Original Contribution

Wheeze and Food Allergies in Children Born via Cesarean Delivery

The Upstate KIDS Study

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We examined whether cesarean delivery (CD) increased the risk of wheeze or food allergy in early childhood compared with vaginal delivery and whether these associations were mediated by breastfeeding. The study population was the Upstate KIDS cohort (2008–2010) of mothers and infants from the State of New York (excluding New York City). Infant's wheeze was reported by questionnaire every 4–6 months until 3 years of age, as were food allergies beginning at 8 months. Modified Poisson regression was used to compare risks of the outcomes according to mode of delivery (MOD). Potential confounders were identified a priori using directed acyclic graphs. Emergency CD ($n = 1,356$) was associated with elevated risk of wheeze, adjusting for pregnancy complications, maternal atopy, gestational age, birth weight, and smoking during pregnancy (risk ratio = 2.47, 95% confidence interval: 1.31, 4.66), and an increased risk of food allergy, adjusting for maternal atopy, prepregnancy body mass index, smoking during pregnancy, and parity (risk ratio = 3.02, 95% confidence interval: 1.26, 7.25). Neither outcome was significantly associated with planned CD ($n = 1,565$ infants). Breastfeeding mediated the association between MOD and wheeze but not food allergy. Other factors not associated with early-life microbial transfer, but relating to the development of the outcomes, might contribute to the association between MOD and wheeze/food allergy.

breastfeeding; cesarean delivery; food allergy; mediation; Upstate KIDS; wheeze

Abbreviations: CD, cesarean delivery; MOD, mode of delivery; VD, vaginal delivery.

The prevalence of allergic conditions in children has increased over the last two decades (1). Although genetic variation might predispose some individuals to allergic disorders, other factors such as maternal obesity, exposure to extremely sterile environments, and other early-life exposures might also play a role (2–4). Lack of microbiome seeding at birth has been suggested as a biomechanism influencing the increase in asthma and allergic disorders (5, 6). At birth, mammals inoculate their newborns with maternal birth canal microbes, which are thought to contribute to the development of the neonate's immune system. The primary introduction of the naive human fetus to microbes occurs during labor, when the water breaks and microbes ascend the birth canal, as the baby is descending (7). The neonate acquires the mother's vaginal and fecal microbiota during this process of labor and delivery. This microbial exposure also helps to

initiate the rebalancing of the neonate's immune system, which has a higher proportion of regulatory T cells and a higher T-helper-2:T-helper-1 ratio.

Cesarean delivery (CD) newborns miss the acquisition of their mother's vaginal and rectal bacteria during delivery. This important process could explain why mode of delivery (MOD) has been tied to the risk of allergic disorders in childhood in some studies (8–10). However, other studies have shown no significant association between MOD and the risk of allergic disorders (11, 12). Differences in findings might be attributed to factors that can mediate or alter the influence of microbiome seeding. Studies have demonstrated, for example, that breastfeeding has a protective effect on the early development of allergic disease such as asthma (13, 14), allergic dermatitis (15), and food allergy (16, 17). Specifically, breast milk contains beneficial microbes

that are transferred from mother to child (18). Breastfeeding in the first year of life might be a possible mediator in the causal pathway between MOD and allergic disorders, but studies are lacking.

Therefore, the aims of this study were to assess whether MOD influences the risk of wheeze or food allergy and whether breastfeeding mediated the observed association between MOD and wheeze or food allergy.

METHODS

Study design and population

The Upstate KIDS Study is a longitudinal, prospective birth cohort established to study the relationship between infertility treatment and child development (19). The cohort included live births from the State of New York, excluding New York City, born between September 2008 and December 2010. Mothers who conceived with infertility treatments and all mothers of multiples were invited to participate. For every singleton live birth conceived with infertility treatment, 3 singletons conceived without infertility treatment were sampled, and they were frequency matched on the region of birth (19). All twins and higher-order multiples, regardless of the mode of conception, were also invited to participate. A total of 5,034 mothers and 6,171 infants were enrolled.

