



Cesarean delivery and the risk of allergic rhinitis in children

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ABSTRACT

Background: Cesarean delivery (C-section) may influence the infant microbiome and affect immune system development and subsequent risk for allergic rhinitis (AR).

Objective: To investigate the association between C-section and AR at ages 6, 8, and 10 years.

Methods: Data were collected prospectively through Kaiser Permanente Northern California's (KPNC) integrated healthcare system. Children were eligible if they were born in a KPNC hospital and remained in the KPNC system for minimum 6 years ($n = 117,768$ age 6; $n = 75,115$ age 8; $n = 40,332$ age 10). Risk ratios (RR) for C-section and AR were estimated at each follow-up age and adjusted for important covariates, including intrapartum antibiotics, pre-pregnancy body mass index, maternal allergic morbidities, and breastfeeding. Subanalyses considered information on C-section indication, labor, and membrane rupture.

Results: After adjusting for confounders, we did not observe an association between C-section and AR at follow-up ages 6, 8, or 10 years (RR [CI]: 6 years, 0.98 [0.91, 1.04]; 8 years, 1.00 [0.95, 1.07]; 10 years, 1.03 [0.96, 1.10]). In stratified analyses, there was limited evidence that C-section increases the risk of AR in certain subgroups (eg, children of non-atopic mothers, second or higher birth order children), but most estimated risk ratios were consistent with no association. Estimated associations were unaffected by participant attrition, missing data, or intrapartum antibiotics.

Conclusion: C-section delivery was not associated with AR at follow-up ages of 6, 8, or 10 years in a large contemporary US cohort.

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Introduction

Allergic rhinitis (AR) is the most common allergic disease worldwide and has been increasing in prevalence over the past century.¹ This increase has been attributed to improved hygiene, increased allergen and air pollution exposure and lifestyle changes.^{2,3} These changes may decrease childhood exposure to microorganisms which could increase susceptibility to allergic diseases, a theory known as the hygiene hypothesis.^{4–6} Currently, in the United States, AR prevalence is estimated to be 10% to 40% depending on case definition and study population.^{7,8}

One of the earliest sources of microbial exposure for infants is during delivery.^{9,10} Infants born vaginally have different microbiomes in the first months of life than infants born through cesarean (C-section) delivery, possibly because of differences in the transfer of maternal microbiota during birth.^{11,12} However, the

reported association between mode of delivery and allergic disease may, in part, be because of confounding factors that are associated with C-section and can affect the microbiome (eg, intrapartum antibiotics, absence of labor, higher maternal body mass index (BMI), and breastfeeding initiation and duration), and not differences in the mode of delivery.

The association between C-section and AR was examined in a 2008 meta-analysis of 7 studies (odds ratio [OR] [95% CI]: 1.24 [1.08, 1.43]), but methodological, temporal, and geographic differences between included studies make it difficult to draw a conclusion about the causal relationship between mode of delivery and AR.¹³ Studies published since the meta-analysis report inconsistent conclusions, with effect estimates ranging from 0.80 to 1.86.^{14–19} The limited data on C-section and AR can also be examined in the context of the atopic march, the natural progression of allergic disease from atopic dermatitis to AR and asthma.²⁰ Previous studies of mode of delivery have generally reported a null association with atopic dermatitis and a positive association with asthma.^{13,21}

The aim of this study was to examine the association between mode of delivery and AR among children in an integrated health care delivery system in the United States. We examined this

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question in a large, contemporary longitudinal cohort using electronic health records, pharmacy-dispensing data, state birth records, and prospectively collected breastfeeding survey data. Based on these data, we aimed to estimate the association between C-section and AR more precisely and account for sources of bias that may have influenced previously reported estimates.

Methods

Study Population

The study population included all live, singleton births from January 1, 2005, to January 2, 2012, in the Kaiser Permanente Northern California (KPNC) integrated healthcare delivery system. Multiple births were excluded because of their strong differences in delivery characteristics and early childhood outcomes. Children were included in the study if they had continuous enrollment (allowing for a 90-day gap; short-term gaps in enrollment often occur because of delayed paperwork) through minimum age of 6 years or until the end of the study, December 31, 2017. The age 8- and 10-year follow-up cohorts were a subset of the age 6 cohort, defined by a child remaining enrolled and reaching each follow-up age before the end of the study. Decreased sample size by follow-up age was because of both administrative censoring (ie, not reaching later follow-up ages by December 31, 2017) and dropout from the KPNC system. In addition to information from electronic health records (EHR), children born before 2013 had information from state birth records which was used to supplement information in the EHR. Within our study population, a subsample of births born predominantly after 2008 included more detailed information about labor, delivery, and C-section characteristics; throughout this paper, we will refer to this group as the post-2008 subset. Because of reduced available follow-up time, the post-2008 subset only included full-term births (≥ 37 weeks) with follow-up at ages 6 and 8 years.

Mode of Delivery Definition

Mode of delivery was identified in the EHR. In the full cohort, births were categorized as either C-section deliveries or vaginal

deliveries. In the post-2008 subset, full-term C-section deliveries were more finely categorized in 3 different ways. First, C-sections were classified based on the presence or absence of labor, using labor times recorded in the EHR. Second, C-sections were divided by the likelihood of exposure to maternal vaginal microbiota during delivery, based on membrane rupture times in addition to labor information. Infants were classified as being exposed to the maternal vaginal microbiota if they had a documented labor or membrane rupture time and membrane rupture time was >10 minutes before delivery. The third classification of C-section births was based on the recorded indication for the C-section in the EHR and the birth record. C-section indications were categorized hierarchically into the following 7 exclusive categories: (1) breech or other malpresentation, with no evidence of labor; (2) breech or other malpresentation, with evidence of labor; (3) repeat C-sections, with no evidence of labor; (4) fetal intolerance or non-reassuring fetal status; (5) failure to progress or cephalopelvic disproportion; (6) all other C-sections with evidence of labor; and (7) all other C-sections without evidence of labor.

Allergic Rhinitis Definition

Allergic rhinitis was defined at each age (6, 8, and 10 years) using the International Classification of Disease (ICD) diagnosis codes from the EHR and prescription information from the pharmacy-dispensing dataset. Because of the potential for misclassification and priority of reducing false positives, which determine bias in the risk ratio,²² our primary outcome definition required the following: (1) 2 AR diagnosis codes (ICD-9: 477; ICD-10: J30) minimum 30 days apart; and either (2a) one AR medication, or (2b) a third AR diagnosis code. Allergic rhinitis medications included nasal corticosteroids and second-generation antihistamines.²³ As a broader secondary outcome measure, we defined AR as follows: (1) one AR diagnosis code; and either (2a) 2 prescriptions for AR minimum 30 days apart, or (2b) a second AR diagnosis code. To meet the case definition at each age, minimum one diagnosis code or prescription must have been within the previous 2 years; therefore, it was possible for individuals' disease status to change across follow-up ages. The pattern of meeting the primary case definition across ages is shown in Figure 1. All

