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## SPECIALTY SECTION

This article was submitted to Children and Health, a section of the journal Frontiers in Pediatrics

RECEIVED 15 September 2022

ACCEPTED 28 December 2022

PUBLISHED 17 January 2023

## CITATION

Yang X, Zhou C, Guo C, Wang J, Chen I, Wen SW, Krewski D, Yue L and Xie R-h (2023) The prevalence of food allergy in cesarean-born children aged 0–3 years: A systematic review and meta-analysis of cohort studies. *Front. Pediatr.* 10:1044954. doi: 10.3389/fped.2022.1044954

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# The prevalence of food allergy in cesarean-born children aged 0–3 years: A systematic review and meta-analysis of cohort studies

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**Purpose:** Previous studies reported a higher risk of food allergy for cesarean-born children than vaginal-born children. This study aims to systematically compare the prevalence of food allergy among cesarean-born and vaginal-born children aged 0–3 years.

**Methods:** Three English and two Chinese databases were searched using terms related to food allergies and cesarean sections. Cohort studies that reported the prevalence of food allergy in cesarean-born and vaginal-born children aged 0–3 years were included. Two reviewers performed study selection, quality assessment, and data extraction. The pooled prevalence of food allergy in cesarean-born and vaginal-born children was compared by meta-analysis.

**Results:** Nine eligible studies, with 9,650 cesarean-born children and 20,418 vaginal-born children aged 0–3 years, were included. Of them, 645 cesarean-born children and 991 vaginal-born children were identified as having food allergies. The pooled prevalence of food allergy was higher in cesarean-born children (7.8%) than in vaginal-born children (5.9%). Cesarean section was associated with an increased risk of food allergy [odds ratio (OR): 1.45; 95% confidence interval (CI): 1.03–2.05] and cow's milk allergy (OR: 3.31; 95% CI: 1.98–5.53). Additionally, cesarean-born children with a parental history of allergy had an increased risk of food allergy (OR: 2.60; 95% CI: 1.28–5.27).

**Conclusion:** This study suggests that cesarean sections was associated with an increased risk of food and cow's milk allergies in children aged 0–3 years. Cesarean-born children with a parental history of allergy demonstrated a higher risk for food allergy than did vaginal-born children. These results indicate that caregivers should be aware of the risks of food allergies in cesarean-born children, reducing the risk of potentially fatal allergic events. Further research is needed to identify the specific factors affecting food allergies in young children.

**Systematic Review Registration:** <http://www.crd.york.ac.uk/prospero/>, identifier: International Prospective Register of Systematic Reviews (NO. CRD42019140748).

## KEYWORDS

food allergy, cesarean-born, children aged 0–3 years, meta-analysis, prevalence of food allergy

## Abbreviations

CS, cesarean section; CI, confidence interval; OR, odds ratio; PRISMA, Preferred Reporting Item for Systematic Reviews and Meta-analyses; VD, vaginal delivery.

## Introduction

Food allergy, defined as an adverse immune response to food proteins (1–3), is an important public health problem (4) that is becoming increasingly prevalent (2, 5). Specific foods that have been associated with allergic reactions include cow's milk, egg, wheat, soy, peanut, tree nuts, fish, and shellfish (6). At this time, the reasons for the apparent increase in food allergies in children are unclear (7).

The rate of cesarean section (CS) has been increasing in recent decades (2, 5). CS has been associated with an increased risk of developing asthma (8), allergic rhinitis (9), and other immune disorders in offspring (10). Although neonates acquire maternal vaginal and fecal microbiota during labor and delivery (11), CS interrupts this transfer process, thereby altering bacterial colonization of the gut (12). The altered gut flora of cesarean-born children has been shown to prolong immunological immaturity and thereby increase the risk of allergic diseases (13).

Previous studies that assessed the association between mode of delivery and food allergy have yielded inconsistent results (7, 14–16). One study revealed that CS might be a risk factor for food allergens up to the age of 2 years (effect estimates for allergic sensitization against food allergens [odds ratio (OR) = 1.64 (1.03–2.63)] (14), whereas other studies found no convincing evidence that CS increased the risk of developing allergic diseases in children (15, 16). A systematic review synthesized the available evidence on the association between mode of delivery and food allergy and revealed that cesarean-born children under 10 years of age might have a higher risk of food allergy than vaginal-born children (7). However, no systematic review has estimated the prevalence of food allergy from different sources of foods among cesarean-born and vaginal-born children. This study aims to quantify and compare the prevalence of food allergy for cesarean-born and vaginal-born children aged 0–3 years through a systematic review and meta-analysis.

## Methods

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (17). The protocol was registered with the International Prospective Register of Systematic Reviews (NO. CRD42019140748) at <http://www.crd.york.ac.uk/prospero> (18).