Data were compiled from New York State vital records and written questionnaires completed by the mothers at baseline (4 months postpartum) through 36 months of age. Maternal-level characteristics such as infertility treatment, pregnancy complications, maternal smoking during pregnancy, race/ethnicity, and parity were obtained from the questionnaire. Infant-level data such as wheeze and allergies were collected at baseline and at 8, 12, 18, 24, 30, and 36 months. Analyses were restricted to data from singletons and twins in the study cohort, excluding 134 triplets and quadruplets (due to there being few in number) and 284 infants whose MOD category could not be determined. The final sample size for analysis was 5,753 infants.

Exposure definition

Maternal self-report at baseline of vaginal delivery (VD), planned CD, or emergency CD was used to assign MOD categories. Previously, in a Canadian study, sensitivity and specificity of self-report of CD at 4 months postpartum compared with electronic medical records were high (>99%) (20). Comparison of maternal report of CD with birth certificate indication had a fairly high concordance (80% agreement).

Outcome definition

Due to the difficulty in diagnosing asthma in children younger than 5 years of age (21, 22), wheezing symptoms in early childhood (23) were used as the outcome. In the study questionnaires, maternal report of infant's wheeze status was modeled after the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire, a globally accepted and standardized screening tool for childhood asthma, rhinitis, and eczema (24). The core questions include "ever wheezed" and "wheeze in the last 12 months." Wheeze was described as a high-pitched

whistling sound through breathing that occurs when air moves through narrowed tubes. Wheeze diagnosis was identified by an affirmative response to the question "Has your baby ever had wheezing or whistling in the chest?" This was further ascertained for "during or soon after a cold or flu" and "without a cold or flu." Wheeze was assessed longitudinally (i.e., maternal report of wheeze at each time point through age 36 months). An affirmative response to the question: "Have you been told by a doctor or health practitioner that your baby is allergic to any food, medication or other things?" was used to ascertain food allergy diagnosis. "What are the specific food allergies?" was used to identify food allergy diagnosis at each time point for the following: nuts, peanuts, fish, cow's milk, dairy, shellfish, wheat, gluten, soy, and eggs.

Covariate definitions

Pregnancy smoking status, atopy, maternal education, race/ethnicity, and breastfeeding data were obtained from maternal questionnaires as a primary source and vital records as a secondary source when missing. Atopy was defined as having 2 or more positive responses to maternal history of asthma, hay fever, eczema, and other allergies; mild atopy was defined as having one positive response; and nonatopic status was defined as zero positive responses. Gestational age, birth weight, maternal body mass index, maternal age, and parity were obtained from New York State vital records with maternal questionnaire as a secondary source when missing.

Statistical analyses

Statistical analyses were performed using SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina). Pearson's χ^2 test was used to compare the distribution of baseline maternal and infant variables according to MOD. To address the unique sampling framework of the Upstate KIDS cohort and loss to follow-up, a weighted generalized estimating equation method incorporating a modified Poisson regression with robust error variances was used to estimate risk ratios and 95% confidence intervals, as described by Zou (25, 26). A stabilized inverse probability weight for nonresponse was created at each time point for each outcome. The nonresponse weight was multiplied with the sampling weight to correct for the study's sampling on the region of birth, infertility treatment, and plurality to make our data representative of New York State during 2008–2010 (19). Separate models were fitted for wheeze and food allergy outcomes and adjustments for potential confounders that were identified a priori by directed acyclic graphs (27) (Web Figures 1 and 2, available at <https://academic.oup.com/aje>). Potential confounding variables for associations with MOD were the following: for wheeze, confounders included pregnancy complications, maternal atopy, gestational age, birth weight, and smoking during pregnancy; and for food allergy, they included maternal atopy, prepregnancy body mass index, smoking during pregnancy, and parity.

