

Mode of Birth Is Not Associated With Food Allergy Risk in Infants



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What is already known about this topic? Previous research on the association between mode of birth and risk of food allergy has produced mixed findings. Caveats of prior studies include food allergy not confirmed by food challenge and insufficient details regarding delivery conditions.

What does this article add to our knowledge? Using challenge-confirmed food allergy and detailed information on delivery conditions in a population-based cohort, we found that caesarean delivery, whether elective or emergency, or with or without labor, was not associated with risk of food allergy.

How does this study impact current management guidelines? There was insufficient evidence that mode of delivery has a meaningful impact on the risk of developing food allergy in infants. These findings can assist caregivers in evaluating the risks and benefits of caesarean delivery and may provide reassurance for mothers who require such interventions that there is little evidence that their infants will be at an increased risk of food allergy after caesarean delivery.

BACKGROUND: The association between mode of delivery and the risk of food allergy remains unclear due to the absence of studies with both challenge-proven food allergy outcomes and detailed information on the type of caesarean delivery.

OBJECTIVE: We assessed whether emergency or elective caesarean, or caesarean delivery in the presence or absence of labor initiation, is associated with the risk of food allergy.

METHODS: The HealthNuts study recruited 5276 12-month-old infants who underwent skin prick testing and oral food challenge to ascertain food allergy status, and linked the child's study data to additional birth data from the Victorian Perinatal Data Collection.

RESULTS: Parents of 3006 children consented to data linkage, and birth data were obtained on 2045. In this subgroup, 30%

were born by caesarean and 13% had food allergy. Caesarean delivery, compared with vaginal birth, was not associated with the risk of food allergy (adjusted odds ratio [aOR]: 0.95, 95% confidence interval [CI]: 0.70, 1.30). Neither caesarean delivery before the onset of labor, nor after the onset of labor, was associated with the risk of food allergy (aOR: 0.83, 95% CI: 0.55-1.23 and aOR: 1.13, 95% CI: 0.75-1.72, respectively). Delivery by elective or emergency caesarean, compared with vaginal delivery, was not associated with risk of food allergy (aOR: 1.05, 95% CI: 0.71-1.55 and aOR: 0.86, 95% CI: 0.56-1.31). There was no evidence of effect modification by breastfeeding, older siblings, pet dog ownership, or maternal allergy.

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Abbreviations used

aHR- Adjusted hazard ratio
 aOR- Adjusted odds ratio
 aRR- Adjusted risk ratio
 CI- Confidence interval
 ICD- International Classification of Disease
 IPW- Inverse probability weighting
 nTreg- Naïve regulatory T cells
 OFC- Oral food challenge
 OR- Odds ratio
 SPT- Skin prick test
 VPDC- Victorian Perinatal Data Collection
 WGA- Weight for gestational age

CONCLUSION: Caesarean delivery, either with or without labor, or elective or emergency, was not associated with the risk of food allergy in a population-based cohort of 12-month-old infants. © 2022 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2022;10:2135-43)

Key words: Caesarean; Food allergy; Egg allergy; Peanut allergy; Labor; Emergency caesarean; Elective caesarean; Data linkage

The microbial exposure hypothesis proposes that altered exposure to a variety of microbes and infections in early life can influence the developing immune system, predisposing to allergic disease.¹ Consistent with this hypothesis, children with food allergy exhibit altered gut microbial composition compared with children without food allergy.^{2,3} Furthermore, it has been shown that mode of delivery may influence the composition of the infant microbiome,⁴⁻⁶ suggesting a plausible pathway by which mode of delivery can modify the risk of developing allergic disease.

Caesarean delivery in the absence of labor may bypass the opportunity for neonatal gut colonization with maternal gut and vaginal flora. Compared with vaginally born infants, the microbiome of caesarean born infants have more bacteria species that are usually found on the skin, mouth, and the surrounding environment, whereas infants born vaginally have microbiota dominated by vaginal or intestinal bacteria species.⁷⁻¹⁰ On the other hand, the gut microbiome of infants born by caesarean delivery after the initiation of labor have higher diversity compared with those born by caesarean before the onset of labor and membrane rupture.¹¹ Alternatively, aberrations in infant immune programming have been associated with the presence or absence of labor. Infants exposed to labor (vaginal delivery and cesarean after the onset of labor) compared with infants not exposed to labor (cesarean in the absence of labor) have reduced naïve regulatory T cells (nTreg) at birth. Although mode of delivery was not associated with food allergy, this lower nTreg at birth was associated with an increased risk of food allergy, suggesting that labor-associated immune activation is associated with the risk of allergic disease.¹²

A systematic review in 2013 that included 13 studies that assessed the association between mode of delivery and the risk of food allergy showed mixed associations with generally small effect sizes, and few studies used gold standard food allergy outcomes.¹ Of the 4 studies that included challenge-confirmed food allergy outcomes, only 1 (n = 2656) found that mode of delivery was associated with increased risk of cow's milk allergy up to age 2

years, which was seen only in children with maternal allergy.¹³ A major caveat of these findings is that early studies failed to consider additional details of the caesarean delivery.

Few studies distinguish between the types of caesarean, that is, elective or emergency, or with or without labor, which is relevant to the proposed biological pathways. Of the studies that did consider the different types of caesareans, unfortunately they relied on imprecise measures of food allergy, such as self-report.^{14,15} Recently, a large prospective Swedish study (n = 1,086,378) found that compared with vaginal birth, caesarean birth was associated with an increased risk of food allergy diagnosis (adjusted hazard ratio [aHR]: 1.21, 95% confidence interval [CI]: 1.18-1.25) with the association being similar when caesarean delivery was categorized into elective (aHR: 1.17, 95% CI: 1.10-1.24) versus emergency caesarean (aHR: 1.25, 95% CI: 1.18-1.32).¹⁶ However, food allergy was measured using International Classification of Disease (ICD) codes from health care registries, which have low sensitivity to true of IgE-mediated food allergy and may have captured non-IgE food allergies. In addition, this finding may reflect differential health care seeking behavior across the exposure groups, which may have overestimated the association.

Our HealthNuts study that measured food allergy using the gold standard oral food challenge (OFC) did not find evidence that mode of delivery increased the risk of egg allergy;^{17,18} however, this analysis could not account for type of caesarean (with or without labor) as data were not available at the time of analysis. We have now addressed this limitation by linking HealthNuts study data to Victorian Perinatal Data Collection (VPDC) and assessed whether delivery by elective or emergency caesarean, or caesarean in the absence or presence of labor, is associated with the risk of food allergy.