### Search strategy

With the support of two research librarians with expertise in systematic reviews in health services, a systematic search of the literature was conducted to identify relevant studies using EMBASE, MEDLINE, Web of Science, CNKI, and Wanfang. The literature search included all published articles from inception to May 31, 2022. A combination of key terms and/or subject headings was applied, including food allergy terms (food hypersensitivity or (food or egg or nut or nuts\* or peanut\* or cashew or pistachio or

hazelnut\* or almond\* or fish or soy or legume\* or kiwi or apple or fruit or peach or milk or dairy or shellfish or wheat) or (allerg\* or hypersensitivit\*) and cesarean section-related terms (c section\* or Cesarean\* or Caesarean\*) (Supplementary Table S1). The databases were then combined and searched using the Covidence (a web-based software platform).

### Study selection

Titles and abstracts of articles retrieved by searching the five electronic databases were screened independently by two reviewers (XY and CG) to determine if they satisfied the predetermined inclusion/exclusion criteria. Fulltext screening was then performed to identify studies included in the systematic review. Disagreements regarding eligibility were resolved by discussion with the third reviewer (R-hX).

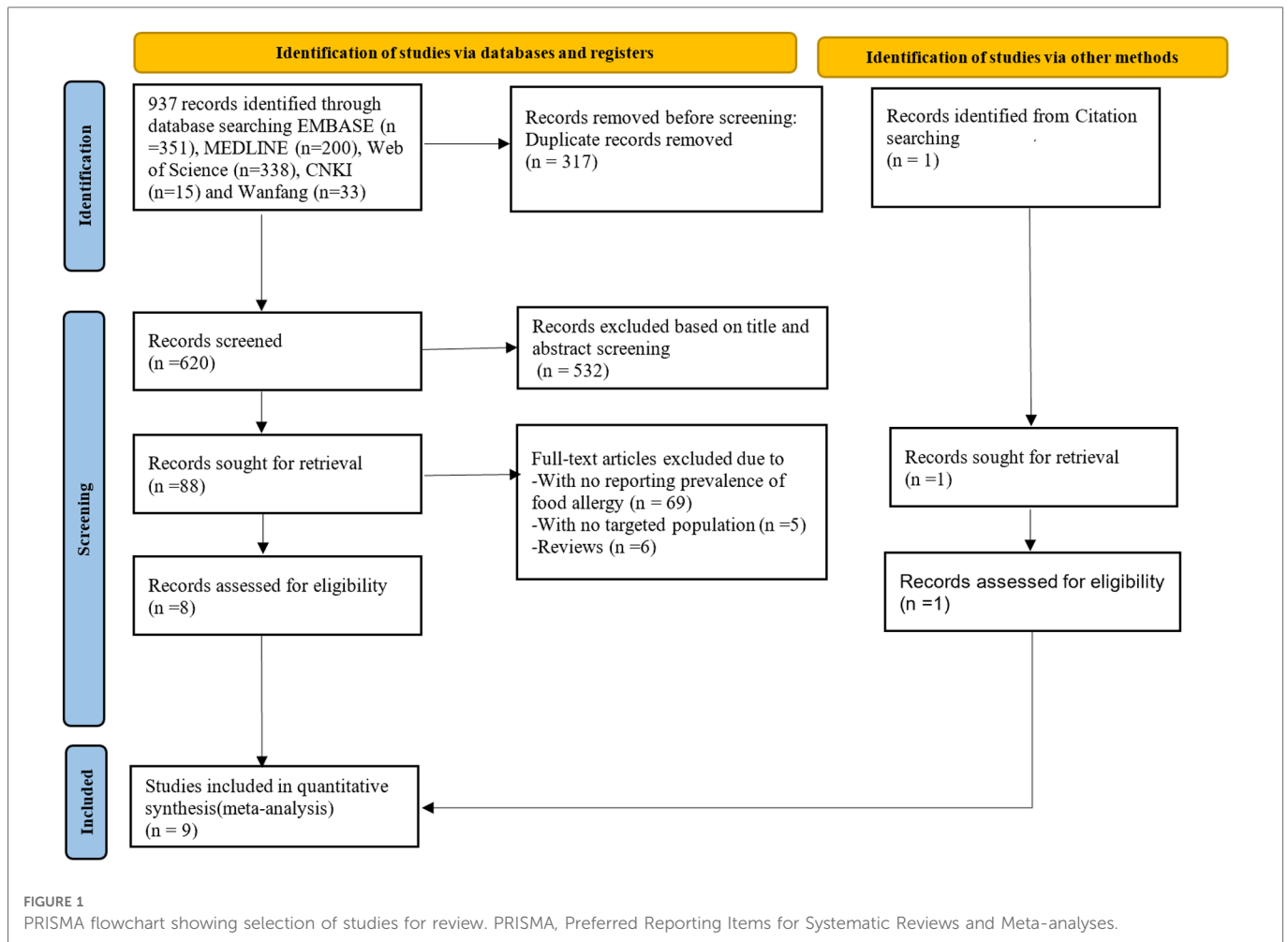
### Inclusion/exclusion criteria

Studies were included in this systematic review, if they: (1) targeted cesarean-born and vaginal-born children aged 0–3 years; (2) identified food allergy based on either self-report questionnaires (i.e., participants or their parents reported that they had any of the outcomes or not), or objective methods [i.e., skin prick test (SPT), specific immunoglobulin E (IgE), open food challenge (OFC)/double-blind placebo-controlled food challenge (DBPCFC), or convincing clinical history (i.e., outcomes confirmed by a physician)] (19); (3) had information about the sample size and prevalence of food allergy among cesarean-born and vaginal-born children aged 0–3 years; and (4) were published in English or Chinese.

Although food allergies typically appear around 1 year of age, there may be delays in identifying and reporting. By expanding the age range to include children up to 3 years old, we expected to achieve a more complete ascertainment of food allergies in young children. Due to the pre-specified age range in this study, with cesarean- and vaginal-born infants assessed in the same fashion; we did not expect bias to enter our review. Studies were excluded if they were abstracts, interviews, commentaries, or reviews. In addition, studies that did not report the prevalence of food allergy in children aged 0–3 were excluded.

### Data extraction

Two reviewers (XY and CZ) independently extracted relevant data from eligible studies using a standard form, including: the last name of the first author, publication year, country of origin, age of children, the identified methods of food allergy, parental history of food allergy, the study period, the number of cesarean-born and vaginal-born children, and the number of food, cow's milk, and egg allergies occurring in cesarean-born, and vaginal-born children. Any disagreements between the two reviewers were resolved by discussion with the third reviewer (R-hX).