Given the hypothesis that breastfeeding might mediate the effect of MOD on wheeze and food allergy, we conducted mediation analysis using the counterfactual approach to evaluate the potential mediating impact that breastfeeding might have as a mediator in the association. The fundamental basis of

this approach is on the notion of a counterfactual conditional statement (28) where each subject in the cohort is observed under one set of conditions and also considered under circumstances that, contrary to fact (counterfactual), did not occur. The counterfactual-based definitions of direct and indirect effects are estimated from the regression models. This counterfactual approach to mediation analysis allows for the decomposition of a total effect into direct and indirect effects even when there are interactions and nonlinear distributions (29). The controlled direct effect, defined as the effect of an exposure on an outcome that would be observed if the mediator were controlled uniformly at a fixed value (30, 31), is reported in our mediation analysis. We estimated the controlled direct effect of MOD on the outcomes, assuming all infants were uniformly breastfed in the first year of life. This allowed us to statistically model an ideal scenario where all infants were breastfed and to evaluate the mediating effects of breastfeeding on the associations. Mediation weights were multiplied by combined nonresponse and sampling weights. The effect estimates and percentile confidence intervals were obtained via bootstrapping (32). For simplification, we performed the mediation analysis using MOD as a binary variable (all CD compared with VD).

Institutional review boards for the New York State Department of Health (#07-097) and the University at Albany (#08-179) approved this study. The board at the New York State Department of Health served as the institutional review board designated by the National Institutes of Health for this study under a reliance agreement.

RESULTS

Of the 5,753 infants included in the study analyses, 1,356 infants (23.57%) were delivered via emergency CD and 1,565 infants (27.20%) via planned CD. Approximately 49% of the infants were delivered via VD. Tables 1 and 2 describe maternal and infant characteristics stratified by MOD. When compared with VD infants, CD infants were more likely to be delivered by mothers who were older than 30 years and who were overweight or obese prior to pregnancy. About 44% of babies delivered via planned CD were between 37 and 38 weeks of gestation (early term) compared with 27% of VD babies. VD infants were also more likely to be breastfed in the first year of life compared with CD infants.

The most common reasons for undergoing emergency CD were a failure to progress or pregnancy-related maternal conditions such as placental abruption and placenta previa. A history of previous CD, nonpregnancy-related maternal conditions (e.g., active genital herpes and HIV infection), refused vaginal birth after cesarean, and elective CD were identified as the most common reasons for planned CD (data not shown).

The proportion of wheeze differed significantly by MOD at all time points from 12 months onward (Table 3), while the proportion of food allergy by MOD was not statistically different at any time point (Table 4). In prospective analyses, when compared with infants delivered vaginally, a higher risk for wheeze was observed among the infants delivered via emergency CD (adjusted risk ratio = 2.47, 95% confidence interval: 1.31, 4.66) (Table 5). Given that maternal atopy is a known risk factor for asthma, we assessed the modifying effect of maternal atopy

on the association between MOD and wheeze as a product term in our statistical model. Maternal atopy was not a significant effect modifier (P for mild atopy = 0.71; P for severe atopy = 0.28) but was a significant confounder in the association between MOD and wheeze in the first 3 years of life. The risk for food allergy was significantly higher in emergency-CD infants compared with VD infants (risk ratio = 3.02, 95% confidence interval: 1.26, 7.25). No significant risk was observed among planned-CD infants (Table 5). Like the association between MOD and wheeze, maternal atopy was also not a significant effect modifier in the association between MOD and food allergy (data not shown).

The subanalysis assessing the potential mediating effects of breastfeeding suggested that breastfeeding in the first year of life mediates the impact of MOD on the development of wheeze but not food allergy in infants in the first 3 years of life, under a number of stringent assumptions. The controlled direct effect, which captures the effect of the exposure (MOD) on the outcomes if the intermediate (breastfeeding in the first year of life) is set to a fixed level, was reported. We assumed that all infants were continuously and consistently breastfed through the first year of life. When comparing the mediation results with the generalized estimating equation model, the risk of wheeze among CD infants was attenuated when assuming all infants were breastfed at 4, 8, and 12 months (Table 6). For example, the risk for wheeze decreased from 1.95 to 0.97 assuming all infants were breastfed at 4 months. However, the risk for food allergy was largely unchanged at 4 and 8 months of breastfeeding, but we observed a decreased risk for food allergy at 12 months after birth (Table 7). The estimates reported should be interpreted with caution because most women in the cohort did not breastfeed their infants in the first year of life.

