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Association between cesarean delivery and childhood allergic diseases in a longitudinal population-based birth cohort from Japan

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The association between cesarean delivery and childhood allergic diseases, such as atopic dermatitis, food allergy, and bronchial asthma, remains unclear, with limited evidence from Asian populations. We analyzed population-based data of 2,114 children born in Japan in 2010 from the Longitudinal Survey of Babies in the 21st Century, linked to the Perinatal Research Network Database. Comparisons were made between children born by cesarean delivery and those born vaginally. Longitudinal outcomes were atopic dermatitis, food allergy, and bronchial asthma during childhood for each age group up to 9 years of age. We performed Poisson regression analyses with robust variance, and adjusted for child and parent variables, followed by supplementary analyses using generalized estimating equations (GEE). Children born by cesarean delivery did not have a higher risk of most outcomes compared to those born vaginally. GEE analysis found no association between cesarean delivery and atopic dermatitis (adjusted risk ratio [aRR] 0.8, 95% confidence interval [CI] 0.5–1.2), food allergy (aRR 1.1, 95% CI 0.7–1.7), bronchial asthma (aRR 1.0, 95% CI 0.8–1.4), or allergic rhinoconjunctivitis (aRR 0.9, 95% CI 0.8–1.1). This study shows no clear evidence of an association between delivery mode and childhood allergic diseases in Japan.

The global prevalence of allergic diseases continues to rise but the underlying causes of this increase remain poorly understood[1]. In addition, cesarean delivery rates have increased globally over the past decade[2], and Japan reported a rise in this rate from 18.4% in 2008 to 21.6% in 2020[3]. Cesarean deliveries are associated with decreased gut microbial diversity and a diminished infant immune system capacity to develop appropriate response mechanisms[4–6]. While the indications for cesarean deliveries are multifactorial, the mode of delivery may have clinical implications for children, particularly concerning allergic diseases.

Numerous studies such as systematic reviews have shown a potential association between cesarean delivery and allergic conditions[1,4,7–12]. However, many of these studies were based on data from Western countries, with limited information available from Asian populations[12,13]. Findings from Western countries may be limited in applicability to Asian populations because of differences in cultural practices, lifestyles, socioeconomic factors, and genetic backgrounds[12,13]. In Japan, despite the rising cesarean delivery rate, the incidence of atopic dermatitis and bronchial asthma has remained relatively stable since 2000. For example, nationwide cross-sectional surveys in Japan using the Japanese version of the core questions from the International Study of Asthma and Allergies in Childhood demonstrated that the prevalence of current wheeze and eczema among 6- to 8-year-olds declined from 13.6 to 10.2% and from 15.8 to 14.6%, respectively, between 2005 and 2015[14]. These trends differed from those observed in Western populations, where the prevalence of such conditions has increased[15]. In contrast, food allergy and allergic rhinitis have slightly increased in Japan[14,16], suggesting disease-specific trends in allergic conditions. While some systematic reviews have included several studies from Asia—for example, a comprehensive systematic review identified 34 Asian studies among 113[11]—findings remain inconsistent[10,12,17]. Differences in study design, population characteristics, and definitions of allergic outcomes likely contribute to these mixed results. Therefore, further research from Asian settings, using uniform methodologies, is needed

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to clarify the association between the mode of delivery and allergic diseases. Cultural, lifestyle, and genetic factors may influence how cesarean delivery affects allergy development, reinforcing the need for region-specific studies.

Therefore, this study aimed to investigate the associations between cesarean delivery and atopic dermatitis, food allergy, bronchial asthma, and allergic rhinoconjunctivitis in childhood, using data from a longitudinal survey in Japan.

Methods

Study design, setting, and participants

The Ministry of Health, Labour, and Welfare launched the Longitudinal Survey of Babies in the 21 st Century to investigate Japan's declining birth rate[18–20]. This survey included 43,767 children born between May 10 and May 24, 2010, and this comprised approximately 1/24 of all births in Japan that year. The initial questionnaire was sent to the guardians when the children were 6 months of age. Subsequent annual questionnaires were also sent to the guardians of 38,554 children (response rate of 88.1%) until the children were 5.5 years of age, with further surveys conducted at the ages of 7, 8, and 9 years. This survey covered various topics, such as the children's physical growth, medical history, parents' employment and education levels, parental smoking habits, and parenting concerns. In addition, by linking birth record data from the Japanese Vital Statistics, various official birth-related information was collected for each participant.