## Quality assessment

The risk of bias and quality of the study were assessed by two reviewers (CG and CZ) independently using the Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument (JBI-MASARI) (Supplementary Table S2). Any disagreements with respect to validity were resolved by the third reviewer (LY).

## Data analysis

Data analysis was conducted in the “meta” and “metaphor” modules using R software (version 3.6.2) (19). Heterogeneity across studies was assessed using the Higgins  $I^2$  statistic (20). In cases of significant heterogeneity ( $I^2 > 0.5$ ), the random effects model of Der Simonian and Laird (20) was used to obtain the prevalence of food allergy; otherwise, in cases of no inconsistency in the risk estimate ( $I^2 < 0.5$ ), a fixed effects model was used. When significant heterogeneity was observed, mixed-model meta-regression analysis was also conducted to explore the influence of potential moderators of heterogeneity using the restricted maximum-likelihood method. Subgroup analyses were conducted in terms of parental history of food allergy and identified methods of food

allergy. Influence analysis was performed by serially removing each study one by one and excluding low-quality studies to examine their influence on the strength and stability of the pooled results. Potential publication biases were assessed graphically using funnel plots and statistically significance with  $P < 0.05$  using Egger’s tests (21).

## Results

### Search results

A total of 937 studies were identified through the searching of the five electronic databases. After removing duplicates and title/abstract screening for eligibility, 88 studies were selected for full text review. Of which, 80 were excluded because of their inability to satisfy the inclusion and exclusion criteria; and one study identified through citation searching was included. Finally, nine eligible studies (14, 16, 22–28) were chosen for data analysis (Figure 1).

### Characteristics of selected studies

The nine eligible studies (14, 16, 22–28) included in this review were published between 2003 and 2022 in seven countries: Norway, Germany, Australia, Sweden, China, and America. Their

TABLE 1 Characteristics of the nine included studies.

Author (year)	Country	Age of children (month)	Identified methods of allergy	Parental history of allergy	Study period	CS (n)	CS FA cases			VD (n)	VD FA cases		
							FA	CM	Egg		FA	CM	Egg
Eggesbø et al. (2003) (23)	Norway	0–24	Parental perceived reactions	N/A	1992–1995	328	9	NI	4	2,475	22	NI	17
Laubereau et al. (2004) (24)	Germany	0–12	Specific IgE test	Yes	1995–1998	104	18	9	NI	520	48	22	NI
Negele et al. (2004) (14)	Germany	0–24	Specific IgE test	N/A	1997–1999	348	39	NI	NI	1,681	153	NI	NI
Eggesbø et al. (2005) (25)	Norway	0–24	Parental perceived reactions	Yes	N/A	299	NI	5	NI	1,875	NI	7	NI
Kvenshagen et al. (2009) (26)	Norway	0–24	SPT + positive food challenge test	N/A	N/A	171	13	NI	NI	341	22	NI	NI
Koplin et al. (2012) (27)	Australia	11–15	SPT	N/A	2007–2011	1,641	NI	NI	136	3,292	NI	NI	316
Yang et al. (2018) (28)	China	0–12	Specific IgE test + positive food challenge test	N/A	2014–2015	2,355	NI	102	NI	4,413	NI	80	NI
Adeyeye et al. (2019) (22)	America	0–36	Parental perceived reactions	N/A	2008–2010	2,921	413	NI	NI	2,832	413	NI	NI
Currell et al. (2022) (16)	Australia	11–15	SPT + specific IgE test	N/A	2007–2011	1,483	153	NI	NI	2,989	333	NI	NI

N/A, not available; FA, food allergy; CM, cow’s milk; CS, cesarean section; VD, vaginal delivery; NI, no information; IgE, immunoglobulin E; SPT, skin prick test.