DISCUSSION

An increased risk of wheeze from birth through age 36 months was observed in children delivered via emergency CD compared with children delivered vaginally. While prior studies of MOD and wheeze are sparse, several studies have assessed the association between MOD and asthma and have found significantly increased risk among those delivered via CD (8, 33–36). However, other studies have observed no significant association between MOD and childhood asthma (11, 37, 38). Although most of these studies have examined all CD combined, those that have examined planned versus emergency CD have observed different associations. A study observed a higher asthma risk in emergency-CD children relative to those delivered via planned CD (39) while others have observed an increased risk in planned-CD children (8, 36).

The microbiome-seeding hypothesis suggests that increased disease development and altered immune development among children delivered by CD could be the result of delayed gut colonization due to lack of or limited contact with maternal vaginal and fecal microflora (40, 41). The rupture of fetal membranes is quite frequent before emergency CD, possibly leading to the spread of vaginal bacteria to the fetus (42). Thus, children delivered by CD, particularly those delivered by planned CD, are hypothesized to have less exposure to maternal vaginal and fecal

Table 1. Maternal Characteristics According to Mode of Delivery, Upstate KIDS Study, New York, 2008–2010

Characteristic	Emergency Cesarean Delivery (n = 989)		Planned Cesarean Delivery (n = 1,155)		Vaginal Delivery (n = 2,570)		P Value
	No.	%	No.	%	No.	%	
Maternal age, years							<0.0001 ^a
<20	26	2.63	14	1.21	141	5.49	
20–29	374	37.82	363	31.43	1,134	44.12	
30–39	499	50.46	664	57.49	1,186	46.15	
≥40	90	9.1	114	9.87	109	4.24	
Maternal education							<0.0001 ^a
Less than HS	52	5.26	47	4.07	184	7.16	
HS or GED equivalent	122	12.34	132	11.43	362	14.09	
Some college	287	29.02	335	29	811	31.56	
College	227	22.95	267	23.12	539	20.97	
Advanced degree	301	30.43	374	32.38	674	26.23	
Maternal race/ethnicity							0.1115
Non-Hispanic white	764	77.25	957	82.86	2,074	80.7	
Non-Hispanic black	57	5.76	50	4.33	117	4.55	
Non-Hispanic Asian	28	2.83	28	2.42	65	2.53	
Hispanic	65	6.57	54	4.68	160	6.23	
Mixed race/other	75	7.58	66	5.71	154	5.99	
Maternal atopy ^b							0.037 ^a
Atopic	606	62.28	753	66.23	1,683	67.29	
Mildly atopic	241	24.77	271	23.83	563	22.51	
Nonatopic	126	12.95	113	9.94	255	10.2	
Prepregnancy BMI ^{b,c}							<0.0001 ^a
<18.5 (underweight)	26	2.63	19	1.65	81	3.16	
18.5–24.9 (normal weight)	392	39.72	455	39.46	1,309	51.03	
25.0–29.9 (overweight)	257	26.04	298	25.85	636	24.8	
≥30.0 (obese)	312	31.61	381	33.04	539	21.01	
Nulliparity ^b							<0.0001 ^a
Yes	610	62.18	380	33.07	1,136	44.55	
No	371	37.82	769	66.93	1,414	55.45	
Infertility treatment							<0.0001 ^a
Yes	364	36.8	412	35.67	597	23.23	
No	625	63.2	743	64.33	1,973	76.77	

Abbreviations: BMI, body mass index; GED, General Education Development certificate; HS, high school.