METHODS

Study design

The HealthNuts study is a population-based longitudinal cohort study based in Melbourne, Australia, that was established to measure the prevalence and risk factors of food allergy. Detailed methodology for the HealthNuts study has been described previously.^{19,20} Briefly, 5276 infants aged 11 to 15 months attending council run immunization sessions were recruited between September 2007 and August 2011. At recruitment, questionnaires captured information on the infant's demographics, environmental exposures, and allergy history. Infants underwent skin prick testing (SPT) to ascertain sensitization to egg, peanut, sesame, and either shellfish or cow's milk. Infants with a wheal diameter of ≥ 1 mm to egg, peanut, or sesame were invited to attend the HealthNuts study clinic at the Royal Children's Hospital for an OFC. At the OFC visit, blood samples were collected and measured for food-specific IgE using the ImmunoCAP FEIA system. Food sensitization was defined as SPT ≥ 2 mm and/or food-specific IgE ≥ 0.35 kU/L. During the OFC, infants consumed a maximum of 2 teaspoons of peanut butter, 1 whole egg white, or 2 teaspoons of tahini, unless a reaction occurred. The criterion for a positive OFC was one of the following reactions within 2 hours of last allergen dose: 3 or more concurrent noncontact hives lasting for more than 5 minutes, perioral or periorbital angioedema, vomiting, or evidence of anaphylaxis, in a child with a positive test of sensitization.^{19,21} Infants were also considered food allergic if they had a reaction consistent with the OFC stopping criteria within the previous 1 month for egg and 2 months for

peanut and sesame, and a positive test of sensitization. Food tolerance was defined as a negative OFC or negative SPT (0 mm) at recruitment. Infants with a positive OFC but no evidence of sensitization were deemed inconclusive.²² Ethical approval was obtained from the Office for Children HREC (ref. no. CDF/07/492), Department of Human Services HREC (ref. no. 10/07), and Royal Children's Hospital HREC (ref. nos. 27047 and 32294).

Data linkage

Data have also been collected from participants at later ages; however, the methods from these subsequent follow-up visits are not described in detail here as the present study only used food allergy outcome data at age 1 year. When participants were 6 years old, consent was requested to link the participant's study data to data from other registries including VPDC. The VPDC records detailed obstetric and neonatal information relating to every birth in Victoria. Hospitals and birth centers document and submit birth-related data to the VPDC.²³ A request was submitted to the VPDC to release data of those who consented; the VPDC also sought permission from hospitals to release the data for the purpose of the study (Figure 1). For the present study, data relating to mode of birth were requested from the VPDC. Mode of delivery was defined as either a vaginal delivery or delivery by caesarean section, which included all types of caesareans. For additional analyses, caesarean delivery was further classified as elective (planned) or emergency (unplanned), and if the caesarean (elective or emergency) was performed before or after the onset of labor; vaginal delivery was the comparison group for all analyses.

Potential confounders and effect modifiers

To identify possible confounders for the association between mode of delivery and food allergy risk, a directed acyclic graph was constructed using Dagitty software (Figure E1, available in this article's Online Repository at www.jaci-inpractice.org).²⁴ Variables that were potentially associated with both the exposure and outcome were adjusted for. These included maternal country of birth (born in Australia, far east Asia, UK/Europe, or other),^{25,26} maternal age at infant's birth,²⁷⁻³⁰ premature birth (≤ 36 weeks of gestation),^{16,31,32} socioeconomic status (measured by Socio-Economic Indexes for Area),³³⁻³⁵ and weight for gestational age (WGA).¹⁶ WGA was included in addition to prematurity, as in addition to capturing gestational age, it also captures growth of the fetus that has been associated with the risk of food allergy.³⁶ WGA was based on Australian standards for birth WGA³⁷ and derived from birthweight and estimated gestational age data obtained from both the HealthNuts recruitment questionnaire and linked VPDC data. WGA was categorized into 3 categories: small for gestational age (birthweight below the 10th percentile), large for gestational age (greater than the 90th percentile for gestational age), and normal WGA (between 10th and 90th percentile).

Factors related to the microbial hypothesis that were assessed as effect modifiers for the association between mode of delivery and food allergy included pet dog exposure, breastfeeding (never, ≤ 6 months, and > 6 months), and having siblings. Maternal allergy was assessed as a potential effect modifier based on previous research showing evidence for an interaction between mode of delivery and maternal allergy.^{13,15}

Statistical analysis

Logistic regression was used to model the association between mode of delivery and the risk of food allergy, with models adjusted for potential confounders as described above. Separate models were

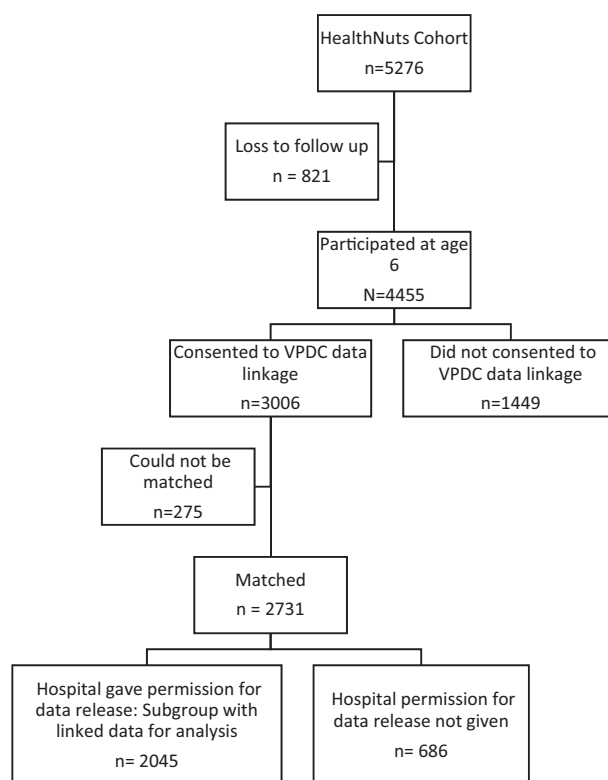


FIGURE 1. Flow chart showing participation of HealthNuts and data linkage. VPDC, Victorian Perinatal Data Collection.

constructed for the different caesarean variables (all caesarean, caesarean with or without labor, and elective or emergency caesareans) with all caesarean variables compared with the baseline of vaginal delivery. As a secondary analysis, the outcomes of any food, egg, and peanut sensitization were also considered, with sensitization defined as SPT ≥ 2 mm only as this was available for the whole cohort. Effect modification was assessed by fitting models with and without interaction terms between mode of delivery and the effect modifier, and was compared using likelihood ratio tests; P value $< .1$ was considered evidence of effect modification.

To assess for potential selection bias between participants who did and did not have linked VPDC data and whether this may have influenced effect estimates, demographic and clinical characteristics were compared using the Pearson χ^2 test for categorical variables and the unpaired t -test for continuous variables; characteristics with a P value of $< .05$ from comparisons were considered different. Inverse probability weights (IPW) were calculated as the inverse of the probability of having VPDC data or not, obtained from a logistic regression model that included variables that were associated with the presence linked VPDC data.³⁸ A sensitivity analysis was conducted in which these sampling weights were applied to the logistic regression models of the association between delivery mode and food allergy. Stata 16.0 was used for all statistical analyses.