TABLE 2 Methodological qualities of nine included studies based on JBI-MAStARI.

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9
Eggesbø et al. (23)	Y	Y	Y	Y	Y	Y	Y	Y	Y
Laubereau et al. (24)	Y	Y	Y	Y	Y	Y	Y	Y	Y
Negele et al. (14)	Y	Y	Y	Y	Y	Y	Y	Y	Y
Eggesbø et al. (25)	Y	Y	Y	Y	Y	Y	Y	Y	Y
Kvenshagen et al. (26)	Y	Y	Y	Y	Y	Y	Y	Y	Y
Koplin et al. (27)	Y	Y	Y	Y	Y	Y	Y	Y	Y
Yang et al. (28)	Y	Y	Y	Y	Y	Y	Y	Y	Y
Adeyeye et al. (22)	Y	Y	Y	Y	Y	Y	Y	Y	Y
Currell et al. (16)	Y	Y	Y	Y	Y	Y	Y	Y	Y
Overall score (%)	Y	Y	Y	Y	Y	Y	Y	Y	Y

JBI-MAStARI, Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument; Y, yes; N, no; U, unclear; NA, not applicable; Q1–Q9 (Supplementary Table S2).

sample sizes ranged from 104 to 2,921, with a total of 9,650 cesarean-born children and 20,418 vaginal-born children aged 0–3 years. Of them, 645 cesarean-born children and 991 vaginal-born children had food allergies. Three studies (22, 23, 25) used exclusively perceived parental reactions to identify food allergy, and six (14, 16, 24, 26–28) used objective methods [SPT, IgE, OFC/DBPCFC,

or clinical diagnosis (i.e., outcomes confirmed by a physician)]. Two studies (24, 25) recruited children whose parents had a history of allergy. Six studies (14, 16, 22–24, 26) reported the prevalence of any food allergy; three studies (23, 24, 28) reported cow’s milk allergy; and two studies (23, 27) reported egg allergy in cesarean-born and vaginal-born children (Table 1).

## Methodological quality

**Table 2** presents the results of the quality assessment of the nine studies (14, 16, 22–28) using the JBI-MAStARI quality scoring tool for cohort studies. The quality of these nine studies was generally high.

## The pooled prevalence of food allergy for cesarean-born and vaginal-born children

**Figures 2, 3** summarize the pooled prevalence of food allergy of cesarean-born and vaginal-born children. The pooled prevalence of food allergy was 7.8% [95% confidence interval (CI): 4.7%–11.5%,

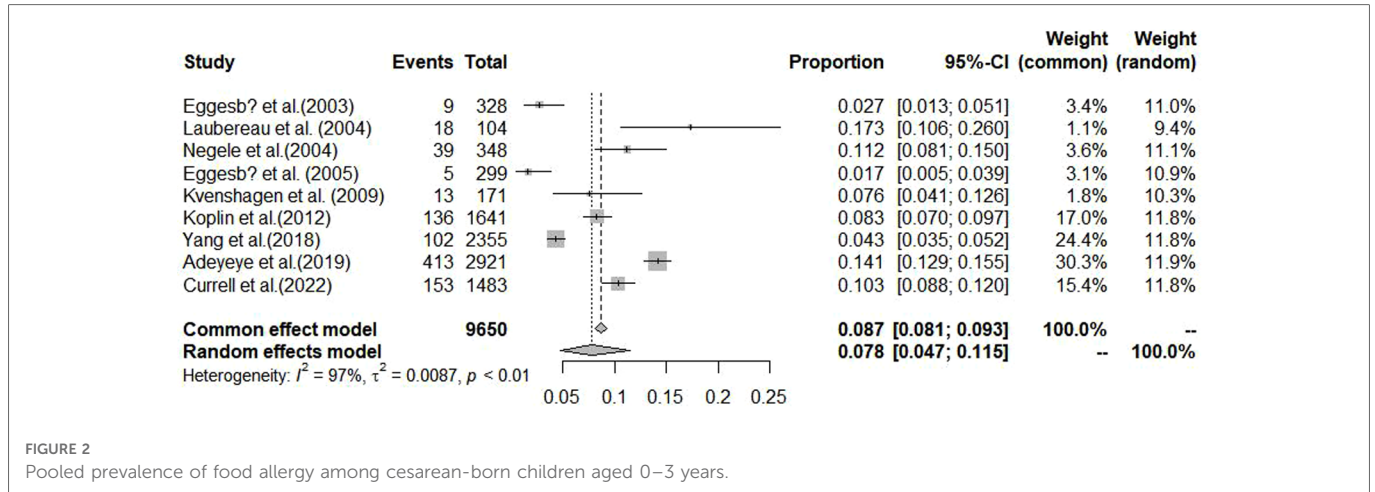


FIGURE 2 Pooled prevalence of food allergy among cesarean-born children aged 0–3 years.