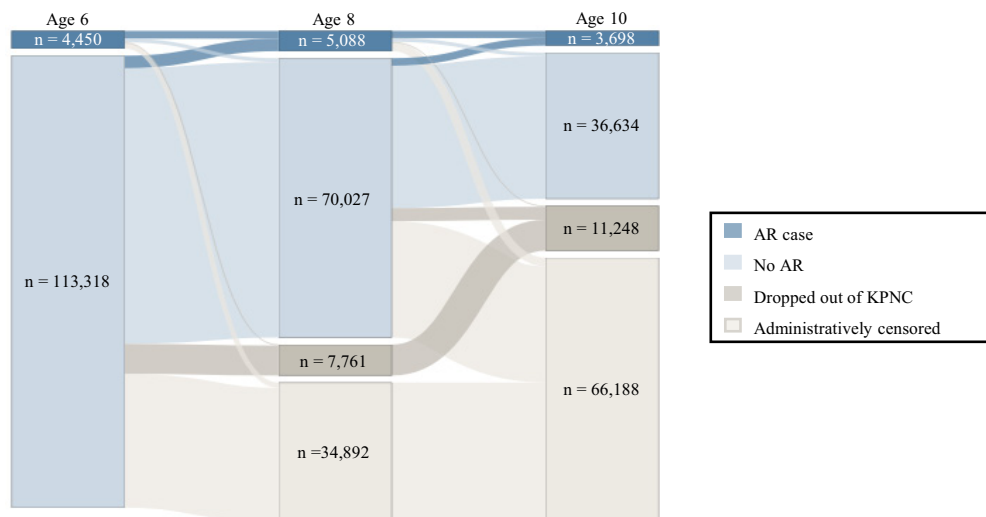


Figure 1. Sankey plot depicting the number of children meeting the case definition for allergic rhinitis (primary definition) at each follow-up age and showing the loss to follow-up over time. It shows the number of participants at each follow-up age that was classified as an AR case (dark blue) or not as an AR case (light blue). At ages 8 and 10 years, the gray boxes represent the number of children who were lost to follow-up. The dark gray represents the number of participants that dropped out of Kaiser Permanente Northern California; the light gray represents the number of participants who were administratively censored (child had not reached follow-up age when the study ended). AR, allergic rhinitis; KPNC, Kaiser Permanente Northern California.

Table 1

Maternal and Child Characteristics, Age 6 Years

	C-section ^b (%) (n = 31,708)	Primary AR ^b (%) (n = 4450)	Total ^a (%) (n = 117,768)
Maternal characteristics			
Age			
<25	17.8%	4.0%	10.3%
25-29	22.2%	3.6%	27.5%
30-34	26.9%	3.7%	35.5%
35-39	33.9%	3.9%	21.2%
40+	41.3%	4.1%	5.4%
Education			
<12 years	23.6%	3.8%	4.9%
12-15 years	26.6%	4.2%	44.0%
16 + years	27.4%	3.4%	50.1%
Missing	32.8%	4.2%	1.0%
Race			
White	26.5%	3.1%	40.8%
Black	33.0%	6.9%	5.9%
API	26.4%	3.8%	26.6%
Hispanic	26.6%	4.0%	22.4%
Other	27.4%	4.1%	4.3%
Pre-pregnancy BMI			
Underweight (<18.5)	17.3%	3.5%	2.0%
Normal (18.5-24.9)	22.8%	3.6%	45.3%
Overweight (25-29.9)	28.4%	4.0%	24.4%
Obese (≥30)	36.8%	4.4%	19.3%
Missing	24.7%	3.1%	9.0%
Antibiotics during pregnancy			
Yes	28.3%	4.6%	29.6%
No	26.4%	3.5%	70.4%
Asthma			
None	26.4%	3.4%	82.9%
History	30.7%	6.1%	10.9%
Active	26.8%	4.3%	6.2%
Allergic rhinitis			
Yes	28.0%	5.1%	42.7%
No	26.1%	2.8%	57.3%
Atopic dermatitis			
Yes	28.3%	4.8%	10.9%
No	26.8%	3.6%	89.1%
Food allergy			
Yes	29.5%	6.4%	3.2%
No	26.8%	3.7%	96.8%
Other allergy			
Yes	29.2%	5.3%	11.6%
No	26.6%	3.6%	88.4%
Child characteristics			
Sex			
Male	28.1%	4.5%	51.2%
Female	25.7%	3.0%	48.8%
Gestational age			
Preterm	39.9%	4.6%	6.7%
Full term	26.0%	3.7%	93.3%
Birthweight			
<2500 g	41.7%	4.6%	4.5%
2500-4000 g	24.8%	3.7%	83.8%
>4000 g	36.8%	3.8%	11.7%
Birth order			
First born	28.6%	4.5%	42.4%
Second born	26.4%	3.4%	36.8%
Third + born	23.3%	2.8%	21.8%
Breastfeeding			
None	31.0%	3.8%	10.0%
<3 mos.	28.8%	4.1%	19.7%
3-6 mos.	27.1%	4.2%	11.9%
>6 mos.	25.2%	3.6%	45.6%
Missing	26.7%	3.6%	12.9%

Abbreviations: API, Asian or Pacific Islander; AR, allergic rhinitis; BMI, body mass index; C-section, cesarean delivery.

^aPercents represent the row percents (i.e., the percent of participants within each category that had a C-sections or AR).^bPercents represent the percent of the total population that is within each category (i.e., column percents).

individuals who met the criteria for the primary AR definition also met the less strict criteria for the secondary AR definition. To compare with previous studies, we conducted a sensitivity analysis with AR defined as any AR diagnosis code in the EHR before each follow-up age.

Covariates

Maternal information was collected through linked EHRs in the KPNC system and supplemented with state birth records to fill in missing information. Maternal characteristics that were considered

Table 2

Risk Ratio and 95% Confidence Interval Estimates for Association Between Covariates and Allergic Rhinitis in the Unadjusted Model and the Primary Adjusted Model

	Age 6 (n = 117,768)	Age 8 (n = 75,115)	Age 10 (n = 40,332)
Primary AR definition			
Unadjusted (RR [CI])	1.10 (1.04, 1.18)	1.14 (1.08, 1.21)	1.14 (1.07, 1.22)
Adjusted (RR [CI]) ^a	0.98 (0.91, 1.04)	1.00 (0.95, 1.07)	1.03 (0.96, 1.10)
Secondary AR definition			
Unadjusted (RR [CI])	1.14 (1.08, 1.19)	1.16 (1.11, 1.22)	1.12 (1.06, 1.19)
Adjusted (RR [CI]) ^a	1.01 (0.96, 1.07)	1.04 (0.99, 1.09)	1.02 (0.96, 1.09)

Abbreviations: AR, allergic rhinitis; BMI, body mass index; NICU, neonatal intensive care unit; RR, risk ratio.

^aAdjusted for maternal age, education, race, pre-pregnancy BMI, smoking, antibiotics during pregnancy, maternal asthma, atopic dermatitis, allergic rhinitis, food allergy, other allergy, sex, gestational age, birthweight, NICU admission, birth order, and breastfeeding.

as potential confounders included age at child's birth (<25, 25–29, 30–34, 35–39, ≥40 years), education (<12 years, 12–15 years, ≥16 years, missing), self-identified race (white, black, Asian or Pacific Islander, Hispanic, other), pre-pregnancy BMI (underweight [<18.5], normal [18.5–24.9], overweight [25–29.9], obese [≥30], missing), smoking during pregnancy, antibiotics during pregnancy, asthma during pregnancy (active, history, none), atopic dermatitis, allergic rhinitis, food allergies, and other allergies.

Child characteristics included as covariates from the EHR were sex, gestational age at delivery (<31 weeks, 31 weeks ... 40 weeks, ≥41 weeks), birthweight (<2500 g, 2500–4000 g, >4000 g), neonatal intensive care unit admission >2 days, and birth order (first born, second born, third + born). Infant feeding information was collected prospectively through parental surveys at well-baby visits. Breastfeeding duration was classified based on the duration of any breastfeeding (never, <3 months, 3–6 months, >6 months, missing). A list of ICD codes used in the outcome and covariate definitions is listed in eTable 1.