RESULTS

Participation

Of the 5276 original participants of the HealthNuts cohort study, 4455 participated at age 6 and 3006 families (67%)

TABLE I. Characteristics of the HealthNuts cohort presented separately for those with and without linked VPDC data

Characteristic	Linked with VPDC (N = 2045), % (n/N)	Did not link with VPDC (N = 3231), % (n/N)	P value*
Any food allergy at 12 mo	13.0 (253/1944)	9.5 (281/2963)	<.001
Any food sensitization at 12 mo	18.7 (367/1965)	16.5 (509/3094)	.04
Mode of birth (HealthNuts data)			
Vaginal birth	70.0 (1428/2041)	64.7 (2072/3203)	<.001
Caesarean	30.0 (611/2041)	35.3 (1131/3203)	
Mode of birth (VPDC data)			
Vaginal birth	69.9 (1428/2042)	—	
Caesarean	30.1 (614/2042)	—	
Vaginal birth	69.9 (1428/2042)	—	
Caesarean with labor	12.5 (256/2042)	—	
Caesarean without labor	17.5 (358/2042)	—	
Vaginal birth	69.9 (1428/2042)	—	
Emergency caesarean	14.9 (304/2042)	—	
Elective caesarean	15.2 (310/2042)	—	
Mother's country of birth			
Australian	76.2 (1526/2004)	69.0 (2161/3133)	<.001
Far east Asian	8.6 (172/2004)	11.0 (343/3133)	
UK/Europe	7.6 (153/2004)	10.0 (314/3133)	
Other	7.6 (153/2004)	10.1 (315/3133)	
Parent's country of birth			
Both Australian	62.2 (1240/1995)	57.3 (1783/3113)	.005
1 or both far east Asian	10.4 (208/1995)	12.5 (390/3113)	
1 or both UK/Europe	14.5 (290/1995)	15.6 (485/3113)	
Other	12.9 (257/1995)	14.6 (455/3113)	
Mother's age at birth years			
Mean (SD)	33.1 (4.6)	32.8 (4.9)	.02
Mother smoked during pregnancy	3.9 (78/2000)	5.2 (161/3117)	.036
Socioeconomic status† (1 = most disadvantaged)			
1	19.4 (397/2042)	20.7 (665/3219)	.002
2	19.1 (389/2042)	20.5 (661/3219)	
3	23.7 (483/2042)	19.2 (619/3219)	
4	19.5 (399/2042)	19.3 (620/3219)	
5	18.3 (374/2042)	20.3 (654/3219)	
Family history of allergy (asthma, eczema, food allergy, hay fever)	73.0 (1492/2045)	67.1 (2169/3231)	<.001
Female sex	48.1 (979/2034)	49.8 (1600/3210)	.23
Gestational age at birth weeks (HealthNuts data)			
Mean (SD)	39.6 (1.5)	39.4 (1.5)	<.001
Gestational age at birth weeks (VPDC data)			
Mean (SD)	39.2 (2.6)	—	
Prematurity‡	5.4 (106/1954)	6.5 (199/3052)	.11
Birthweight grams (HealthNuts data)			
Mean (SD)	3429 (553)	3370 (554)	<.001
Birthweight grams (VPDC data)	3437 (540)	—	
Weight for gestational age§ (HealthNuts data)			
Normal	84.2 (1721/2045)	83.4 (2696/3231)	.02
SGA	7.3 (150/2045)	9.3 (300/3231)	
LGA	8.5 (174/2045)	7.3 (235/3231)	
Weight for gestational age§ (VPDC data)			
Normal	83.3 (1704/2045)	—	
SGA	6.3 (128/2045)		
LGA	10.4 (213/2045)		
Any breastfeeding	95.8 (1919/2003)	93.5 (2943/3147)	<.001

(continued)

TABLE I. (Continued)

Characteristic	Linked with VPDC (N = 2045), % (n/N)	Did not link with VPDC (N = 3231), % (n/N)	P value*
Duration of breastfeeding			
Never	4.1 (84/2045)	6.3 (204/3231)	<.001
<6 mo	25.1 (514/2045)	29.6 (955/3231)	
>6 mo	70.8 (1447/2045)	64.1 (2072/3231)	
No. of siblings			
None	50.4 (1021/2027)	49.0 (1561/3188)	.70
1	32.4 (657/2027)	33.8 (1077/3188)	
2	12.9 (262/2027)	12.7 (405/3188)	
3 or more	4.3 (87/2027)	4.6 (145/3188)	
Any siblings	49.3 (1004/2035)	51.1 (1643/3216)	.22
Pet dog inside first 12 mo	22.4 (458/2044)	19.0 (614/3228)	.003

Denominators may differ from the column header due to some missing data for characteristics.

SD, Standard deviation; VPDC, Victorian Perinatal Data Collection.

*P values calculated from the χ^2 test comparing infants from the HealthNuts cohort with VPDC linkage with those without VPDC-linked data.

†Socioeconomic status was defined using socioeconomic indexes for area (SEIFA) based on measures of disadvantage assigned to postcodes using Australian census data.³³

‡Prematurity was defined as birth <36 weeks of gestation.

§Weight for gestational age was categorized based on an infant's birthweight and gestational age at birth, according to Australian birthweight standards.³⁷ Small for gestational age (SGA) was defined as birthweight <10th percentile for gestational age and large for gestational age (LGA) was defined as birthweight >90th percentile for gestational age.

consented to data linkage. Nine percent (n = 275) of participants, despite consenting, could not be matched, and of those who were matched, 25% did not have data released because the governing hospital did not consent. Overall, data from a sample of 2045 participants (39% of the original cohort) were able to be linked and were included in this data analysis. Figure 1 presents the participation flow.

Table I describes the family and infant characteristics between HealthNuts participants with and without linked VPDC data. The proportion of infants with food sensitization and allergy was higher in the VPDC-linked group (13.0% and 18.7%, respectively), compared with those without linked data (9.5% and 16.5%, respectively). Caesarean delivery accounted for 30.0% of births in the VPDC-linked group and 35.3% of births in the group without linked data. Of those with linked data, 70% (n = 1428) of infants were born via a vaginal birth, 12.5% were born by caesarean after the onset of labor, and 17.5% were born by caesarean before the onset of labor. In the VPDC-linked group, emergency caesarean accounted for 14.9% of births and elective caesarean accounted for 15.2%. Other characteristics differed between those who did and did not have linked data including parent's country of birth, mothers age at birth, maternal smoking in pregnancy, socioeconomic status, family history of allergy, WGA, breastfeeding initiation, and exposure to pet dogs in the household.