The Perinatal Research Network (PRN) database, which was used to link individual perinatal information in this study, is a national registry that tracks births and stillbirths occurring after 22 weeks of gestation. This approach was initiated by the Japan Society of Obstetrics and Gynecology in the early 2000 s. Maternal and child medical centers that manage high-risk pregnancies contribute data to the PRN. Obstetricians record data in a standardized format, such as maternal characteristics, pre-existing medical conditions, pregnancy complications, delivery details, neonatal transport, and other relevant factors. In 2010, the PRN recorded data on 83,383 births from 139 facilities, accounting for 7.6% of all births in Japan that year. The cesarean delivery rate for May 2010 births recorded in this database was 33.4%, which is higher than the national average of 19.2% in September 2011.

This population-based cohort study successfully linked data on 2,140 children to the PRN database using birth information including sex, birth weight, maternal age at delivery, and gestational age. The analysis included a cohort of 2,114 children with clearly specified delivery methods and excluded 26 children with ambiguous responses such as "other" (Fig. 1).

This study was approved by the Institutional Review Board of the Graduate School of Biomedical Sciences, Okayama University (No. 2310-018), and the Clinical Research Management Review Committee of the Japanese Society of Obstetrics and Gynecology (No. 150). It was conducted in accordance with the principles outlined in the Declaration of Helsinki. The requirement for patient informed consent was waived because this study utilized secondary data from national surveys and databases managed by relevant authorities and obstetrics and gynecology societies.

Exposure and outcomes

The primary exposure was the mode of delivery (cesarean vs. vaginal) as recorded in the PRN database. The second through ninth surveys inquired whether the child had been seen by a doctor at least once in the past year

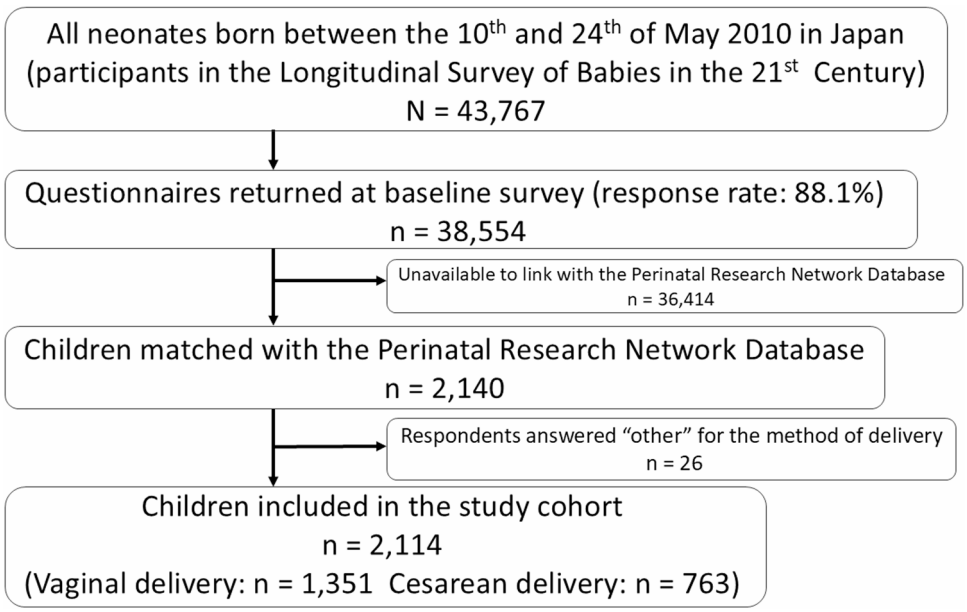

Fig. 1. Flowchart of the participants.

or in the past 1.5 years (seventh survey only) for several common diseases. We selected four types of allergic diseases for analysis, namely atopic dermatitis, food allergy, bronchial asthma, and allergic rhinoconjunctivitis, and used doctor visits for these conditions as the primary outcomes of this study. The disease status was tracked up to 9 years of age (ninth survey). Therefore, we examined whether there was at least one visit for each disease during the following age intervals: 6 months to 1.5 years, 1.5–2.5 years, 2.5–3.5 years, 3.5–4.5 years, 4.5–5.5 years, 5.5–7 years, 7–8 years, and 8–9 years.