Statistical Analysis

Distributions of covariates were compared among exposure and outcome groups at each age of follow-up. Risk ratios (RR) and 95% confidence intervals (CI) for AR were estimated using modified Poisson regression models with robust variance estimation. The association between C-section and AR at each age was assessed using our a priori-adjusted model (primary model), which was informed by directed acyclic graphs and included all covariates listed previously.

Missingness of covariate information (education [1% missing], pre-pregnancy BMI [9% missing], and breastfeeding [13% missing], at age 6 years) was handled in 3 different ways, and results from the primary model using each method were compared. Our a priori analysis plan included a “missing” category for each covariate. Second, we conducted a complete case analysis by excluding all individuals who had missing covariate information. Third, we used multiple imputation (20 iterations) to impute missing covariates. We used inverse probability weights (IPW) to determine whether

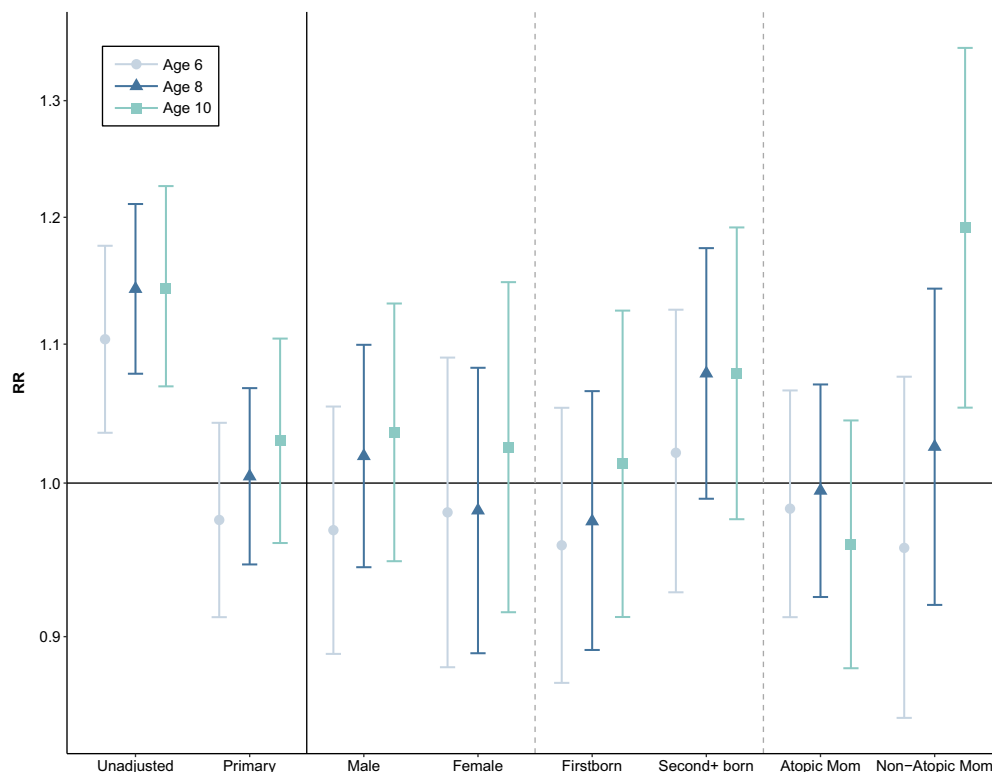


Figure 2. Risk ratio and 95% confidence interval estimates for the association between cesarean delivery and allergic rhinitis (primary definition) at ages 6, 8, and 10 years stratified by age at sex, birth order, and maternal atopy. Risk ratios and 95% CIs for primary adjusted model and each stratified model in the full cohort ($n_6 = 117,768$; $n_8 = 75,115$; $n_{10} = 40,332$). Numeric results were provided in eTable 3. RR, risk ratio.

missing outcome data at each age, because of either administrative censoring or dropout from the KPNC system, had an effect on the estimates. Loss to follow-up, including both administrative censoring and dropout, is indicated in Figure 1.

Effect modification by sex (male/female), gestational age (pre-term/full term), birth order (first born/second + born), maternal atopy (any/none of the following: AR; atopic dermatitis; food allergy; other allergy), and pre-pregnancy BMI (normal/overweight/obese) was examined. Among full-term births in the post-2008 subset, risk ratios were estimated separately for full-term C-sections with and without evidence of labor, with and without exposure to the maternal vaginal microbiota, and by C-section indication (relative to all full-term vaginal deliveries in the post-2008 subset).

To account for intrapartum antibiotics (IABX) as a potential mediator, we conducted the following 2 analyses: (1) an analysis that controlled for IABX in the primary model; and (2) an analysis stratified by group B *Streptococcus* (GBS) status. These analyses were restricted to full-term infants because of lack of GBS laboratory testing results among most preterm births. The analysis conditioning on GBS (#2 in the previous text), the primary reason for IABX apart from C-section, is motivated by concern that conditioning directly on an intermediate can induce collider bias under certain conditions.²⁴

All analyses were completed using the primary and secondary AR definitions, and results were compared across definitions and follow-up ages. Unless otherwise stated, results presented throughout this study refer to the estimated associations for the primary AR definition, which should be less biased by outcome misclassification because of the minimized false positives.²² Results for each age (6, 8, and 10 years) are represented using subscripts

(eg, RR_6 and n_6). All analyses were completed in SAS 9.4 (SAS Institute, Cary, North Carolina).

Results

Our cohort included 117,768 children followed through the age of 6 years ($n_8 = 75,115$; $n_{10} = 40,332$). The majority of attrition was due to administrative censoring (study period ended before child reached follow-up age). Of children in the age 6 cohort, 66% did not have follow-up data at age 10 years; 56% because of administrative censoring and 10% because of un-enrollment from KPNC (Figure 1). The proportion of children meeting the primary AR definition was 3.8%, 6.8%, and 9.2%, respectively, for ages 6, 8, and 10 years. Maternal and child demographics for the age 6 cohort are listed in Table 1. The same patterns were observed for ages 8 and 10 years follow-up groups; distributions of covariates did not differ based on follow-up age or outcome definition. Both C-section delivery and AR were most common among mothers who were more than 40 years old, black, and obese, and among children who were male, born preterm, had a birthweight <2500 g, and were firstborn children. In addition, C-sections were more common among mothers with more years of education and among children who were never breastfed.

Primary Definition Results

Although C-section was positively associated with AR in unadjusted analyses (Table 2), after controlling for potential confounders, no associations were observed in our primary model (RR_6 [CI]: 0.98 [0.91, 1.04]; RR_8 [CI]: 1.00 [0.95, 1.07]; RR_{10} [CI]: 1.03 [0.96, 1.10]). Models adjusted for only 1 covariate did not reveal any single covariate that could account for the decreased estimates. In a post-