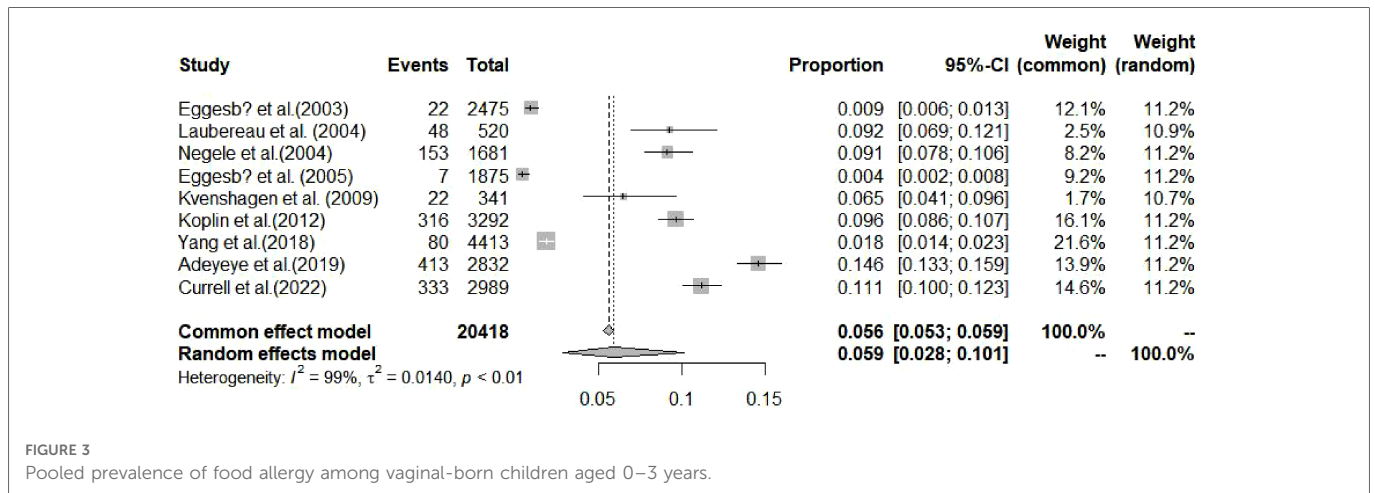


FIGURE 3 Pooled prevalence of food allergy among vaginal-born children aged 0–3 years.

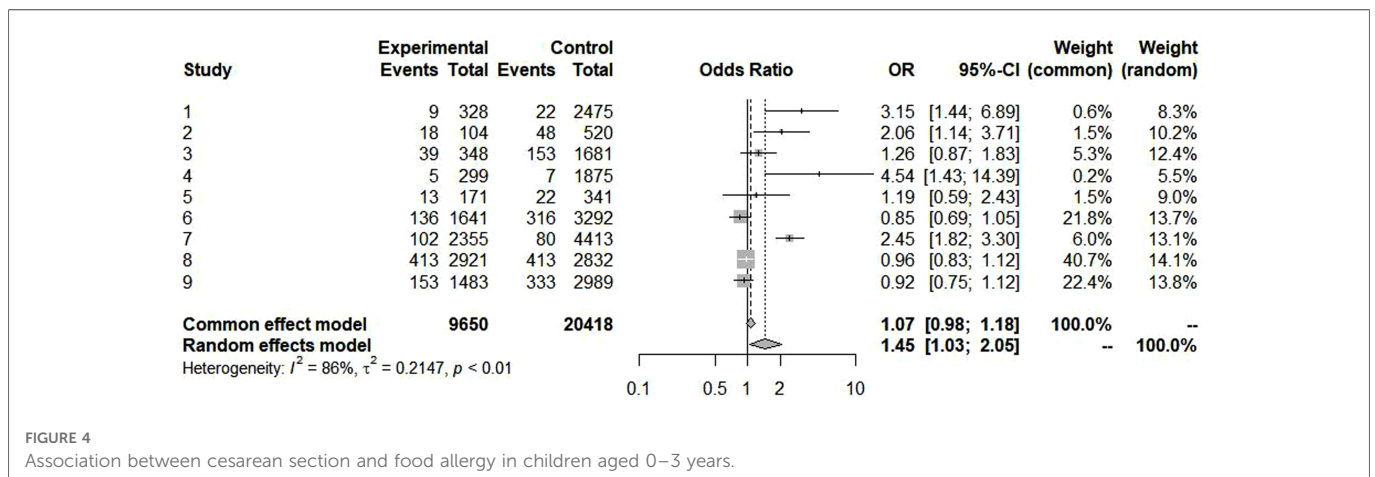


FIGURE 4 Association between cesarean section and food allergy in children aged 0–3 years.