^a $P < 0.05$ was the threshold for statistical significance in χ^2 tests comparing the 3 categories of mode of delivery according to maternal characteristics.^b Number of missing values: for maternal atopy = 103; for prepregnancy BMI = 9; for nulliparity = 34.^c BMI was calculated as weight (kg)/height (m)².

microflora compared with those born by emergency CD and VD. Considering this hypothesis, the association between allergic disorders would be expected to be stronger among those born via planned CD. A significantly increased risk of wheeze in the group of infants delivered via emergency CD—but not planned CD—in the Upstate KIDS Study, suggests that there was not a strong causal effect due to vaginal microflora. Other factors not

associated with early-life microbial transfer, but relating to the development of the outcomes, might also contribute to the observed association between MOD and wheeze and food allergy. For example, recent studies have determined that maternal obesity might influence neonatal and childhood morbidities, including development of allergic disorders through increased inflammation and/or altered immune response (43, 44).

Table 2. Infant Characteristics According to Mode of Delivery, Upstate KIDS Study, New York, 2008–2010

Characteristic	Emergency Cesarean Delivery (n = 1,356)		Planned Cesarean Delivery (n = 1,565)		Vaginal Delivery (n = 2,832)		P Value
	No.	%	No.	%	No.	%	
Gestational age ^a , weeks							<0.0001 ^b
<37 (preterm)	674	49.71	284	18.15	376	13.28	
37–38 (early term)	291	21.46	693	44.28	775	27.37	
39–40 (full term)	324	23.89	557	35.59	1,440	50.85	
>40 (late term)	67	4.94	31	1.98	241	8.51	
Birth weight, g							<0.0001 ^b
<1,500 (very low birth weight)	122	9.00	13	0.83	47	1.66	
1,500–2,499 (low birth weight)	429	31.64	275	17.57	293	10.35	
2,500–3,999 (normal birth weight)	740	54.57	1,152	73.61	2,260	79.69	
≥4,000 (high birth weight)	65	4.79	125	7.99	232	8.19	
Plurality							<0.0001 ^b
Singleton	630	46.46	768	49.07	2,366	83.55	
Twins	726	53.54	797	50.93	466	16.45	
Breastfed at discharge ^c							0.0015 ^b
Yes	1,008	75.79	1,190	76.82	2,248	80.23	
No	322	24.21	359	23.18	554	19.77	
Breastfed at 4 months ^c							<0.0001 ^b
Yes	462	40.6	540	41.06	1,279	54.68	
No	676	59.4	775	58.94	1,060	45.32	
Breastfed at 8 months ^c							<0.0001 ^b
Yes	194	21.92	266	24.79	770	39.23	
No	691	78.08	807	75.21	1,193	60.77	
Breastfed at 12 months ^c							<0.0001 ^b
Yes	96	12.72	117	13.62	388	23.76	
No	659	87.28	742	86.38	1,245	76.24	

^a According to American Congress of Obstetricians and Gynecologists (ACOG) classification (59, 60).

^b $P < 0.05$ was the statistical significance threshold in χ^2 tests comparing the 3 categories of mode of delivery according to infant characteristics.

^c Number of missing values: for breastfed at discharge = 72; for breastfed at 4 months = 961; breastfed at 8 months = 1,832; for breastfed at 12 months = 2,506.

Increasing maternal body mass index is also associated with pregnancy complications such as hypertensive disorders and diabetes and increased rates of CD (45). Hence, we adjusted for maternal body mass index in our investigations, and the findings remained robust.

There are few studies evaluating the impact of MOD on the risk of food allergy in early childhood, particularly those assessing CD as either planned or emergency. Previous studies have observed significant associations between all CD combined and food allergy/food atopy (42, 46, 47). All CD combined was significantly associated with food allergy in infants followed from birth through 36 months of age in a recent study (46). In the Upstate KIDS cohort, only emergency CD was significantly associated with doctor-diagnosed food allergy. If the mechanism of microbiome seeding accounts for

associations between MOD and the outcomes, we expect that CD would be associated with allergies regardless of indication (planned versus emergency) as observed in the previous studies. We are unable to account for the reason we found associations only with emergency CD but speculate that potential misclassification of CD indication (e.g., planned CD as emergency CD) and the inclusion of twins, who are disproportionately delivered via CD, might play a role.