Cesarean delivery and the risk of food allergy

In the entire HealthNuts cohort, food allergy occurred in 10.3% of infants born by caesarean compared with 11.3% of infants born vaginally. In the subgroup with linked data, food allergy was present in 12.7% of infants born by caesarean compared with 13.2% of those born vaginally. In both the whole cohort and the subgroup with linked data, there was no evidence of an association between mode of delivery and the risk of any food allergy, egg allergy, or peanut allergy (Table II).

Cesarean with or without labor and the risk of food allergy

Cesarean delivery was further categorized into whether it occurred with or without labor. Food allergy occurred more

frequently among infants who were born by caesarean after labor had started (14.2%) compared with infants who were born vaginally (13.3%) or via caesarean without labor (11.0%). In adjusted models, there was no evidence that caesarean delivery, either with or without labor, was associated with the risk of any food allergy, egg allergy, or peanut allergy (Table II). The direction of effect for caesarean with labor and the risk of peanut allergy suggested a possible increase in risk; however, the confidence intervals indicate that the possibility of no effect or reduced risk cannot be excluded.

Elective or emergency caesarean and the risk of food allergy

Food allergy occurred less frequently in infants born by emergency caesarean (11.2%) compared with elective caesarean (13.4%) and vaginal delivery (13.3%). There was insufficient evidence that the risk of food allergy differed by elective or emergency caesarean for any food allergy, egg allergy, or peanut allergy (Table II).

Assessment of effect modifiers

There was no evidence that the following factors modified the association between mode of delivery and risk of food allergy: duration of breastfeeding (P = .41), older siblings (P = .61), having a pet dog inside within the first year (P = .55), or maternal history of allergy (P = .68). Results were similar for egg and peanut allergy (data not shown).

Sensitivity analysis

In the sensitivity analysis where sampling weights were applied to account for possible selection bias due to differences in characteristics between those with and without linked data, the direction and magnitude of the odds ratio estimates for the association between mode of delivery and food allergy outcomes were consistent with the unweighted models (Table III).

Cesarean delivery and the risk of food sensitization

There was no evidence that mode of birth (any caesarean, caesarean with or without labor, or elective or emergency caesarean, all compared with vaginal birth) was associated with the risk of

TABLE II. The association between mode of delivery and any food allergy, egg allergy, and peanut allergy

	Any food allergy					Egg allergy					Peanut allergy				
	n/N (%)	Crude OR (95% CI)	P value	Adjusted OR* (95% CI)	P value	n/N (%)	Crude OR (95% CI)	P value	Adjusted OR* (95% CI)	P value	n/N (%)	Crude OR (95% CI)	P value	Adjusted OR* (95% CI)	P value
Whole HealthNuts cohort															
Vaginal birth	333/2989 (11.1)	Reference		Reference		301/3035 (9.9)	Reference		Reference		92/2972 (3.1)	Reference		Reference	
All caesarean	153/1483 (10.3)	0.92 (0.75, 1.12)	.41	0.95 (0.77, 1.16)	.60	127/1508 (8.4)	0.84 (0.67, 1.04)	.10	0.85 (0.68, 1.07)	.17	48/1475 (3.3)	1.05 (0.74, 1.50)	.78	0.99 (0.69, 1.42)	.94
Subgroup linked with VPDC data															
Vaginal birth	168/1259 (13.3)	Reference		Reference		149/1276 (11.7)	Reference		Reference		50/1283 (3.9)	Reference		Reference	
All caesarean	67/544 (12.3)	0.91 (0.67, 1.23)	.55	0.95 (0.70, 1.30)	.76	52/553 (9.4)	0.79 (0.56, 1.10)	.15	0.80 (0.57, 1.13)	.21	25/559 (4.5)	1.15 (0.71, 1.89)	.57	1.11 (0.69, 1.91)	.61
Vaginal birth	168/1259 (13.3)	Reference		Reference		149/1276 (11.7)	Reference		Reference		50/1283 (3.9)	Reference		Reference	
Cesarean with labor	32/225 (14.2)	1.08 (0.72, 1.62)	.72	1.13 (0.75, 1.72)	.55	23/228 (10.1)	0.85 (0.53, 1.35)	.49	0.89 (0.56, 1.42)	.63	14/232 (6.0)	1.58 (0.86, 2.91)	.14	1.61 (0.86, 3.01)	.14
Cesarean without labor	35/319 (11.0)	0.80 (0.54, 1.18)	.26	0.83 (0.55, 1.23)	.35	29/325 (8.9)	0.74 (0.49, 1.1)	.16	0.74 (0.48, 1.14)	.18	11/327 (3.4)	0.86 (0.44, 1.67)	.65	0.82 (0.41, 1.64)	.58
Vaginal birth	168/1259 (13.3)	Reference		Reference		149/1276 (11.7)	Reference		Reference		50/1283 (3.9)	Reference		Reference	
Emergency cesarean	30/267 (11.2)	0.82 (0.54, 1.24)	.35	0.86 (0.56, 1.31)	.48	22/274 (8.0)	0.66 (0.41, 1.05)	.08	0.68 (0.42, 1.10)	.12	13/278 (4.7)	1.21 (0.65, 2.26)	.55	1.19 (0.62, 2.27)	.60
Elective cesarean	37/277 (13.4)	1.00 (0.68, 1.47)	1.0	1.05 (0.71, 1.55)	.82	30/279 (10.8)	0.91 (0.60, 1.38)	.66	0.92 (0.60, 1.41)	.71	12/281 (4.3)	1.1 (0.58, 2.09)	.77	1.10 (0.56, 2.14)	.78

CI, Confidence interval; OR, odds ratio; SEIFA, socioeconomic index for areas; VPDC, Victorian Perinatal Data Collection; WGA, weight for gestational age.

*Adjusted for maternal country of birth, maternal age at birth, maternal smoking during pregnancy, prematurity (≤ 36 weeks of gestational age), SEIFA, and WGA.

TABLE III. The weighted association between mode of delivery and any food allergy, egg allergy, and peanut allergy, weighted for factors that were associated with the presence of linked birth data

	Any food allergy		Egg allergy		Peanut allergy	
	Adjusted OR* (95% CI)	P value	Adjusted OR* (95% CI)	P value	Adjusted OR* (95% CI)	P value
Vaginal birth	Reference		Reference		Reference	
All caesarean	0.90 (0.63, 1.28)	.56	0.78 (0.53, 1.14)	.19	1.20 (0.67, 2.16)	.55
Vaginal birth	Reference		Reference		Reference	
Cesarean with labor	1.06 (0.66, 1.69)	.81	0.88 (0.53, 1.48)	.64	1.51 (0.73, 3.14)	.27
Cesarean without labor	0.78 (0.50, 1.22)	.28	0.70 (0.44, 1.13)	.15	0.97 (0.48, 1.98)	.93
Vaginal birth	Reference		Reference		Reference	
Emergency cesarean	0.84 (0.52, 1.36)	.48	0.74 (0.44, 1.24)	.25	1.12 (0.51, 2.46)	.77
Elective cesarean	0.96 (0.62, 1.48)	.85	0.82 (0.51, 1.32)	.40	1.28 (0.64, 2.56)	.49

CI, Confidence interval; OR, odds ratio; SEIFA, socioeconomic index for areas; WGA, weight for gestational age.