TABLE 3 Subgroup analysis of the pooled prevalence of food allergy among children aged 0–3 years.

Subgroup	Cesarean section					Vaginal delivery					OR
	Studies (n)	FA (n)	n	Pooled prevalence (% 95% CI)	P	Studies (n)	FA (n)	n	Pooled prevalence (% 95% CI)	P	
Identified methods of food allergy											
Parental perceived	3	427	3,548	5.2 (0.5–14.3)	0.37	3	442	7,182	3.3 (0.00–14.4)	0.39	2.13 (0.80–5.64)
Objective measures	6	461	6,102	9.1 (6.2–12.4)		6	952	13,236	7.5 (4.6–11.0)		1.32 (0.91–1.90)
Type of food allergy											
FA	6	645	5,355	9.9 (6.1–14.6)	<0.01	6	991	10,838	7.8 (3.9–12.8)	<0.01	1.29 (0.93–1.79)
CM	3	116	2,758	6.2 (0.7–16.8)		3	109	6,808	1.8 (0.3–4.5)		3.31 (1.98–5.53)
Egg	2	140	1,969	5.3 (1.2–12.1)		2	333	5,767	3.9 (0.00–17.1)		1.77 (0.38–8.19)
Parental history of allergy											
Yes	2	23	403	8.0 (5.2–11.4)	0.95	2	55	2,395	3.4 (0.00–17.1)	0.55	2.60 (1.28–5.27)
No	7	865	9,247	7.5 (0.00–29.1)		7	1,339	18,023	6.8 (3.2–11.4)		1.29 (0.91–1.83)
Children's age											
0–12	2	120	2,459	9.5 (1.0–25.5)	0.01	2	128	4,933	4.8 (0.3–14.5)	<0.01	2.37 (1.82–3.09)
0–24	6	355	4,270	6.5 (3.5–10.3)		6	853	12,653	5.1 (1.7–10.3)		1.36 (0.87–2.13)
0–36	1	413	2,921	14.1 (12.9–15.5)		1	413	2,832	14.6 (13.3–15.9)		2.37 (1.82–3.09)
Country											
China	1	102	2,355	4.3 (3.5–5.2)	0.02	1	80	4,413	1.8 (1.4–2.3)	<0.01	1.32 (0.94–1.84)
Other countries	8	786	7,295	8.3 (4.9–12.5)		8	1,314	16,005	6.6 (3.1–11.2)		2.45 (1.82–3.30)

P, P-value of test of difference within each subgroup; FA, food allergy; CM, cow's milk; CI, confidence interval.

$I^2 = 96.6\%$ , 95% CI: 95.1%–97.7%] in cesarean-born children (Figure 2) and 5.9% (95% CI: 2.8%–10.1%;  $I^2 = 99.3\%$ , 95% CI: 99.1%–99.4%) in vaginal-born children (Figure 3). Overall, CS was associated with an increased risk of food allergy (OR: 1.45, 95% CI: 1.03–2.05;  $I^2 = 86.0\%$ , 95% CI: 75.5–92.1) (Figure 4).

### Subgroup analysis

Table 3 presents results from our subgroup analysis. The prevalence of food allergy was higher in cesarean-born children than in vaginal-born children aged 0–3 years according to identified methods of food allergy, type of food allergies, parental history of allergy, age group and country. In addition, cesarean-born children with cow's milk allergy (OR: 3.31; 95% CI: 1.98–5.53) and with a parental history of allergy (OR: 2.60; 95% CI: 1.28–5.27), had a higher risk of food allergy than did vaginal-born children.

### Influence analysis and publication bias

Influence analysis based on one-by-one removal of the nine eligible studies (14, 16, 22–28) indicated that the pooled prevalence of food allergy in cesarean-born children varied from 7.1% (95% CI: 6.5%–

7.7%) to 10.8% (95% CI: 10.1%–11.5%), with the corresponding  $I^2$  statistic ranging from 91.8% to 96.1%, while the pooled prevalence of food allergy in vaginal-born children varied from 5.6% (95% CI: 5.3%–5.9%) to 8.2% (95% CI: 7.8%–8.7%), with the corresponding  $I^2$  statistic varying from 97.6% to 98.7% (Table 4). Although the number of the studies included in the final analysis was less than 10, the funnel plot was used to evaluate their potential publication bias (Figure 5), providing no evidence of potential publication bias, with P-value for the Egger's rank test being 0.6.