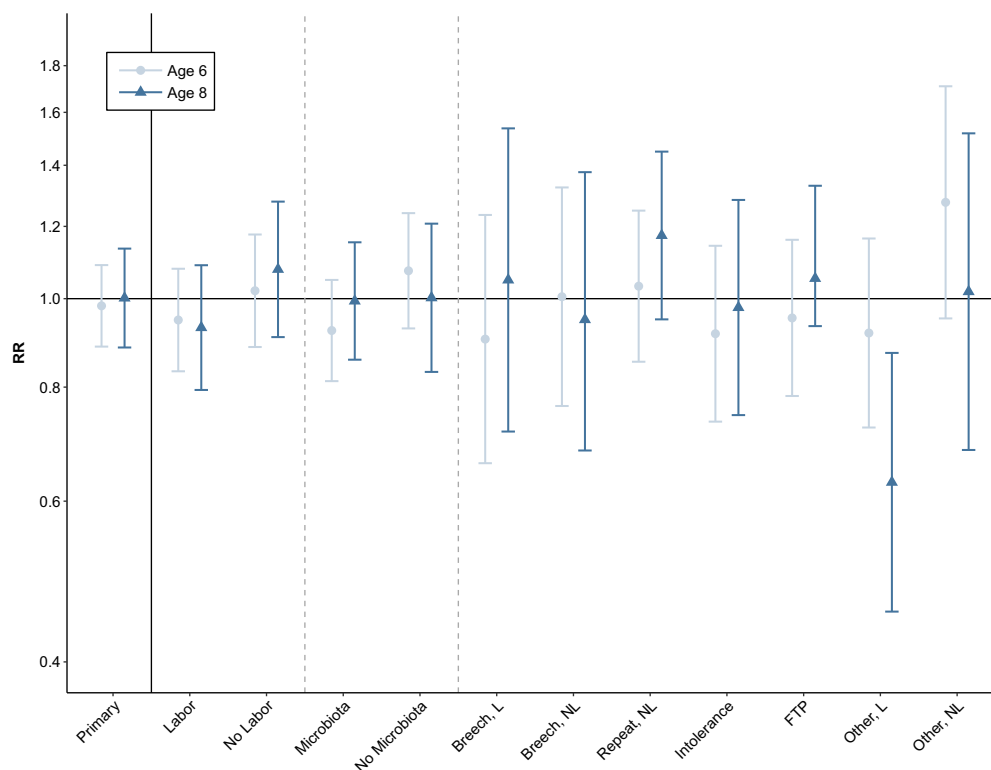


Figure 3. Risk ratio and 95% confidence interval estimates for the association between cesarean delivery and allergic rhinitis (primary definition) at ages 6 and 8 years among the post-2008 subset by presence or absence of labor, exposure to maternal microbiota, and C-section indication (full-term births only). Risk ratios and 95% CIs for primary adjusted model and each stratified model in the full cohort ($n_6 = 52,104$; $n_8 = 18,256$). Numeric results were provided in eTable 5. FTP, failure to progress; L, labor; NL, no labor; RR, risk ratio.

hoc stepwise analysis, inclusion of all covariates except antibiotics during pregnancy, maternal education, and smoking during pregnancy were necessary to reach risk ratios comparable with the primary model.

Covariates that were significantly (P value < .05) associated with an increased risk of AR in our primary model across all follow-up ages included fewer years of education, non-white race, antibiotics during pregnancy, maternal allergies and asthma, male sex, and second or higher birth order (eTable 3 in the online repository). Children of mothers with allergies or asthma were more likely to develop AR compared with children of mothers without allergies or asthma (allergic rhinitis RR_{10} [CI]: 1.56 [1.46, 1.67]; atopic dermatitis RR_{10} [CI]: 1.09 [1.00, 1.19]; food allergy RR_{10} [CI]: 1.31 [1.15, 1.50]; active asthma RR_{10} [CI]: 1.31 [1.20, 1.43]) (eTable 3 in the online repository). These findings were consistent with those reported in the literature.

The 3 methods of handling missing covariate information (inclusion of “missing” category, complete case analysis, and multiple imputation) did not produce meaningfully different risk ratios, and we therefore kept our a priori method of including “missing” covariate categories, which preserved sample size. Using IPW to account for loss to follow-up did not alter estimates, suggesting differences in risk ratios across ages were not due to imbalanced dropout. Stratification by sex, gestational age, or pre-pregnancy BMI yielded similar risk ratio estimates across strata. However, differences in the C-section risk ratios were suggested between birth order strata and between maternal atopy strata for all follow-up ages (Fig 2; eTable 2 in the online repository). The association between C-section and AR was stronger among children of mothers without allergies (RR_{10} [CI]: 1.19 [1.05, 1.35]) than mothers with allergies (RR_{10} [CI]: 0.96 [0.88, 1.04]). The Z-test for comparison of C-section β -estimates across maternal allergy categories was 2.84, P value = .002. Although not significantly different (P value > .05), the risk ratio for the effect of C-section on childhood AR was consistently stronger among children who were second or higher birth order compared with children who were first born (RR_{10} [CI]: 1.08 [0.98, 1.19] vs RR_{10} [CI]: 1.01 [0.91, 1.13]; Z-test = 0.84, P value = .20).

Secondary Definition Results

Using the secondary, broader AR outcome definition, the proportion of children meeting the outcome definition across follow-up ages was 6.1%, 9.5%, and 11.9%, respectively. Results were consistent with those based on our primary outcome definition for the primary model (Table 2) and all stratified models (eTable 4 and eFig 1 in the online repository). The sensitivity analysis based on an outcome definition of only one AR diagnosis code yielded risk ratios that were generally compatible with our other AR definitions (RR_6 [CI]: 1.04 [1.01, 1.07]; RR_8 [CI]: 1.03 [1.00, 1.06]; RR_{10} [CI]: 1.03 [1.00, 1.06]).

Analysis of C-Section Characteristics

Among the post-2008 subset ($n_6 = 52,104$; $n_8 = 18,256$), risk ratios from the primary model were comparable with results from the full cohort (RR_6 [CI]: 0.98 [0.89, 1.09]; RR_8 [CI]: 1.00 [0.88, 1.13]). When C-sections were divided by labor or microbiota exposure, risk ratios between C-section groups did not show clear differences for the primary AR outcome definition; all were compatible with the null for both follow-up ages (Fig 3; eTable 5 in the online repository). For the secondary AR definition, children born through C-section without labor had an increased risk of AR compared with children born vaginally (RR_8 [CI]: 1.17 [1.01, 1.35]). However, significant effect modification by labor was only evident for the age 6 cohort (Z-test = 2.91, P value = .004). The risk ratio for C-section

without vaginal microbiota exposure (RR_6 [CI]: 1.19 [1.07, 1.33]) was higher than the risk ratio for C-section with microbiota exposure (RR_6 [CI]: 0.91 [0.83, 1.01]) at age 6 (Z-test = 3.51, P value < .001); there was no difference between C-section microbiota groups at age 8 years (Z-test = 1.00, P value = .32) (eTable 5 and eFig 2 in the online repository).

When C-sections were divided by indication, there was no evidence that any particular C-section indication was associated with an elevated risk of AR (Fig 3; eTable 5 in the online repository). For the secondary AR definition, indications that included the absence of labor (breech or other malpresentation, no labor; repeat C-section, no labor; other, no labor) had marginally elevated risk ratios; however, most estimates were still compatible with the null (eTable 5 and eFig 2 in the online repository).

Intrapartum Antibiotic Analysis

Analyses among full-term infants designed to remove any indirect effects of C-section mediated by intrapartum antibiotics (including IABX as a covariate and stratifying by GBS status) were consistent with results from the primary model. Results were similar for both the primary and secondary AR definitions (eTable 6 in the online repository).

Discussion

In this large longitudinal birth cohort study of mother-child-linked KPNC members, we observed no overall association between C-section and AR when adjusted for important covariates. Our estimates, both unadjusted and adjusted, were lower than the previous reported pooled OR of 1.24 (CI: 1.08, 1.43).¹³ Before our study, there had only been 2 moderately sized ($n = 8953$ and $n = 3464$), US-based cohorts examining C-section and AR diagnosis in childhood with both reporting a positive association.^{25,26} This study investigated this association in a larger US cohort using more current data, which was necessary because sociodemographic and racial patterns of AR vary across time and location. Our study was also able to account for several potentially important confounders that meaningfully attenuated our unadjusted risk ratio.