*Adjusted for maternal country of birth, maternal age at birth, maternal smoking during pregnancy, prematurity (<36 weeks of gestational age), SEIFA, and WGA. Covariates that were included in the inverse probability weighting model were any food allergy, any food sensitization, mode of delivery, maternal and parent country of birth, mother's age at infant's birth, maternal smoking in pregnancy, SEIFA, family history of allergy, WGA, breastfeeding, and pet dog exposure.

any food, egg, or peanut sensitization (see [Tables E1 and E2](#) in this article's Online Repository at www.jaci-inpractice.org).

DISCUSSION

In this population-based cohort with linked birth registry data and objective measures of food allergy, there were no meaningful differences in the likelihood of food allergy observed for infants born by caesarean delivery compared with those born by vaginal delivery. In addition, there was no evidence of a difference in likelihood of food allergy if the caesarean was performed before or after the onset of labor, or whether it was an emergency or elective caesarean. There was no evidence of effect modification by several factors examined including breastfeeding, the presence of older siblings, having a pet dog within the first 12 months of life, or maternal history allergy.

The infant immune system undergoes rapid development during the neonatal period. Mode of delivery and the presence or absence of labor may interfere with the normal development of the immune system; proposed pathways include altered microbial exposure at birth and reduced activation of the immune system at birth due to the absence of labor.³⁹⁻⁴³ One of the biological mechanisms by which microbiota influences the developing immune system is that the composition of gut microbiota triggers differentiation of certain immune cells, which affect regulation of immune system responses, including inflammation or promotion of tolerance.⁴⁴ Labor may also play an important role, with the presence of labor associated with reduced regulatory T cells at birth.¹² If the immune system is programmed toward inflammatory responses during the critical intrapartum period, an infant may be predisposed toward an allergic phenotype.^{11,45} However, our findings do not support that mode of delivery, in the presence or absence of labor, has a meaningful impact on food allergy outcomes.

There is a body of literature that supports the null findings of the present study. The odds ratio estimates of 8 of 13 studies included in a systematic review, which examined the effect of caesarean birth on the risk of food allergy, found no clear association.¹ However, some studies have reported associations between mode of delivery and the risk of food allergy. A large Swedish study (n = 1,086,378) found that caesarean delivery,

compared with vaginal delivery, increased the risk of food allergy in children aged less than 13 years (aHR: 1.21, 95% CI: 1.18-1.25) and this association was similar when caesarean was further classified as elective or emergency.¹⁶ Food allergy was defined using ICD codes that was not corroborated with measures of IgE sensitization, and therefore may have low specificity to true IgE-mediated food allergy and capture non-IgE-mediated food allergies as well. This finding may also reflect differential health care seeking behavior across the exposure groups; that is, health care seeking behavior could be stronger in those receiving a caesarean who in turn may be more likely to seek a diagnosis for adverse food reactions, which may have overestimated the association.

The Upstate KIDS cohort found that although there was no evidence of an association between all caesarean deliveries and risk of self-reported food allergy (adjusted risk ratio [aRR]: 1.59, 95% CI: 0.73-3.44), emergency (aRR: 3.02, 95% CI: 1.26-7.25) and not elective caesarean (aRR: 0.48, 95% CI: 0.14-1.65) were associated with increased risk of self-reported food allergy. The authors noted that this finding was not consistent with the proposed hypothesis that altered immune development and susceptibility to food allergy would be greater in the infants delivered by elective caesarean compared with those born by emergency caesarean or vaginal delivery, and speculate that misclassification of type of caesarean delivery indication, or the inclusion of twins that are more likely to be delivered by caesarean, may have contributed to the unexpected finding.¹⁴ Emergency caesarean can also occur before the onset of labor and membrane rupture, and without differentiating between whether the caesarean was performed before labor may have limited their ability to directly address the proposed hypothesis. The Swedish study and Upstate KIDS study did not distinguish whether the elective or emergency caesarean occurred before or after the onset of labor and membrane rupture, which is an important consideration given the proposed biological pathways. Exposure to labor has been associated with immunological changes in infants at birth that are subsequently associated with the risk of food allergy. Although the Barwon Infant Study did not observe an association between mode of delivery and challenge-confirmed food allergy, the presence of labor (vaginal delivery and caesarean after the onset of labor) was associated with

reduced nTreg at birth that were subsequently associated with food allergy at age 1 year.¹² Several factors relating to birth, such as mode of delivery, duration of labor and membrane rupture, and microbial or antibiotic exposure, may impact immunological responses and predisposition to allergic disease. Unfortunately, the data received from VPDC on these factors were too incomplete to examine this hypothesis further.

The long-held paradigm that the uterus and infant gut are sterile before birth has also been recently contested, with some studies proposing that initial colonization of the neonatal gut occurs *in utero*.^{46,47} If the process of gut colonization begins *in utero*, factors that occur during pregnancy may impact the infant's microbiome and associated risk of allergic disease, rather than only the mode of delivery. Of note, studies that have reported an association between mode of delivery and food allergy have higher rates of caesarean (around 50%)¹⁵ compared with the present study. If these higher rates of caesarean are reflective of higher rates of maternal complications indicating the need for a caesarean, for example, gestational diabetes that has been shown to impact the gut microbiota of their week old infants,⁴⁸ this may potentially explain why these studies found a greater effect size than the present study.

The strengths of this study are that food allergy was measured using the gold standard OFC that reduces potential for misclassification when less precise measures such as SPT, serum IgE, or self-report are used. Data linkage with VPDC added additional information on birth factors to the HealthNuts cohort. These data specified whether the caesarean delivery occurred in the presence or absence of labor, providing an opportunity to explore a potentially important microbial exposure at birth, which other studies have been unable to.

There were several limitations of this study. Differences existed in some characteristics between the subgroup whose data were linked to VPDC. The resulting subgroup that formed the basis of this analysis was over-represented by those with food allergy and vaginal birth, compared with the group without VPDC-linked data. These differences may have resulted in selection bias; however, IPW, which reweighted characteristics of included participants to reflect the characteristics of the original cohort, did not materially affect our findings. In addition, some requested birth factor data relevant to the hypotheses proposed, such as duration of membrane structure or antibiotic exposure during labor, were missing substantial amounts of data. This limited the exploration of other potential pathways or confounders and should be explored in future research.

In conclusion, we found insufficient evidence that mode of delivery and conditions surrounding caesarean delivery have a meaningful impact on the risk of developing food allergy in infancy. These results may be useful for caregivers when considering the risks and benefits of caesarean delivery, and provide reassurance for mothers who require such intervention that there is little evidence that their infants are likely to be at a substantially increased risk of food allergy.