### Meta-regression analysis

Meta-regression analysis revealed that the identified methods of food allergy and the infants' age were the significant sources of heterogeneity in estimates of the prevalence of food allergy ( $P < 0.05$ ) (Table 5).

## Discussion

### Main findings of the study

Meta-analysis of the nine studies included in our systematic review found that the pooled prevalence of food allergy was 7.8%

TABLE 4 Influence analysis of the nine eligible studies.

Study	Cesarean section			Vaginal delivery		
	Pooled prevalence (%)	95% CI (%)	I <sup>2</sup> (%)	Pooled prevalence (%)	95% CI (%)	I <sup>2</sup> (%)
Omitting Eggesbo et al. (23)	9.43	8.85–10.04	95.7	7.65	7.27–8.04	98.3
Omitting Laubereau et al. (24)	9.91	8.55–9.71	96.0	6.76	6.42–7.12	98.7
Omitting Negele et al. (14)	9.13	8.56–9.73	96.1	6.62	6.28–6.99	98.7
Omitting Eggesbo et al. (25)	9.44	8.87–10.05	95.7	7.48	7.11–7.87	98.5
Omitting Kvenschagen et al. (26)	9.23	8.66–9.83	96.1	6.83	6.49–7.19	98.7
Omitting Koplin et al. (27)	9.39	8.77–10.05	95.9	6.29	5.94–6.67	98.7
Omitting Yang et al. (28)	10.77	10.08–11.51	91.8	8.21	7.79–8.65	97.6
Omitting Adeyeye et al. (22)	7.06	6.47–7.70	92.4	5.58	5.25–5.93	98.4
Omitting Currell et al. (16)	9.00	8.40–9.64	96.1	6.09	5.74–6.45	98.7

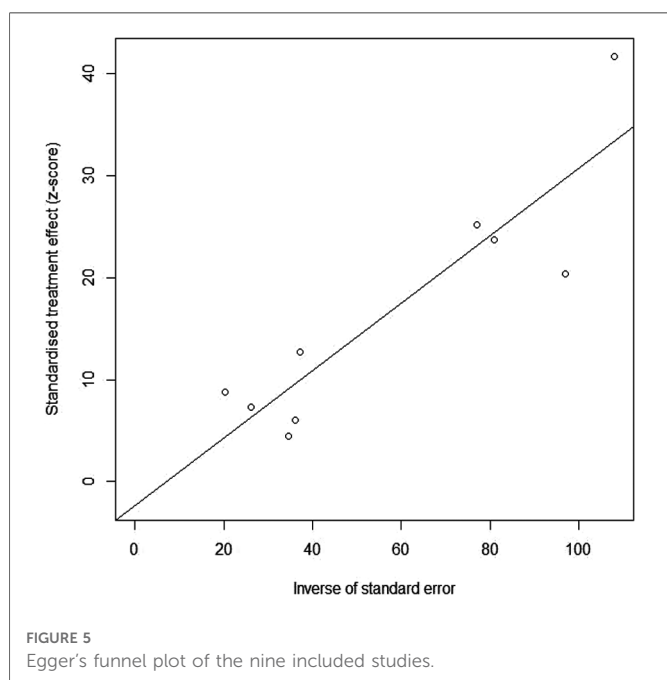
CI, confidence interval.

in cesarean-born children, which was higher than 5.9% in vaginal-born children, with an OR = 1.45 (95% CI: 1.03–2.05). Cesarean section was associated with an increased risk of both food allergy and cow’s milk allergy in children. Cesarean-born children aged 0–3 years with a parental history of allergy also developed food allergies at a higher rate than vaginal-born children of the same age (OR: 2.60; 95% CI: 1.28–5.27).

### Strengths and limitations

To the best of our knowledge, this is the first systematic review/meta-analysis that compared the pooled prevalence of food allergy from various sources of foods for cesarean-born and vaginal-born children aged 0–3 years. Our consistent findings from the subgroup, influence analyses and meta-regression analysis indicated the robustness of the results. Also, we did not find any publication bias.

Several limitations of this study must be acknowledged. First, although the overall sample size was large, the small sample size for specific food allergies complicated the interpretation of these results. For example, only two studies (23, 27) included children who were allergic to eggs. Second, heterogeneities have been partly explained by our subgroup analyses or meta-regressions. Our influence analysis showed considerable variations in the results from one-by-one removal and the potential existence of influential cases/outliers. Thus, we could not adjust for potential confounders in the meta-analysis due to heterogeneity for specific foods, including important sources of food allergies such as peanuts, fish, and wheat, as this information was not available in the original studies. Third, the original studies lacked information regarding breastfeeding, formula feeding, eczema, and the timing to take complementary foods, precluding an analysis of the potential influence of these factors on our meta-analytic results.