Stratification by sex, maternal allergies, maternal BMI, birth order, or gestational age also yielded results that were generally consistent with the null. However, we observed some evidence of an increased risk of AR associated with C-section among children of non-atopic mothers. This result was not consistent with a previous study that examined the association between mode of delivery and AR among children with a history of parental atopy (OR [CI]: 1.8 [1.0, 3.1]).¹⁵ There was also a suggested increased risk of AR associated with C-section among second or higher order children in our primary model, a group that has a lower baseline risk of AR, as indicated in our study and in previous studies.^{27,28} This result was also consistent with our analysis of C-sections by indication showing an increased risk at age 8 years observed among children born through repeat C-section with no evidence of labor (ie, all of whom are second or higher birth order).

Subgroup analyses by C-section characteristics revealed that C-sections without exposure to the maternal microbiome (no evidence of labor; no microbiota exposure; breech, no labor; repeat, no labor; other, no labor) in general had elevated risk ratios compared with C-sections that would have been exposed to the maternal microbiota. Recent research has shown that mode of delivery affects the infant microbiome¹²; however, it is important to observe how these alterations translate into evidence of increased morbidity. Despite finding risk ratios that were generally compatible with the null, our results are an important next step to understanding how the infant microbiome, in conjunction with maternal and infant characteristics, can affect health later in life.

The few significant results observed should be interpreted in light of the number of risk ratios estimated in our study.

The reliance on EHR data to determine AR status may have incorrectly classified some children as being non-diseased. This is because in the general population, AR is often self-diagnosed and treated with over-the-counter medications, which would not be recorded in the EHR. Therefore, the AR cases in our study consisted of children who had more severe AR that required physician visits and prescription medications. Our strict AR definition was selected for its high specificity; the higher the specificity, the less bias there is in the risk ratio, independent of the sensitivity.²² We chose to require minimum 2 ICD diagnosis codes minimum 30 days apart because this represented 2 separate clinical encounters vs our secondary definition which could be met with only one clinical encounter.

A strength of our study was the use of prospectively collected delivery, AR, and covariate information. Our large sample size and nature of prospective EHR data allowed us to include potential confounders, such as breastfeeding duration, pre-pregnancy BMI, maternal allergies, and gestational age, which were often excluded in previous studies. Covariates, such as pre-pregnancy BMI, maternal allergies, and breastfeeding, collected through repeat maternal surveys, had not been considered together before our study. Only one previous study¹⁸ included maternal pre-pregnancy BMI in their analyses and 2 included maternal allergies as covariates.^{18,26} In our study, these 2 covariates had the strongest effects in the single covariate-adjusted models, and their exclusion in previous studies may have led to a spurious association between C-section and AR. Despite the benefits of EHR data, there is the potential for unmeasured confounding because of the lack of control for paternal characteristics and lifestyle factors, but only if they are associated with both C-section and AR.

We assessed selection bias due to missing outcome data in our study by using IPW. Selection bias was a concern because it is possible that dropout from the KPNC system differed based on AR status. When we applied IPW to our primary model, which considers the likelihood of a child staying enrolled in KPNC based on measured variables, our estimates did not meaningfully change, and therefore, we can conclude that selection bias due to dropout had little effect on the risk ratios at follow-up ages 8 and 10 years.^{29,30} Similarly, our approach to account for missing covariates (breastfeeding, pre-pregnancy BMI, and education) did not suggest an effect of missing data on the estimated association.

In this study, we did not observe an association between C-section delivery and the risk of AR at ages 6, 8, or 10 years in a large US cohort. In subgroup analyses, there appeared to be an increased risk of AR associated with C-section among second or higher born children and among children of mothers without a history of clinically diagnosed allergic conditions, but these positive findings should be interpreted in light of the multiple comparisons and lack of previous support for these findings. Thorough examination did not reveal evidence that our results were biased because of loss to follow-up, missing covariate information, or IABX.

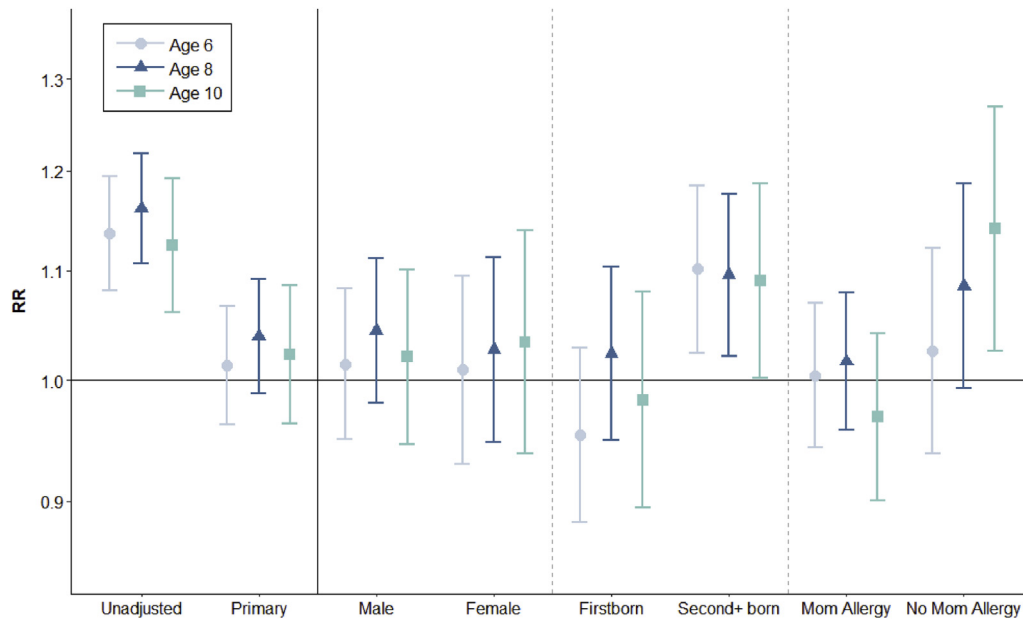
Supplementary Data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.jana.2020.04.028>.

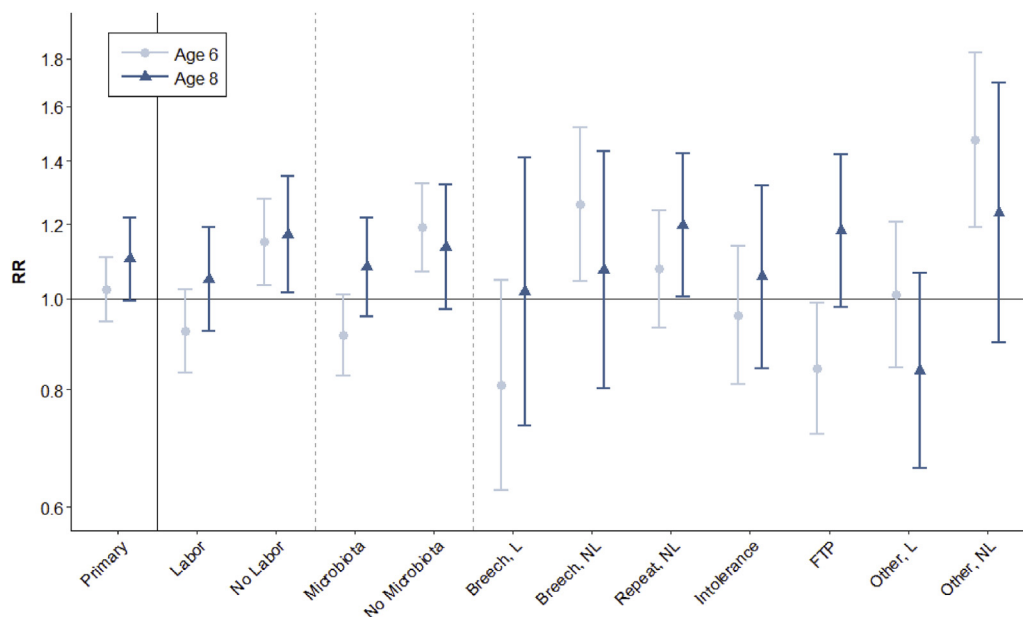
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Appendix