Statistical analysis

We first compared the baseline characteristics of parents and children between the cesarean and vaginal delivery groups. We also compared the characteristics between children in the study cohort and the entire longitudinal survey cohort to evaluate potential selection bias. The differences in the proportion between the two groups were tested using the $\chi 2$ test. We then conducted Poisson regression models with robust variance estimators to evaluate the relationships between the mode of delivery and atopic dermatitis, food allergy, and bronchial asthma for each age from 0.5 to 9 years. In addition, to assess the cumulative association between the mode of delivery and these outcomes, we estimated overall risk ratios (RRs) by pooling the data across all ages and determining whether each child had experienced the outcome at least once by age 9. Additionally, to account for within-subject correlation in repeated measurements, we performed a generalized estimating equation (GEE) analysis using all available survey data. This approach allowed for an overall assessment of the delivery mode's effect on allergic outcomes across the entire study period. We estimated the RRs and 95% confidence intervals (CIs) for the outcomes using the vaginal delivery group as a reference and adjusted for child and parental factors.

The selection of potential confounders was based on previous studies and subject-matter knowledge[1,7,21]: sex (dichotomous), multiple births (dichotomous), maternal age at delivery (< 30 years, 30–34 years, ≥ 35 years; categorical), multiparity (dichotomous), in vitro fertilization (dichotomous), maternal smoking during pregnancy (dichotomous), maternal alcohol consumption during pregnancy (dichotomous), maternal educational attainment (bachelor's degree or higher, technical/associate's degree, high school diploma or less; categorical), paternal age at delivery (categorized analogous to maternal age), paternal educational attainment (categorized analogous to maternal education), place of residence at birth (special ward or designated city, city, and town or village; categorical), and maternal complications (dichotomous). Maternal complications were considered present if the mother had any of the following conditions: hypertensive disorders of pregnancy, eclampsia, chronic hypertension, gestational diabetes mellitus, thyroid disorders, autoimmune diseases, or mental health disorders. We excluded missing cases and conducted our analyses with complete cases only.

Exposure to vaginal flora following premature rupture of membranes may lead to early fetal colonization regardless of the mode of delivery. Therefore, we conducted a GEE analysis excluding children born to mothers with premature rupture of membranes in the sensitivity analysis. In addition, the type of cesarean delivery may influence the association with allergies. Accordingly, we performed another GEE analysis, separating the cesarean delivery group into elective and emergency cesarean deliveries. Stata SE version 18 (StataCorp., College Station, TX, US) was used for all analyses. P values less than 0.05 were considered statistically significant.

Results

Baseline characteristics stratified by the mode of delivery are shown in Table 1. Children born by cesarean delivery had higher proportions of multiparous mothers, preterm birth, low birth weight, small for gestational age, multiple pregnancies, in vitro fertilization, older parents, urban residence, and maternal complications, and a lower proportion of maternal alcohol consumption during pregnancy than those who were born by vaginal delivery. Table 2 shows the demographic and clinical characteristics of children in this study cohort compared to those in the entire Longitudinal Survey of Babies in the 21 st Century. The study cohort had higher proportions of primiparous mothers, preterm birth, low birth weight, multiple pregnancy, older parents, higher parental education attainment, and urban residence. Additionally, they had higher incidences of bronchial asthma and allergic rhinoconjunctivitis from 0.5 to 9 years of age.

Figures 2, 3, 4 and 5 show the adjusted RRs for the associations between the mode of delivery and atopic dermatitis, food allergy, bronchial asthma, and allergic rhinoconjunctivitis from 0.5 to 9 years of age. We did not observe a higher risk of most outcomes in children born by cesarean delivery than in those born by vaginal delivery. However, children born by cesarean delivery had an increased risk of food allergy at 7–8 years of age (RR 3.5, 95% CI 1.1–10.7).