### Interpretation

Sensitization to food allergens during early childhood could be an important predictor for developing allergic airway diseases later in childhood (29). Our study found that more than 7.8% of cesarean-born children aged 0–3 years were allergic to any food sources, higher than the rate of 5.9% of vaginal-born children and higher than the 6% reported in children aged 0–3 years observed in another systematic review in the general population regardless of mode of delivery (30). These results support our hypothesis that CS may increase the risk of developing food allergies in children (31).

One possible explanation for the increased prevalence of food allergy in cesarean-born children aged 0–3 years is that their gut microbiota are different from those of vaginal-born children (15, 32). The intestinal microbiota and early-life microbial exposure play important roles in the development of the immune system (32), as well as in educating the immune system (33). CS could lead to delayed bacterial colonization of the gut because it limited newborn exposure to maternal vaginal and fecal microflora (34). The interruption of natural colonization has been speculated to derive from the altered immune development as well as allergic

TABLE 5 Meta-regression analyses of the effects of potential modifying factors of the prevalence of food allergy in children.

	No. of studies	Cesarean section				Vaginal delivery			
		Estimate	Standard error	Z-value	P-value	Estimate	Standard error	Z-value	P-value
Identified methods of food allergies	9	1.6711	0.5548	3.0119	0.0026	2.8570	0.7481	3.8191	0.0001
Type of food allergies	9	-0.3700	0.2119	-1.7465	0.0807	-0.4098	0.3339	-1.2271	0.2198
Parental history of allergy	9	0.8918	0.6577	1.3558	0.1752	0.6929	0.8962	0.7732	0.4394
Age	9	1.2916	0.6211	2.0796	0.0376	2.0614	0.8697	2.3702	0.0178
Country	9	0.4890	0.7654	0.6389	0.5229	0.3506	1.1407	0.3073	0.7586

diseases among children (34). Previous studies demonstrated that mode of delivery is an imperative independent factor impacting natural colonization, especially in the first months of life (35–37). Thus, CS may be associated with an increased risk of immune and metabolic disorders, as compared with vaginal delivery (VD) (38). However, some studies showed conflicting results, namely, that CS was not associated with food allergy risk in infants (15, 16). These might be because there are diverse ways to distinguish whether an elective or emergency cesarean is with or without labor and to measure food allergy, leading to contradicting results (16).

Cow's milk protein allergy (CMPA) is considered the most common food allergy in infants (39). The subgroup analyses conducted in the present study suggest that cesarean-born children have a higher risk of cow's milk allergy than in vaginal-born children. The underlying mechanism is unknown but may be related to the gut microbiota composition in feces from children with food allergies (28, 40) which have higher proportions of the *Clostridium coccoides* group and *Atopobium* cluster as well as a higher proportion of the (sum of) different bacterial groups in comparison to healthy infant feces (40). It has also been shown that bacterial colonization of the gut in cesarean-born children aged 0–3 years differs from that in vaginal-born children (24).

The pooled prevalence of food allergy in cesarean-born children aged 0–3 years whose parents had a history of allergy was higher than that in vaginal-born infants, consistent with a previous study (7). Genetic predisposition seems to be the biggest risk factor for allergic diseases (41). Currently, it is widely accepted that children with a family history of “allergy” are at generally increased risk of food allergy (42). A family study has shown that food sensitization and allergy are more common in those with a first degree relative with food allergy (43). A study in Korea has demonstrated maternal allergy is associated with an increased risk of parent-reported food allergy in children's first year of life (44). However, genetics alone cannot explain the rising global prevalence of food allergy (41); CS and parental history of allergy may have cooperative effects on food allergy in children.

## Conclusion

Cesarean section was associated with an increased risk of food allergy and cow's milk allergy in cesarean-born children aged 0–3. Cesarean-born children with a parental history of allergy developed

a higher risk for food allergies than did vaginal-born children. These results indicate that caregivers should be aware of the risks of food allergy in cesarean-born children, reducing the risk of potentially fatal allergic events. Further research is needed to identify the specific factors affecting food allergies in young children.

## Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

## Author contributions

R-hX substantially contributed to the conception of the review. XY, CZ, and CG contributed to the acquisition. XY and CG contributed to the data analysis. XY, JW, and CZ contributed to the interpretation of these results. XY drafted the manuscript. R-hX, LY, IC, SWW, and DK critically reviewed and revised the manuscript. All authors contributed to the article and approved the submitted version.

## Funding

This study was funded by Jiangsu Provincial Department of Education (grant no. 20KJB330006), Canadian Institute of Health Research (grant nos. FDN-148438, PJT-178049, and P14-175351), and Clinical Research Startup Program of Southern Medical University by High-level University Construction Funding of Guangdong Provincial Department of Education (grant no. LC2019ZD019).

## Acknowledgments

We thank all authors of the eligible articles and the two research librarians, Lindsey Sikora and Risa Shorr, from the University of Ottawa and Ottawa Hospital Research Institute, for assistance in designing the literature search.



## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fped.2022.1044954/full#supplementary-material>.

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