eFigure 1. Risk ratio and 95% confidence interval estimates for the association between cesarean delivery and allergic rhinitis (secondary definition) at ages 6, 8, and 10 years stratified by age at sex, birth order, and maternal atopy. Risk ratios and 95% CIs for primary adjusted model and each stratified model in the full cohort ($n_6 = 117,768$; $n_8 = 75,115$; $n_{10} = 40,332$). Numeric results were provided in [eTable 4](#).



eFigure 2. Risk ratio and 95% confidence interval estimates for the association between cesarean delivery and allergic rhinitis (secondary definition) at ages 6 and 8 years among the post-2008 subset by presence of absence of labor, exposure to maternal microbiota, and cesarean delivery indication. Risk ratios and 95% CIs for primary adjusted model and each stratified model in the full cohort ($n_6 = 52,104$; $n_8 = 18,256$). Numeric results were provided in [eTable 5](#). FTP, failure to progress; intolerance, fetal intolerance; L, labor; NL, no labor.

eTable 1

International Classification of Diseases, 9th and 10th Revisions, Codes Used to Define Outcome and Maternal Covariates

	9th revision	10th revision
Allergic rhinitis	477	J30
Asthma ^a	493	
Atopic dermatitis	691.8	L20
Food allergy	V15.01, V15.02, V15.03, V15.04, V15.05, 692.5, 693.1, 995.6, 995.7	Z91.01, L25.4, L27.2, T78.0, T78.1
Other allergy	V15.06, V15.07, V15.08, V15.09, 995.3	Z91.03, Z91.04, T78.4

^aAll information collected before the introduction of ICD-10 codes in the Kaiser Permanente Northern California system (2015).**eTable 2**

Risk Ratio and 95% Confidence Interval Estimates for the Association Between Cesarean Delivery and Allergic Rhinitis at Ages 6, 8, and 10 Years Using the Primary Allergic Rhinitis Definition

	Age 6 (n = 117,768)		Age 8 (n = 75,115)		Age 10 (n = 40,332)	
	C-section, n (%)	RR (95% CI)	C-section, n (%)	RR (95% CI)	C-section, n (%)	RR (95% CI)
Unadjusted	31,708 (26.9%)	1.10 (1.04, 1.18)	20,404 (27.2%)	1.14 (1.08, 1.21)	10,914 (27.1%)	1.14 (1.07, 1.22)
Primary ^a	31,708 (26.9%)	0.98 (0.91, 1.04)	20,404 (27.2%)	1.00 (0.95, 1.07)	10,914 (27.1%)	1.03 (0.96, 1.10)
Sex ^b						
Male	16,966 (28.1%)	0.97 (0.89, 1.05)	10,986 (28.5%)	1.02 (0.94, 1.10)	5916 (28.4%)	1.04 (0.95, 1.13)
Female	14,742 (25.7%)	0.98 (0.88, 1.09)	9418 (25.8%)	0.98 (0.89, 1.08)	4998 (25.6%)	1.02 (0.92, 1.15)
Gestational age ^b						
Preterm	3167 (39.9%)	0.97 (0.78, 1.19)	2076 (40.3%)	1.00 (0.82, 1.22)	1094 (40.0%)	0.94 (0.74, 1.18)
Full term	28,541 (26.0%)	0.97 (0.90, 1.04)	18,328 (26.2%)	1.00 (0.94, 1.07)	9820 (26.1%)	1.03 (0.96, 1.11)
Birth order ^b						
First born	14,287 (28.6%)	0.96 (0.87, 1.05)	9274 (29.4%)	0.97 (0.89, 1.07)	4986 (29.6%)	1.01 (0.91, 1.13)
Second + born	17,421 (25.7%)	1.02 (0.93, 1.13)	11,130 (25.6%)	1.08 (0.99, 1.17)	5928 (25.3%)	1.08 (0.98, 1.19)
Maternal atopy ^b						
Yes	16,978 (27.9%)	0.98 (0.91, 1.07)	11,235 (28.0%)	0.99 (0.92, 1.07)	6172 (28.0%)	0.96 (0.88, 1.04)
No	14,730 (25.9%)	0.96 (0.85, 1.08)	9169 (26.2%)	1.03 (0.92, 1.14)	4742 (26.0%)	1.19 (1.05, 1.35)
Pre-pregnancy BMI ^b						
Normal	12,162 (22.8%)	0.99 (0.89, 1.10)	7543 (23.1%)	1.04 (0.94, 1.14)	3666 (23.3%)	1.04 (0.92, 1.17)
Overweight	8152 (28.4%)	0.99 (0.87, 1.12)	5109 (28.9%)	0.99 (0.88, 1.11)	2496 (28.7%)	0.98 (0.85, 1.13)
Obese	8369 (36.8%)	0.91 (0.80, 1.03)	5180 (37.1%)	0.94 (0.83, 1.06)	2550 (37.3%)	1.03 (0.89, 1.19)

Abbreviations: BMI, body mass index; C-section, cesarean delivery; NICU, neonatal intensive care unit; RR, risk ratio.

Bold values indicated a *P*-value < .05.^aAdjusted for maternal age, education, race, pre-pregnancy BMI, smoking, antibiotics during pregnancy, maternal asthma, atopic dermatitis, allergic rhinitis, food allergy, other allergy, sex, gestational age, birthweight, NICU admission, birth order, and breastfeeding.^bAdjusted for covariates listed previously, excluding adjustment for specific stratification variable.

eTable 3

Risk Ratio and 95% Confidence Interval Estimates for Association Between Covariates and Allergic Rhinitis in the Primary Adjusted Model, Primary AR Definition