We conducted a subanalysis evaluating the impact of breastfeeding as a mediator in the association between MOD and wheeze/food allergy. While this subanalysis required a few assumptions that might not be fulfilled, breastfeeding from birth through the first year of life was identified as a mediator in the association between MOD and wheeze but not food allergies. The significant association observed between MOD and wheeze

Table 3. Current Wheeze According to Mode of Delivery, Upstate KIDS Study, New York, 2008–2010

Infant's Age	Emergency Cesarean Delivery (n = 1,356)		Planned Cesarean Delivery (n = 1,565)		Vaginal Delivery (n = 2,832)		P Value
	No.	%	No.	%	No.	%	
4 months	231	17.04	222	14.19	391	13.81	0.097
8 months	91	6.71	89	5.69	174	6.14	0.30
12 months	74	5.46	57	3.64	119	4.20	0.03 ^a
18 months	85	6.27	66	4.22	132	4.66	0.039 ^a
24 months	73	5.38	47	3.00	97	3.43	0.0005 ^a
30 months	72	5.31	55	3.51	107	3.78	0.012 ^a
36 months	65	4.79	54	3.45	97	3.43	0.044 ^a

^a $P < 0.05$ was the threshold for statistical significance in χ^2 tests comparing the 3 categories of mode of delivery according to current wheeze at each time point.

in the generalized estimating equation model was mitigated when assuming all infants were breastfed. Furthermore, because it is unclear whether breastfeeding should be evaluated as a confounder or a mediator, we assessed breastfeeding as a confounder at any time point in the first year of life. In the final model, the association between MOD and wheeze was attenuated, with the risk decreasing from 1.95 (95% confidence interval: 1.17, 3.25) to 1.09 (95% confidence interval: 0.61, 1.93) after adjusting for breastfeeding as a confounder. However, the association was largely unchanged for risk of food allergy and the width of the confidence intervals increased due to small numbers (results not shown).

Breastfeeding has previously been identified as a protective factor against the risk of developing allergic disorder (13, 15, 48). Variability in breast milk transfer is dependent on the MOD. Both maternal and infant stress during labor and delivery adversely affect lactogenesis (49, 50). Stress could also affect the release of oxytocin, inhibiting milk-ejection reflex in mothers who undergo CD (49). Furthermore, mothers who undergo CD might experience a longer delay in making contact with

Table 4. Doctor-Diagnosed Food Allergy According to Mode of Delivery, Upstate KIDS Study, New York, 2008–2010

Infant's Age	Emergency Cesarean Delivery (n = 1,356)		Planned Cesarean Delivery (n = 1,565)		Vaginal Delivery (n = 2,832)		P Value
	No.	%	No.	%	No.	%	
8 months	36	2.65	41	2.62	99	3.50	0.17
12 months	34	2.51	32	2.04	69	2.44	0.65
18 months	42	3.10	33	2.11	68	2.40	0.21
24 months	39	2.88	29	1.85	64	2.26	0.18
30 months	33	2.43	31	1.98	64	2.26	0.70
36 months	24	1.77	39	2.49	49	1.73	0.19

Table 5. Risk Ratios for Wheeze and Food Allergy According to Mode of Delivery, Upstate KIDS Study, New York, 2008–2010

Mode of Delivery ^a	Wheeze Outcome ^b		Food Allergy Outcome ^c	
	RR	95% CI	RR	95% CI
Cesarean delivery (all)	1.95	1.17, 3.25	1.59	0.73, 3.44
Emergency cesarean delivery	2.47	1.31, 4.66	3.02	1.26, 7.25
Planned cesarean delivery	1.61	0.66, 3.91	0.48	0.14, 1.65

Abbreviations: CI, confidence interval; RR, risk ratio.

^a Vaginal delivery was the reference group.