Figure 6 shows the results of the GEE analysis from 0.5 to 9 years of age. The risk of allergic outcomes was comparable between children born by cesarean delivery and those born by vaginal delivery. The adjusted RRs were as follows: atopic dermatitis (RR 0.8, 95% CI 0.5–1.2), food allergy (RR 1.1, 95% CI 0.7–1.7), bronchial asthma (RR 1.0, 95% CI 0.8–1.4), and allergic rhinoconjunctivitis (RR 0.9, 95% CI 0.8–1.1).

Supplementary Figure S1 online shows the sensitivity analysis restricted to children without premature rupture of membranes using the GEE analysis. In addition, Supplementary Figure S2 online shows another sensitivity analysis in which the cesarean group was divided into elective and emergency cesarean deliveries. The findings of these sensitivity analyses were not different from those of the primary GEE analyses.

Discussion

In this study, we investigated the associations between the mode of delivery and atopic dermatitis, food allergy, and bronchial asthma during childhood using a longitudinal population-based cohort survey in Japan. We did not observe a higher risk of most outcomes in children born by cesarean delivery than in those born by vaginal delivery. The results of the GEE analysis also did not show an association between the mode of delivery and childhood allergic diseases.

	Delivery method			
	Vaginal delivery	Cesarean delivery	All	
	(*N* = 1,351)	(*N* = 763)	(*N* = 2,114)	*P* value[a]
Preterm birth				< 0.001
Term birth	1,232 (91.2)	567 (74.3)	1,799 (85.1)	
Preterm birth	119 (8.8)	196 (25.7)	315 (14.9)	
Low birth weight, < 2500 g	192 (14.2)	279 (36.6)	471 (22.3)	< 0.001
Small for gestational age	50 (3.7)	71 (9.3)	121 (5.7)	< 0.001
Male sex	722 (53.4)	404 (52.9)	1,126 (53.3)	0.803
Parity				< 0.001
Primipara	753 (55.7)	328 (43.0)	1,081 (51.1)	
Multipara	598 (44.3)	435 (57.0)	1033 (48.9)	
Type of pregnancy				< 0.001
Singleton	1,331 (98.5)	634 (83.1)	1,965 (93.0)	
Multiple	20 (1.5)	129 (16.9)	149 (7.0)	
In vitro fertilization	52 (3.8%)	64 (8.4%)	116 (5.5%)	< 0.001
Maternal smoking during pregnancy	50 (3.7)	31 (4.1)	81 (3.8)	0.677
Missing	359 (26.6)	181 (23.7)	540 (25.5)	
Maternal alcohol consumption during pregnancy	49 (3.6)	12 (1.6)	61 (2.9)	0.004
Missing	363 (26.9)	180 (23.6)	543 (25.7)	
Maternal age at delivery (years)				< 0.001
< 30	454 (33.6)	180 (23.6)	634 (30.0)	
30–34	476 (35.2)	274 (35.9)	750 (35.5)	
≥ 35	421 (31.2)	309 (40.5)	730 (34.5)	
Paternal age at delivery (years)				< 0.001
< 30	337 (24.9)	136 (17.8)	473 (22.4)	
30–34	410 (30.3)	215 (28.2)	625 (29.6)	
≥ 35	572 (42.3)	392 (51.4)	964 (45.6)	
Missing	32 (2.4)	20 (2.6)	52 (2.5)	
Maternal education attainment				0.624
Bachelor's degree or higher	368 (27.2)	197 (25.8)	565 (26.7)	
Vocational school/junior college graduate	495 (36.6)	296 (38.8)	791 (37.4)	
High school graduate or below	314 (23.2)	177 (23.2)	491 (23.2)	
Missing	174 (12.9)	93 (12.2)	267 (12.6)	
Paternal education attainment				0.836
Bachelor's degree or higher	623 (46.1)	347 (45.5)	970 (45.9)	
Vocational school/junior college graduate	185 (13.7)	104 (13.6)	289 (13.7)	
High school graduate or below	350 (25.9)	208 (27.3)	558 (26.4)	
Missing	193 (14.3)	104 (13.6)	297 (14.0)	
Place of residence at birth				0.004
Special ward or designated city	615 (45.5)	293 (38.4)	908 (43.0)	
City	661 (48.9)	420 (55.0)	1,081 (51.1)	
Town or village	75 (5.6)	50 (6.6)	125 (5.9)	
Maternal complications	153 (11.3)	134 (17.6)	287 (13.6)	< 0.001

Table 1. Demographic and clinical characteristics of children born by vaginal delivery and those born by Cesarean delivery. Categorical variables are shown by number (%).[a]The differences between the vaginal and cesarean delivery groups were tested using the $\chi 2$ test.

