	1.50 (1.02–2.20)

OR, odds ratio; CI, confidence interval.

^aAdjusted for age (as a continuous variable), sex, race, birth order, birth weight, community of residence, parental or guardian education, health insurance coverage, parental history of asthma and allergy, exposure to in utero smoking, exposure to secondhand smoke, maternal age at childbirth, requirement for special care after birth, calendar period of birth, and history of pneumonia, bronchitis, bronchiolitis, and croup.

baseline about the presence of carpet, pets, and mold or mildew at home. We observed little change to the associations between C-section and atopic diseases when we adjusted for these potential confounders. In addition, associations between C-section and atopic diseases remained similar irrespective of these exposures.

Our findings also are consistent with a number of previous studies (4–6). Earlier studies showed a positive association between maternal asthma and C-section (28, 29). In our study, we also observed greater C-section rates in mothers with a history of asthma, but the associations between C-section and atopic diseases were not modified by maternal history of asthma or maternal smoking during pregnancy.

Definitions of asthma and allergy in this study were based on physician-diagnosed asthma and paternal report of allergic history, respectively. Although some researchers recommend testing for bronchial hyperresponsiveness (BHR) to define asthma, others have shown that such testing decreased sensitivity, and combining BHR results with questionnaire data further decreased it (30, 31). Based on this evidence, it does not appear that the validity of questionnaire-based classification of asthma phenotype is improved by testing BHR in children (32). We used the International Study of Asthma and Allergies in Childhood definition for asthma, one that has been used widely in epidemiologic studies of asthma (33). Because asthma is the most common chronic illness in childhood, children with asthma may need to access health care more often than their healthy peers. In this study, the majority of subjects had health insurance. When we adjusted for health insurance status, we found little change in any of the estimates, suggesting that health care access did not account for the observed results. There may have been some misclassification in assessing the hay fever, allergy, and respiratory infection outcomes by using our questionnaire data. However, the misclassification is likely to be nondifferential and may have biased results toward null.

Although we adjusted for parental education and health insurance coverage as surrogate for subject SES and community of residence as surrogate for air pollution, we acknowledge the possibility of residual confounding by these factors. In addition, SES may have affected the ascertainment of physician-diagnosed asthma. Residual confounding also is possible for the other variables used to obtain adjusted estimates, and there may be other potential confounders that were not adjusted for in our analysis. However, the consistent effect estimates for different outcomes provide some support that the findings did not result from ascertainment bias, residual confounding, or failure to adjust for other potential confounders.

In California, information on birth weight, maternal age at childbirth, and mode of delivery obtained from birth certificates has been found to be valid and reliable, but data on

pregnancy, labor complications, and Apgar scores are less complete (34). Because C-section was associated positively with premature birth ($p = 0.08$) and the latter may result from pregnancy complications, we restricted our analysis to children born at term (≥ 37 weeks of gestation). To address confounding by labor complications, we inquired whether the child was kept in a special care unit at a hospital after birth, and analyses were adjusted accordingly. Because we observed good agreement between maternal recall of birth weight and birth weight information culled from birth certificates (κ statistic = 0.75; 95% CI, 0.71–0.80; data not shown), maternal recall of the child's admission to a special care unit after birth was considered relatively reliable and a potential surrogate for labor complications affecting fetal and neonatal health.

The proportion of children born by C-section increased during the study period and was similar to prevalence rates observed in California and in the United States (35–38). This suggests that our sample was representative of the source population. Because associations between C-section and atopic diseases remained similar by calendar period of birth, these associations may not be explained completely by the change in indications for and management of C-section birth that occurred over time. Birth weight, maternal asthma, and maternal smoking are associated with C-section and potentially could modify the associations between C-section and atopic disease. Unlike previous studies, we addressed the issue of effect modification by these factors in our study and observed that the associations remained similar regardless of birth weight, maternal asthma, and maternal smoking.

In conclusion, our findings suggest that mode of birth may influence asthma and allergy occurrences in children. If this is true, then increases in C-section birth rates during the last several decades also may help to explain the observed increase in asthma occurrences in children.

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