^b Adjusted for pregnancy complications, maternal atopy, gestational age, birth weight, and smoking during pregnancy.

^c Adjusted for maternal atopy, prepregnancy body mass index, smoking during pregnancy, and parity.

their babies (e.g., delay in breastfeeding) (51, 52), and this, in turn, interrupts the natural contact and microbial transfer needed between mother and child. It should also be noted that VD infants were more likely to be breastfed than CD infants. The mediation analysis suggests that breastfeeding might be helpful in reducing the risk associated between MOD and wheeze. Hence, the association between CD and wheeze might be attenuated if more CD infants are breastfed.

Strengths of our study include its longitudinal study design; linkage of maternal questionnaires with birth certificates to improve ascertainment of the main exposure variable and other covariates; and the use of prospectively collected data on wheeze, food allergies, and breastfeeding. In addition, we had sufficient statistical power to examine CD as either emergency or planned; this allowed for the exploration of the potential for exposure to labor and occurrence of rupture of membranes to confer some protection against adverse outcomes in our study population.

There were some inherent limitations in this study, including potential bias and misclassification relating to maternal report on child outcomes. Although we relied primarily on maternal self-report of MOD, a recent study showed that maternal recall of infant characteristics and events that occurred during labor and delivery is excellent at 4 months postpartum and is a valid source of information for research purposes (20). Similarly, a diagnosis

Table 6. Mediation Analysis: Controlled Direct Effects of Breastfeeding in the Association Between Cesarean Delivery (All) and Wheeze in the Upstate KIDS Study, New York, 2008–2010

Time Point	RR ^{a,b}	95% CI
4 months	0.97	0.49, 1.75
8 months	0.68	0.34, 1.18
12 months	0.80	0.31, 1.79

Abbreviations: CI, confidence interval; RR, risk ratio.

^a Adjusted for pregnancy complications, maternal atopy, gestational age, birth weight, and smoking during pregnancy.

^b Risk ratios when compared with the generalized estimating equation model for “cesarean delivery (all)” in Table 5.

Table 7. Mediation Analysis: Controlled Direct Effects of Breastfeeding in the Association Between Cesarean Delivery (All) and Food Allergy in the Upstate KIDS Study, New York, 2008–2010

Time Point	RR ^{a,b}	95% CI
4 months	1.29	0.65, 2.33
8 months	1.92	0.61, 4.22
12 months	0.87	0.36, 1.76

Abbreviations: CI, confidence interval; RR, risk ratio.

^a Adjusted for maternal atopy, prepregnancy body mass index, smoking during pregnancy, and parity.

^b Risk ratios when compared with the generalized estimating equation model for “cesarean delivery (all)” in Table 5.

of asthma is difficult in children less than 5 years of age, because episodic respiratory symptoms are common in children younger than 3 years (53, 54). As a result, the diagnosis of asthma often relies on symptom history, which might be subject to recall bias but has been proven to be the most important basis for defining asthma in both clinical and epidemiologic settings (55). Recent findings show that questionnaires that use a definition of “wheezing in the last 12 months” to identify the population with asthma are valid measures of asthma (56). Furthermore, a previous validation study identified “ever wheezing” as the most sensitive indicator for the diagnosis of asthma (57). The possibility that some of the CDs were misclassified by type of CD cannot be ruled out. Indicators for emergency CD, such as failure to progress or rupture of fetal membranes, might have occurred in some of the planned CDs, leading to some exposure to the maternal microbiome at birth and observed associations. Finally, the lack of statistical power, as reflected in the confidence interval width, might have influenced the observed associations that contradict our hypotheses.

In conclusion, infants who were delivered via CD, particularly emergency CD, were at higher risk of wheeze and food allergy compared with those who were delivered via VD. Further, we demonstrated that breastfeeding might work as a mediator on the association between CD and wheeze, under certain assumptions. Given the significantly increased risk for wheeze and food allergy in emergency-CD infants, and the high number of CD deliveries in the United States (58), it is important to better understand the potential implications of emergency CDs for long-term health outcomes in the children.

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