Numerous cohort studies have examined the association between cesarean delivery and allergic diseases, such as atopic dermatitis, food allergy, bronchial asthma, and allergic rhinoconjunctivitis, but this association remains controversial. While the results of these cohort studies are inconsistent, several systematic reviews summarizing the findings of these studies have shown a generally consistent association between cesarean delivery and allergic disease[9–12]. A comprehensive systematic review of 111 studies showed that cesarean delivery was associated with an increased risk of asthma (odds ratio 1.20, 95% CI 1.16–1.25), allergic rhinitis or conjunctivitis (odds ratio 1.15, 95% CI 1.09–1.22), atopic dermatitis or eczema (odds ratio 1.08, 95% CI 1.04–1.13), and food allergies (odds ratio 1.35, 95% CI 1.18–1.54) in the offspring[11]. The results of the current study are inconsistent with the results from systematic reviews.

	This study cohort	The entire longitudinal survey cohort	
	(*N* = 2,114)	(*N* = 38,554)	*P* value[a]
Preterm birth			< 0.001
Term birth	1,799 (85.1)	36,449 (94.6)	
Preterm birth	315 (14.9)	2,098 (5.4)	
Low birth weight, < 2500 g	471 (22.3)	3,642 (9.4)	< 0.001
Male sex	1,126 (53.3)	19,844 (51.5)	0.108
Parity			< 0.001
Primipara	1,081 (51.1)	18,079 (46.9)	
Multipara	1033 (48.9)	20,475 (53.1)	
Type of pregnancy			< 0.001
Singleton	1,965 (93.0)	37,831 (98.1)	
Multiple	149 (7.0)	723 (1.9)	
Maternal age at delivery (years)			< 0.001
< 30	634 (30.0)	14,664 (38.0)	
30–34	750 (35.5)	14,215 (36.9)	
≥ 35	730 (34.5)	9,675 (25.1)	
Paternal age at delivery (years)			< 0.001
< 30	473 (22.4)	10,644 (27.6)	
30–34	625 (29.6)	13,057 (33.9)	
≥ 35	964 (45.6)	14,198 (36.8)	
Missing	52 (2.5)	655 (1.7)	
Maternal education attainment			< 0.001
Bachelor's degree or higher	565 (26.7)	8,788 (22.8)	
Vocational school/junior college graduate	791 (37.4)	13,687 (35.5)	
High school graduate or below	491 (23.2)	10,802 (28.0)	
Missing	267 (12.6)	5277 (13.7)	
Paternal education attainment			< 0.001
Bachelor's degree or higher	970 (45.9)	14,390 (37.3)	
Vocational school/junior college graduate	289 (13.7)	5,997 (15.6)	
High school graduate or below	558 (26.4)	12,315 (31.9)	
Missing	297 (14.0)	5852 (15.2)	
Place of residence at birth			< 0.001
Special ward or designated city	908 (43.0)	11,008 (28.6)	
City	1,081 (51.1)	24,406 (63.3)	
Town or village	125 (5.9)	3,140 (8.1)	
Atopic dermatitis from 0.5 to 9 years	220 (10.4)	4454 (11.6)	0.087
Missing	184 (8.7)	3570 (9.3)	
Food allergy from 0.5 to 9 years	178 (8.4)	3070 (8.0)	0.499
Missing	184 (8.7)	3570 (9.3)	
Bronchial asthma from 0.5 to 9 years	317 (15.0)	5029 (13.0)	0.013
Missing	184 (8.7)	3570 (9.3)	
Allergic rhinoconjunctivitis from 0.5 to 9 years	771 (36.5)	13,156 (34.1)	0.040
Missing	179 (8.5)	3495 (9.1)	

Table 2. Baseline characteristics of eligible children in this study cohort and the entire longitudinal survey cohort. Categorical variables are shown by number (%).[a]The differences between the vaginal and cesarean delivery groups were tested using the $\chi 2$ test.