	Age 6 (n = 117,768)	Age 8 (n = 75,115)	Age 10 (n = 40,332)
C-section	0.97 (0.96, 1.04)	1.01 (0.95, 1.07)	1.03 (0.96, 1.10)
Age			
<25	0.76 (0.68, 0.87)	0.74 (0.67, 0.82)	0.75 (0.67, 0.85)
25-29	0.86 (0.80, 0.93)	0.90 (0.84, 0.97)	0.93 (0.86, 1.01)
30-34	Ref	Ref	Ref
35-39	1.11 (1.03, 1.20)	1.10 (1.02, 1.18)	1.05 (0.97, 1.14)
40+	1.15 (1.01, 1.31)	1.20 (1.07, 1.35)	1.12 (0.98, 1.29)
Education			
16 + y	Ref	Ref	Ref
<12 y	1.30 (1.12, 1.50)	1.32 (1.15, 1.50)	1.25 (1.08, 1.45)
12-15 y	1.27 (1.19, 1.37)	1.28 (1.21, 1.36)	1.19 (1.11, 1.53)
Missing	1.18 (0.90, 1.56)	1.14 (0.88, 1.47)	1.03 (0.77, 1.39)
Maternal race			
White	Ref	Ref	Ref
Black	2.05 (1.85, 2.28)	1.94 (1.76, 2.14)	1.74 (1.55, 1.96)
API	1.27 (1.17, 1.37)	1.34 (1.25, 1.44)	1.29 (1.19, 1.40)
Hispanic	1.30 (1.20, 1.41)	1.33 (1.23, 1.43)	1.26 (1.16, 1.38)
Other	1.32 (1.14, 1.53)	1.37 (1.21, 1.55)	1.14 (0.99, 1.30)
Maternal asthma			
None	Ref	Ref	Ref
Active asthma	1.39 (1.28, 1.51)	1.33 (1.24, 1.44)	1.31 (1.20, 1.43)
History asthma	1.08 (0.96, 1.22)	1.16 (1.05, 1.29)	1.27 (1.13, 1.43)
Pre-pregnancy BMI			
Underweight	0.96 (0.77, 1.18)	0.86 (0.69, 1.06)	1.28 (1.01, 1.63)
Normal	Ref	Ref	Ref
Overweight	1.07 (1.00, 1.15)	1.06 (0.99, 1.13)	1.00 (0.92, 1.09)
Obese	1.08 (0.99, 1.17)	1.07 (0.99, 1.15)	1.10 (1.01, 1.20)
Missing	0.90 (0.79, 1.02)	0.88 (0.79, 0.97)	0.91 (0.83, 0.99)
Smoking during pregnancy	1.04 (0.94, 1.15)	1.09 (0.99, 1.20)	1.21 (1.09, 1.34)
ABX during pregnancy	1.19 (1.12, 1.27)	1.14 (1.08, 1.21)	1.15 (1.08, 1.23)
Female infant	0.67 (0.63, 0.71)	0.68 (0.64, 0.71)	0.68 (0.64, 0.72)
Gestational age			
<31 wk	1.14 (0.78, 1.67)	0.79 (0.54, 1.15)	1.37 (0.93, 2.04)
31 wk	0.61 (0.29, 1.29)	0.95 (0.55, 1.67)	0.92 (0.46, 1.85)
32 wk	0.99 (0.59, 1.67)	0.91 (0.55, 1.49)	1.23 (0.73, 2.07)
33 wk	0.85 (0.52, 1.37)	0.89 (0.58, 1.34)	0.73 (0.41, 1.31)
34 wk	1.11 (0.82, 1.51)	1.15 (0.87, 1.51)	1.12 (0.81, 1.55)
35 wk	1.17 (0.94, 1.46)	1.16 (0.95, 1.42)	1.04 (0.82, 1.32)
36 wk	1.00 (0.84, 1.18)	0.97 (0.83, 1.14)	1.00 (0.84, 1.20)
37 wk	0.98 (0.87, 1.10)	1.05 (0.94, 1.17)	0.91 (0.80, 1.04)
38 wk	0.95 (0.87, 1.04)	0.99 (0.91, 1.07)	1.05 (0.95, 1.15)
39 wk	0.99 (0.92, 1.07)	1.03 (0.96, 1.10)	0.95 (0.88, 1.04)
40 wk	Ref	Ref	Ref
	0.91 (0.82, 1.01)	0.94 (0.85, 1.03)	0.86 (0.77, 0.96)
Birth order			
First born	Ref	Ref	Ref
Second born	0.73 (0.68, 0.78)	0.77 (0.72, 0.82)	0.77 (0.72, 0.82)
Third + born	0.50 (0.46, 0.55)	0.54 (0.50, 0.58)	0.58 (0.53, 0.64)
	Age 6 (n = 117,768)	Age 8 (n = 75,115)	Age 10 (n = 40,332)
NICU	0.96 (0.85, 1.10)	1.04 (0.93, 1.16)	0.90 (0.79, 1.04)
Maternal atopy			
Allergic rhinitis	1.59 (1.49, 1.69)	1.60 (1.51, 1.70)	1.56 (1.46, 1.67)
Atopic dermatitis	1.11 (1.02, 1.21)	1.08 (1.00, 1.17)	1.09 (1.00, 1.19)
Food allergy	1.31 (1.15, 1.49)	1.31 (1.17, 1.47)	1.31 (1.15, 1.50)
Other allergy	1.17 (1.08, 1.27)	1.29 (1.20, 1.38)	1.15 (1.05, 1.25)
Birthweight			
<2500 g	1.04 (0.88, 1.24)	1.06 (0.91, 1.23)	1.02 (0.85, 1.23)
2500-4000 g	Ref	Ref	Ref
>4000 g	1.05 (0.93, 1.15)	1.06 (0.97, 1.15)	1.07 (0.98, 1.18)
Breastfeeding			
None	Ref	Ref	Ref
<3 mos.	1.10 (0.99, 1.23)	1.01 (0.92, 1.12)	1.05 (0.93, 1.18)
3-6 mos.	1.15 (1.02, 1.30)	1.01 (0.91, 1.13)	1.04 (0.91, 1.19)
>6 mos.	1.04 (0.94, 1.16)	0.91 (0.83, 1.00)	1.02 (0.92, 1.13)
Missing	1.03 (0.91, 1.16)	0.92 (0.84, 1.02)	1.05 (0.95, 1.16)

Abbreviations: ABX, antibiotics; API, Asian or Pacific Islander; AR, allergic rhinitis; BMI, body mass index; C-section, cesarean section; NICU, neonatal intensive care unit; RR, relative risk.

Bold values indicated a *P*-value < .05.

eTable 4

Risk Ratio and 95% Confidence Interval Estimates for the Association Between Cesarean Delivery and Allergic Rhinitis at Ages 6, 8, and 10 Years Using the Secondary Allergic Rhinitis Definition

	Age 6 (n = 117,768)		Age 8 (n = 75,115)		Age 10 (n = 40,332)	
	C-section, n (%)	RR (95% CI)	C-section, n (%)	RR (95% CI)	C-section, n (%)	RR (95% CI)
Unadjusted	31,708 (26.9%)	1.14 (1.08, 1.19)	20,404 (27.2%)	1.16 (1.11, 1.22)	10,914 (27.1%)	1.12 (1.06, 1.19)
Primary ^a	31,708 (26.9%)	1.01 (0.96, 1.07)	20,404 (27.2%)	1.04 (0.99, 1.09)	10,914 (27.1%)	1.02 (0.96, 1.09)
Sex ^b						
Male	16,966 (28.1%)	1.01 (0.95, 1.08)	10,986 (28.5%)	1.04 (0.98, 1.11)	5916 (28.4%)	1.02 (0.95, 1.10)
Female	14,742 (25.7%)	1.01 (0.93, 1.10)	9418 (25.8%)	1.03 (0.95, 1.11)	4998 (25.6%)	1.03 (0.94, 1.14)
Gestational age ^b						
Preterm	3167 (39.9%)	1.03 (0.87, 1.21)	2076 (40.3%)	1.04 (0.88, 1.22)	1094 (40.0%)	
Full term	28,541 (26.0%)	1.01 (0.95, 1.06)	18,328 (26.2%)	1.04 (0.98, 1.09)	9820 (26.1%)	1.03 (0.96, 1.09)
Birth order ^b						
Firstborn	14,287 (28.6%)	0.95 (0.88, 1.03)	9274 (29.4%)	1.02 (0.95, 1.10)	4986 (29.6%)	0.98 (0.90, 1.08)
Second + born	17,421 (25.7%)	1.10 (1.02, 1.18)	11,130 (25.6%)	1.10 (1.02, 1.18)	5928 (25.3%)	1.09 (1.00, 1.19)
Maternal atopy ^b						
Yes	16,978 (27.9%)	1.00 (0.94, 1.07)	11,235 (28.0%)	1.02 (0.96, 1.08)	6172 (28.0%)	0.97 (0.90, 1.04)
No	14,730 (25.9%)	1.03 (0.94, 1.12)	9169 (26.2%)	1.09 (0.99, 1.19)	4742 (26.0%)	1.14 (1.03, 1.27)
Pre-pregnancy BMI ^b						
Normal	12,162 (22.8%)	1.01 (0.93, 1.10)	7543 (23.1%)	1.05 (0.97, 1.14)	3666 (23.3%)	1.02 (0.92, 1.12)
Overweight	8152 (28.4%)	1.02 (0.92, 1.12)	5109 (28.9%)	1.03 (0.93, 1.13)	2496 (28.7%)	1.00 (0.88, 1.14)
Obese	8369 (36.8%)	1.01 (0.91, 1.11)	5180 (37.1%)	0.99 (0.89, 1.09)	2550 (37.3%)	1.07 (0.94, 1.20)

Abbreviations: BMI, body mass index; C-section, cesarean delivery; NICU, neonatal intensive care unit; RR, risk ratio.