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REFERENCES

- Marrs T, Bruce KD, Logan K, Rivett DW, Perkin MR, Lack G, et al. Is there an association between microbial exposure and food allergy? A systematic review. *Pediatr Allergy Immunol* 2013;24: 311-20.e8.
- Kourosch A, Luna RA, Balderas M, Nance C, Anagnostou A, Devaraj S, et al. Fecal microbiome signatures are different in food-allergic children compared to siblings and healthy children. *Pediatr Allergy Immunol* 2018;29:545-54.
- Fazlollahi M, Chun Y, Grishin A, Wood RA, Burks AW, Dawson P, et al. Early-life gut microbiome and egg allergy. *Allergy* 2018;73:1515-24.
- Azad MB, Konya T, Guttman DS, Field CJ, Sears MR, HayGlass KT, et al. Infant gut microbiota and food sensitization: associations in the first year of life. *Clin Exp Allergy* 2015;45:632-43.
- Savage JH, Lee-Sarwar KA, Sordillo J, Bunyavanich S, Zhou Y, O'Connor G, et al. A prospective microbiome-wide association study of food sensitization and food allergy in early childhood. *Allergy* 2018;73:145-52.
- Jakobsson HE, Abrahamsson TR, Jenmalm MC, Harris K, Quince C, Jernberg C, et al. Decreased gut microbiota diversity, delayed Bacteroidetes colonisation and reduced Th1 responses in infants delivered by caesarean section. *Gut* 2014;63:559-66.
- Dominguez-Bello MG, Costello EK, Contreras M, Magris M, Hidalgo G, Fierer N, et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proc Natl Acad Sci U S A* 2010;107:11971-5.
- Backhed F, Roswall J, Peng Y, Feng Q, Jia H, Kovatcheva-Datchary P, et al. Dynamics and stabilization of the human gut microbiome during the first year of life. *Cell Host Microbe* 2015;17:690-703.
- Reyman M, van Houten MA, van Baarle D, Bosch A, Man WH, Chu M, et al. Impact of delivery mode-associated gut microbiota dynamics on health in the first year of life. *Nat Commun* 2019;10:4997.
- Shao Y, Forster SC, Tsaliki E, Vervier K, Strang A, Simpson N, et al. Stunted microbiota and opportunistic pathogen colonization in caesarean-section birth. *Nature* 2019;574:117-21.
- Azad MB, Konya T, Maughan H, Guttman DS, Field CJ, Chari RS, et al. Gut microbiota of healthy Canadian infants: profiles by mode of delivery and infant diet at 4 months. *CMAJ* 2013;185:385-94.
- Collier F, Ponsonby AL, O'Hely M, Tang MLK, Saffery R, Molloy J, et al. Naive regulatory T cells in infancy: associations with perinatal factors and development of food allergy. *Allergy* 2019;74:1760-8.
- Eggesbø M, Botten G, Stigum H, Samuelsen SO, Brunekreef B, Magnus P. Cesarean delivery and cow milk allergy/intolerance. *Allergy* 2005;60:1172-3.
- Adeyeye TE, Yeung EH, McLain AC, Lin S, Lawrence DA, Bell EM. Wheeze and food allergies in children born via cesarean delivery: the Upstate KIDS study. *Am J Epidemiol* 2019;188:355-62.
- Papathoma E, Triga M, Fouzas S, Dimitriou G. Cesarean section delivery and development of food allergy and atopic dermatitis in early childhood. *Pediatr Allergy Immunol* 2016;27:419-24.
- Mitselou N, Hallberg J, Stephansson O, Almqvist C, Melen E, Ludvigsson JF. Cesarean delivery, preterm birth, and risk of food allergy: nationwide Swedish cohort study of more than 1 million children. *J Allergy Clin Immunol* 2018;142: 1510-4.e2.
- Koplin JJ, Dharmage SC, Ponsonby AL, Tang ML, Lowe AJ, Gurrin LC, et al. Environmental and demographic risk factors for egg allergy in a population-based study of infants. *Allergy* 2012;67:1415-22.
- Peters RL, Allen KJ, Dharmage SC, Lodge CJ, Koplin JJ, Ponsonby AL, et al. Differential factors associated with challenge-proven food allergy phenotypes in a population cohort of infants: a latent class analysis. *Clin Exp Allergy* 2015;45: 953-63.