In the present study, children born by cesarean delivery had an increased risk of food allergy at 7–8 years of age (RR 3.5, 95% CI 1.1–10.7). However, a total of 32 time points were analyzed (eight for each diagnosis), and this was the only time point that showed a statistically significant association. Moreover, this finding was based on a small number of affected children (10 in the cesarean group and 7 in the vaginal delivery group). Given the number of comparisons, it is highly likely that this finding represents random variation rather than a true effect of cesarean delivery.

The reason for the discrepancy in results between studies from Japan and other countries remains unclear, but there are several possible explanations. First, the difference in sample size may explain the discrepancy. Systematic reviews and cohort studies with larger sample sizes tend to find an association for this topic. Although this study also performed a GEE analysis and did not find an association, the possibility of an

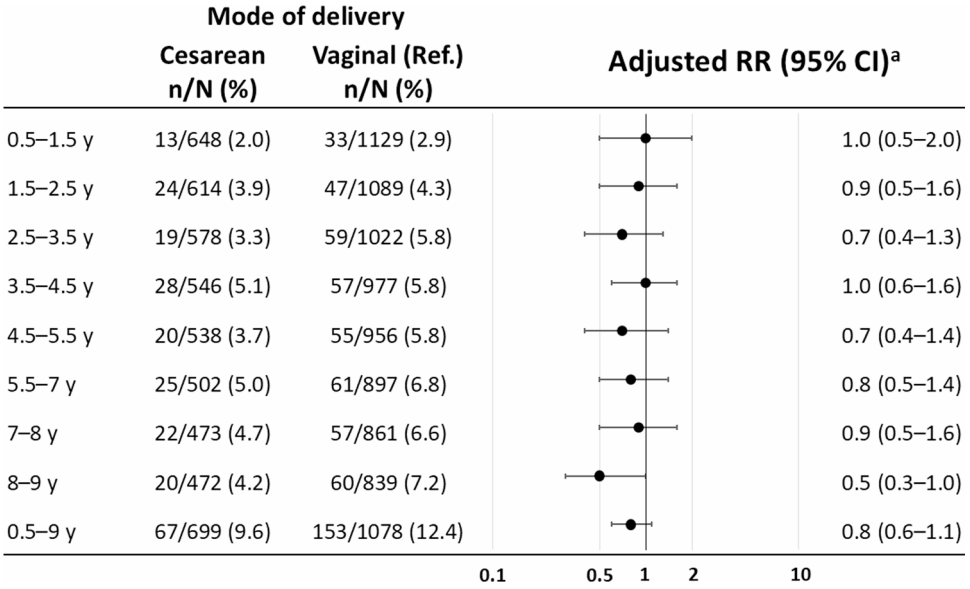

Fig. 2. Adjusted RRs for associations between cesarean delivery and atopic dermatitis from ages 0.5 to 9. CI, confidence interval; Ref, reference; RR, risk ratio. [a]Adjusted for sex, parity, multiple pregnancies, in vitro fertilization, maternal smoking, maternal alcohol consumption, maternal age at delivery, paternal age at delivery, maternal education attainment, paternal education attainment, place of birth and residence, and maternal complications.