Bold values indicated a *P*-value < .05.

^aAdjusted for maternal age, education, race, pre-pregnancy BMI, smoking, antibiotics during pregnancy, maternal asthma, atopic dermatitis, allergic rhinitis, food allergy, other allergy, sex, gestational age, birthweight, NICU admission, birth order, and breastfeeding.

^bAdjusted for covariates listed above, excluding adjustment for specific stratification variable.

eTable 5

Risk Ratio and 95% Confidence Interval Estimates for the Association Between Cesarean Delivery and Allergic Rhinitis Among Full-Term Infants at Ages 6 and 8 Years by C-Section Characteristics

	Age 6 (n = 52,104)			Age 8 (n = 18,256)		
	C-section, n (%)	Primary AR (RR [CI])	Secondary AR (RR [CI])	C-section, n (%)	Primary AR (RR [CI])	Secondary AR (RR [CI])
Primary evidence of labor	13,230 (100%)	0.98 (0.89, 1.09)	1.02 (0.94, 1.11)	4557 (100%)	1.00 (0.88, 1.13)	1.10 (1.00, 1.22)
Yes	7142 (54.0%)	0.95 (0.83, 1.08)	0.92 (0.83, 1.02)	2591 (56.9%)	0.93 (0.79, 1.09)	1.05 (0.92, 1.19)
No	6088 (46.0%)	1.02 (0.89, 1.18)	1.15 (1.03, 1.28)	1966 (43.1%)	1.08 (0.91, 1.28)	1.17 (1.01, 1.35)
exposure to microbiota						
Yes	7566 (57.2%)	0.92 (0.81, 1.05)	0.91 (0.83, 1.01)	2816 (61.8%)	0.99 (0.86, 1.15)	1.08 (0.96, 1.22)
No	5664 (42.8%)	1.07 (0.93, 1.24)	1.19 (1.07, 1.33)	1741 (38.2%)	1.00 (0.83, 1.21)	1.13 (0.97, 1.32)
Cesarean indications						
Breech, NL	1378 (10.4%)	1.00 (0.76, 1.32)	1.26 (1.04, 1.52)	413 (9.1%)	0.95 (0.68, 1.38)	1.07 (0.80, 1.43)
Breech, L	1087 (8.2%)	0.90 (0.66, 1.24)	0.81 (0.63, 1.04)	333 (7.3%)	1.05 (0.72, 1.54)	1.02 (0.73, 1.41)
Repeat, NL	3552 (26.8%)	1.03 (0.85, 1.25)	1.07 (0.93, 1.24)	1226 (26.9%)	1.17 (0.95, 1.45)	1.20 (1.00, 1.43)
Fetal intolerance	1991 (15.0%)	0.92 (0.73, 1.14)	0.96 (0.81, 1.14)	662 (14.5%)	0.98 (0.75, 1.28)	1.05 (0.84, 1.32)
Failure to progress	2580 (19.5%)	0.95 (0.78, 1.16)	0.84 (0.72, 0.99)	902 (19.8%)	1.05 (0.83, 1.33)	1.18 (0.98, 1.42)
Other, L	1893 (14.3%)	0.92 (0.72, 1.16)	1.01 (0.84, 1.21)	779 (17.1%)	0.63 (0.45, 0.87)	0.84 (0.66, 1.07)
Other, NL	749 (5.7%)	1.28 (0.95, 1.71)	1.47 (1.19, 1.83)	242 (5.3%)	1.02 (0.68, 1.52)	1.23 (0.90, 1.70)

Abbreviations: AR, allergic rhinitis; BMI, body mass index; C-section, cesarean delivery; L, labor; NICU, neonatal intensive care unit; NL, no labor; RR, risk ratio.

Bold values indicated a *P*-value < .05.

NOTE. Models adjusted for maternal age, education, race, pre-pregnancy BMI, smoking, antibiotics during pregnancy, maternal asthma, atopic dermatitis, allergic rhinitis, food allergy, other allergy, sex, gestational age, birthweight, NICU admission, birth order, and breastfeeding.

eTable 6

Comparison of Risk Ratio and 95% Confidence Interval Estimates for the Association Between Cesarean Delivery and Allergic Rhinitis Among Full-Term Infants, Accounting for Intrapartum Antibiotics, at Ages 6, 8, and 10 Years

	Model			
	Primary ^a	Primary + IABX ^b	GBS+ ^a	GBS− ^a
Age 6 (n = 109,832)				
C-section (n)	28,541	28,541	6574	20,065
Vaginal (n)	81,291	81,291	19,454	59,973
Primary (RR [CI])	0.97 (0.90, 1.04)	0.97 (0.90, 1.04)	0.87 (0.75, 1.00)	1.01 (0.93, 1.09)
Secondary (RR [CI])	1.01 (0.95, 1.06)	1.01 (0.95, 1.07)	0.94 (0.84, 1.05)	1.03 (0.96, 1.09)
Age 8 (n = 69,964)				
C-section (n)	18,328	18,328	4239	12,767
Vaginal (n)	51,636	51,636	12,351	37,974
Primary (RR [CI])	1.00 (0.94, 1.07)	1.01 (0.95, 1.08)	0.90 (0.78, 1.03)	1.03 (0.95, 1.11)
Secondary (RR [CI])	1.04 (0.98, 1.09)	1.04 (0.99, 1.10)	0.95 (0.85, 1.06)	1.05 (0.99, 1.12)
Age 10 (n = 37,597)				
C-section (n)	9820	9820	2174	6938
Vaginal (n)	27,777	27,777	6461	20,514
Primary (RR [CI])	1.03 (0.96, 1.11)	1.04 (0.97, 1.12)	0.95 (0.81, 1.11)	1.07 (0.98, 1.16)
Secondary (RR [CI])	1.03 (0.96, 1.09)	1.03 (0.97, 1.10)	0.95 (0.83, 1.09)	1.06 (0.98, 1.14)

Abbreviations: BMI, body mass index; C-section, cesarean delivery; GBS, group B *Streptococcus*; IABX, intrapartum antibiotics; NICU, neonatal intensive care unit, RR, risk ratio.

^aModel adjusted for maternal age, education, race, pre-pregnancy BMI, smoking, antibiotics during pregnancy, maternal asthma, atopic dermatitis, allergic rhinitis, food allergy, other allergy, sex, gestational age, birthweight, NICU admission, birth order, and breastfeeding.

^bModel adjusted for all covariates in primary model plus adjusts for intrapartum antibiotics.