19. Osborne NJ, Koplin JJ, Martin PE, Gurrin LC, Thiele L, Tang ML, et al. The HealthNuts population-based study of paediatric food allergy: validity, safety and acceptability. *Clin Exp Allergy* 2010;40:1516-22.
20. Koplin JJ, Wake M, Dharmage SC, Matheson M, Tang ML, Gurrin LC, et al. Cohort Profile: The HealthNuts study: population prevalence and environmental/genetic predictors of food allergy. *Int J Epidemiol* 2015;44:1161-71.
21. Koplin JJ, Tang ML, Martin PE, Osborne NJ, Lowe AJ, Ponsonby AL, et al. Predetermined challenge eligibility and cessation criteria for oral food challenges in the HealthNuts population-based study of infants. *J Allergy Clin Immunol* 2012;129:1145-7.
22. Osborne NJ, Koplin JJ, Martin PE, Gurrin LC, Lowe AJ, Matheson MC, et al. Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and predetermined challenge criteria in infants. *J Allergy Clin Immunol* 2011;127:668-676.e1-2.
23. State of Victoria DoHaHS. Victorian perinatal data collection. Accessed April 26, 2022. <https://www.bettersafercare.vic.gov.au/about/ccopmm>
24. Textor J, van der Zander B, Gilthorpe MS, Liśkiewicz M, Ellison GT. Robust causal inference using directed acyclic graphs: the R package 'dagitty'. *Int J Epidemiol* 2017;45:1887-94.
25. Koplin JJ, Peters RL, Ponsonby AL, Gurrin LC, Hill D, Tang ML, et al. Increased risk of peanut allergy in infants of Asian-born parents compared to those of Australian-born parents. *Allergy* 2014;69:1639-47.
26. Reddy M, Wallace EM, Mockler JC, Stewart L, Knight M, Hodges R, et al. Maternal Asian ethnicity and obstetric intrapartum intervention: a retrospective cohort study. *BMC Pregnancy Childbirth* 2017;17:3.
27. Herstad L, Klungsøyr K, Skjærven R, Tanbo T, Forsén L, Åbyholm T, et al. Elective cesarean section or not? Maternal age and risk of adverse outcomes at term: a population-based registry study of low-risk primiparous women. *BMC Pregnancy Childbirth* 2016;16:230.
28. Bergholt T, Skjeldstad FE, Pyykönen A, Rasmussen SC, Tapper A-M, Bjarnadóttir RI, et al. Maternal age and risk of cesarean section in women with induced labor at term—a Nordic register-based study. *Acta Obstet Gynecol Scand* 2020;99:283-9.
29. Rydahl E, Declercq E, Juhl M, Maimburg RD. Cesarean section on a rise—Does advanced maternal age explain the increase? A population register-based study. *PLoS One* 2019;14:e0210655.
30. Dioun AF, Harris SK, Hibberd PL. Is maternal age at delivery related to childhood food allergy? *Pediatr Allergy Immunol* 2003;14:307-11.
31. MacDorman MF, Declercq E, Zhang J. Obstetrical intervention and the singleton preterm birth rate in the United States from 1991-2006. *Am J Public Health* 2010;100:2241-7.
32. Aitoro R, Paparo L, Amoroso A, Di Costanzo M, Cosenza L, Granata V, et al. Gut microbiota as a target for preventive and therapeutic intervention against food allergy. *Nutrients* 2017;9:672.
33. Pink B. An introduction to socio-economic indexes for areas (SEIFA). Canberra, ACT: Australian Bureau of Statistics; 2006.
34. McGowan EC, Matsui EC, Peng R, Salo PM, Zeldin DC, Keet CA. Racial/ethnic and socioeconomic differences in self-reported food allergy among food-sensitized children in National Health and Nutrition Examination Survey III. *Ann Allergy Asthma Immunol* 2016;117: 570-2.e3.
35. Räisänen S, Gissler M, Kramer MR, Heinonen S. Influence of delivery characteristics and socioeconomic status on giving birth by caesarean section—a cross sectional study during 2000-2010 in Finland. *BMC Pregnancy Childbirth* 2014;14:120.
36. Wooldridge AL, McMillan M, Kaur M, Giles LC, Marshall HS, Gattford KL. Relationship between birth weight or fetal growth rate and postnatal allergy: a systematic review. *J Allergy Clin Immunol* 2019;144:1703-13.
37. Joseph FA, Hyett JA, Schluter PJ, McLennan A, Gordon A, Chambers GM, et al. New Australian birthweight centiles. *Med J Aust* 2020;213:79-85.
38. Williamson EJ, Forbes A. Introduction to propensity scores. *Respirology* 2014;19:625-35.
39. Torow N, Hornef MW. The neonatal window of opportunity: setting the stage for life-long host-microbial interaction and immune homeostasis. *J Immunol* 2017;198:557-63.
40. Tanaka M, Nakayama J. Development of the gut microbiota in infancy and its impact on health in later life. *Allergol Int* 2017;66:515-22.
41. Francino MP. Birth mode-related differences in gut microbiota colonization and immune system development. *Ann Nutr Metab* 2018;73(Suppl 3):12-6.
42. Neu J, Rushing J. Cesarean versus vaginal delivery: long-term infant outcomes and the hygiene hypothesis. *Clin Perinatol* 2011;38:321-31.
43. Schlinzig T, Johansson S, Stephansson O, Hammarstrom L, Zetterstrom RH, von Döbeln U, et al. Surge of immune cell formation at birth differs by mode of delivery and infant characteristics—a population-based cohort study. *PLoS One* 2017;12:e0184748.
44. Ho HE, Bunyavanich S. Role of the microbiome in food allergy. *Curr Allergy Asthma Rep* 2018;18:27.
45. Hansen CH, Nielsen DS, Kverka M, Zakostelska Z, Klimesova K, Hudcovic T, et al. Patterns of early gut colonization shape future immune responses of the host. *PLoS One* 2012;7:e34043.
46. Stinson LF, Boyce MC, Payne MS, Keelan JA. The not-so-sterile womb: evidence that the human fetus is exposed to bacteria prior to birth. *Front Microbiol* 2019;10:1124.
47. Funkhouser LJ, Bordenstein SR. Mom knows best: the universality of maternal microbial transmission. *PLoS Biol* 2013;11:e1001631.
48. Ponzio V, Ferrocino I, Zarovska A, Amenta MB, Leone F, Monzeglio C, et al. The microbiota composition of the offspring of patients with gestational diabetes mellitus (GDM). *PLoS One* 2019;14:e0226545.

ONLINE REPOSITORY

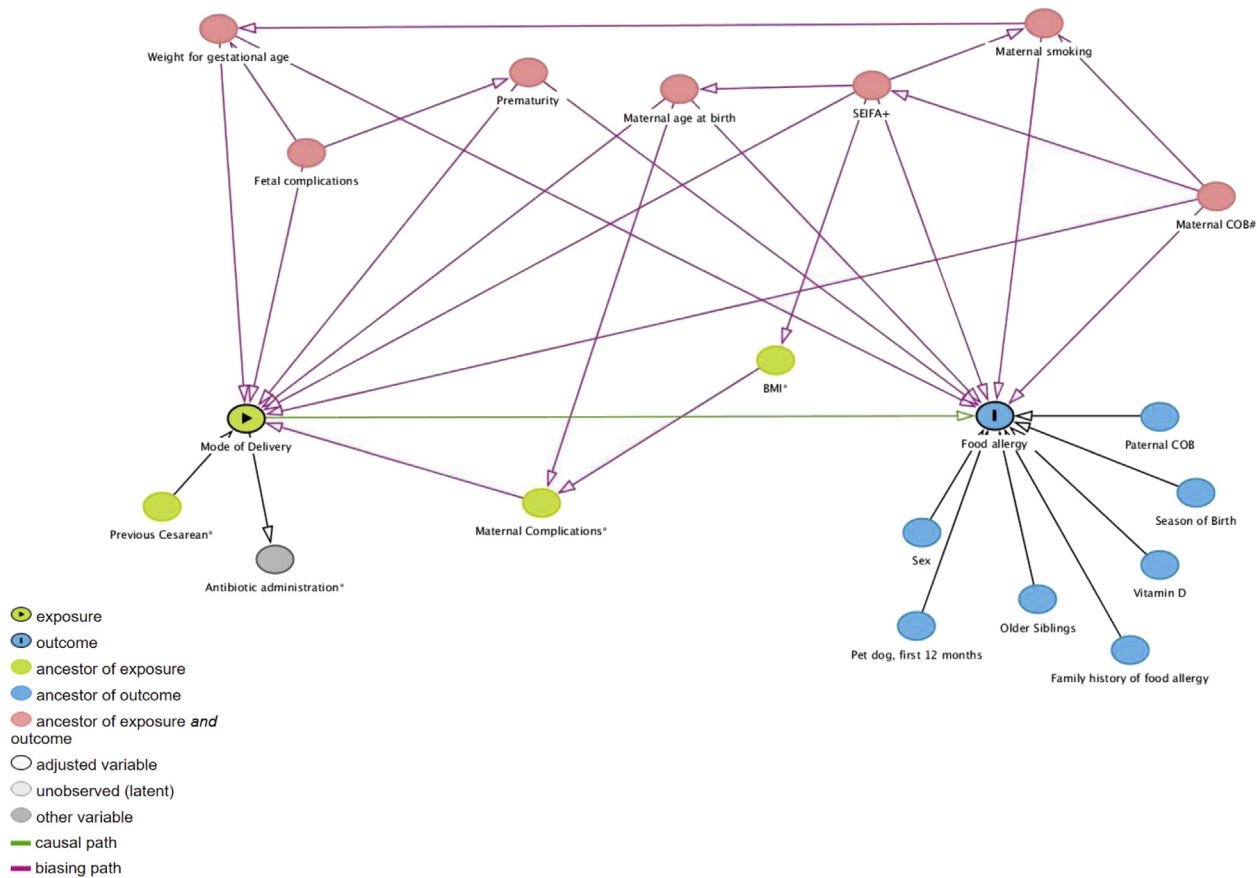


FIGURE E1. Directed acyclic graph showing possible causal pathways for factors associated with mode of delivery (exposure) or food allergy (outcome). *Data requested from VPDC, but were incomplete. #COB (country of birth). +SEIFA (a measure of socioeconomic status as described in methods). SEIFA, Socioeconomic index for areas; VPDC, Victorian Perinatal Data Collection.

TABLE E1. The association between mode of delivery and any food sensitization, egg sensitization, and peanut sensitization

	Any food sensitization					Egg sensitization					Peanut sensitization				
	n/N (%)	Crude OR (95% CI)	P value	Adjusted OR* (95% CI)	P value	n/N (%)	Crude OR (95% CI)	P value	Adjusted OR* (95% CI)	P value	n/N (%)	Crude OR (95% CI)	P value	Adjusted OR* (95% CI)	P value
Whole HealthNuts cohort															
Vaginal birth	423/2941 (14.4)	Reference		Reference		328/3004 (10.9)	Reference		Reference		195/2934 (6.7)	Reference		Reference	
All caesarean	198/1459 (13.6)	0.93 (0.78, 1.12)	.46	0.99 (0.84, 1.18)	.98	155/1492 (10.4)	0.95 (0.77, 1.16)	.59	1.01 (0.84, 1.21)	.92	96/1458 (6.6)	0.99 (0.77, 1.27)	.94	0.97 (0.76, 1.22)	.79
Subgroup linked with VPDC data															
Vaginal birth	207/1236 (16.8)	Reference		Reference		161/1260 (12.8)	Reference		Reference		97/1258 (7.7)	Reference		Reference	
All caesarean	83/530 (15.7)	0.92 (0.70, 1.22)	.57	1.0 (0.77, 1.31)	.99	63/544 (11.6)	0.89 (0.66, 1.22)	.66	0.95 (0.70, 1.28)	.70	43/545 (7.9)	1.03 (0.71, 1.49)	.90	0.94 (0.65, 1.37)	.75
Vaginal birth	207/1236 (16.8)	Reference		Reference		161/1260 (12.8)	Reference		Reference		97/1258 (7.7)	Reference		Reference	
Cesarean with labor	36/217 (16.6)	0.99 (0.67, 1.46)	.95	1.09 (0.76, 1.57)	.64	31/222 (14.0)	1.11 (0.73, 1.68)	.63	1.18 (0.79, 1.75)	.42	18/224 (8.0)	1.05 (0.62, 1.77)	.87	0.92 (0.55, 1.56)	.77
Cesarean without labor	47/313 (15.0)	0.88 (0.62, 1.24)	.46	0.94 (0.67, 1.31)	.71	32/322 (9.9)	0.75 (0.50, 1.12)	.17	0.79 (0.53, 1.16)	.23	25/321 (7.8)	1.01 (0.64, 1.60)	.96	0.96 (0.61, 1.50)	.84
Vaginal birth	207/1236 (16.8)	Reference		Reference		161/1260 (12.8)	Reference		Reference		97/1258 (7.7)	Reference		Reference	
Emergency cesarean	36/259 (13.9)	0.80 (0.55, 1.18)	.26	0.94 (0.66, 1.33)	.72	30/269 (11.2)	0.86 (0.57, 1.30)	.47	0.93 (0.63, 1.38)	.86	18/270 (6.7)	0.85 (0.51, 1.44)	.56	0.77 (0.46, 1.28)	.33
Elective cesarean	47/271 (17.3)	1.04 (0.74, 1.48)	.81	1.07 (0.76, 1.51)	.70	33/275 (12.0)	0.93 (0.62, 1.39)	.72	0.97 (0.65, 1.43)	.86	25/275 (9.1)	1.20 (0.76, 1.90)	.44	1.13 (0.71, 1.79)	.61

CI, Confidence interval; OR, odds ratio; SEIFA, socioeconomic index for areas; VPDC, Victorian Perinatal Data Collection; WGA, weight for gestational age.

*Adjusted for maternal country of birth, maternal age at birth, maternal smoking during pregnancy, prematurity (≤ 36 weeks of gestational age), SEIFA, and WGA.

TABLE E2. The weighted association between mode of delivery and any food allergy, egg allergy, and peanut allergy, weighted for factors that were associated with the presence of linked birth data

	Any food sensitization		Egg sensitization		Peanut sensitization	
	Adjusted OR* (95% CI)	P value	Adjusted OR* (95% CI)	P value	Adjusted OR* (95% CI)	P value
Vaginal birth	Reference		Reference		Reference	
All caesarean	0.87 (0.65, 1.18)	.38	0.83 (0.59, 1.17)	.28	0.96 (0.64, 1.45)	.85
Vaginal birth	Reference		Reference		Reference	
Cesarean with labor	0.91 (0.61, 1.37)	.65	1.03 (0.67, 1.60)	.88	0.98 (0.55, 1.72)	.94
Cesarean without labor	0.85 (0.59, 1.22)	.38	0.68 (0.44, 1.06)	.09	0.95 (0.58, 1.55)	.84
Vaginal birth	Reference		Reference		Reference	
Emergency cesarean	0.74 (0.49, 1.12)	.15	0.82 (0.52, 1.29)	.38	0.77 (0.44, 1.38)	.39
Elective cesarean	1.01 (0.70, 1.46)	.94	0.84 (0.55, 1.28)	.43	1.16 (0.72, 1.91)	.55

CI, Confidence interval; IPW, inverse probability weighting; OR, odds ratio; SEIFA, socioeconomic index for areas; WGA, weight for gestational age.

*Adjusted for maternal country of birth, maternal age at birth, maternal smoking during pregnancy, prematurity (≤ 36 weeks of gestational age), SEIFA, and WGA. Covariates that were included in the IPW model were any food allergy, any food sensitization, mode of delivery, maternal and parent country of birth, mother's age at infant's birth, maternal smoking in pregnancy, SEIFA, family history of allergy, WGA, breastfeeding, and pet dog exposure.