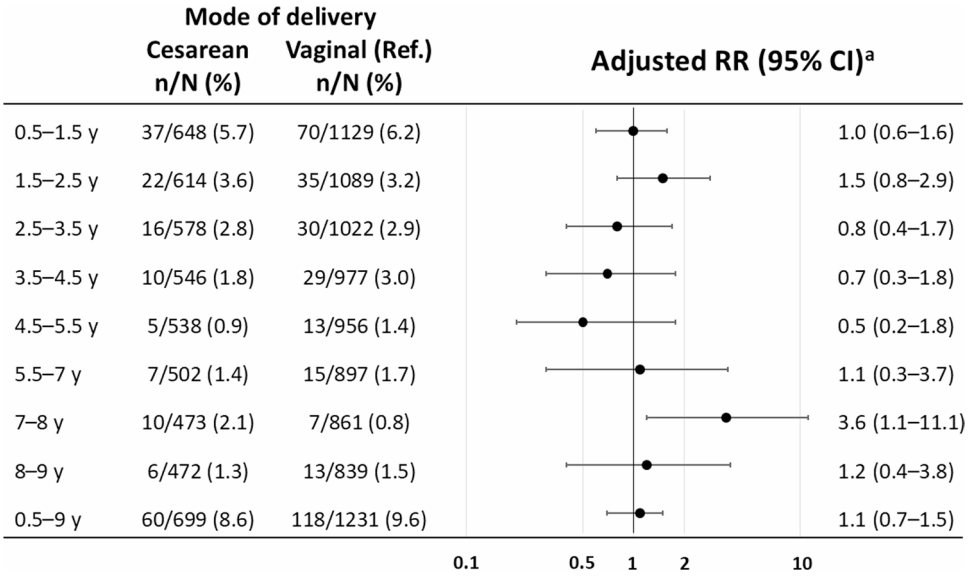

Fig. 3. Adjusted RRs for associations between cesarean delivery and food allergy from ages 0.5 to 9. CI, confidence interval; Ref, reference; RR, risk ratio. [a]Adjusted for sex, parity, multiple pregnancies, in vitro fertilization, maternal smoking, maternal alcohol consumption, maternal age at delivery, paternal age at delivery, maternal education attainment, paternal education attainment, place of birth and residence, and maternal complications.

association cannot be ruled out. Second, differences in race, healthcare systems, and criteria for performing cesarean deliveries between Japan and other countries may have contributed to inconsistencies in the association between cesarean delivery and bronchial asthma[2,22]. For example, Japan has a universal healthcare system with relatively consistent access to prenatal and pediatric care[23], and a relatively lower cesarean section rate than many Western countries[24,25]. In addition, clinical criteria for performing cesarean deliveries may differ[26]. These contextual factors may influence the underlying risk profiles of cesarean-delivered infants and, consequently, the observed associations with allergic diseases. Therefore, our findings should be interpreted in light of these country-specific differences. Third, allergies are multifactorial diseases, involving various factors such as genetic

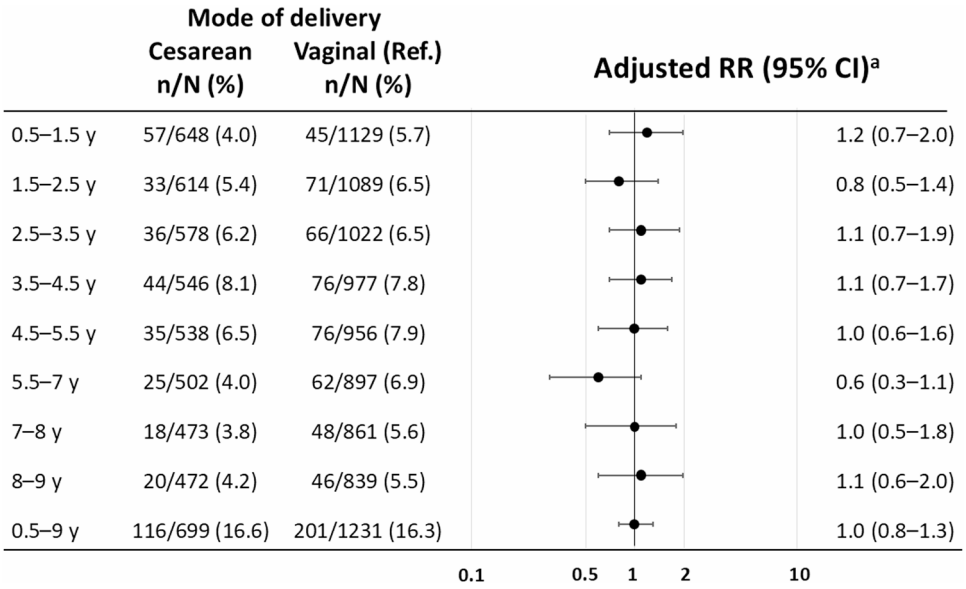

Fig. 4. Adjusted RRs for associations between cesarean delivery and bronchial asthma from ages 0.5 to 9. CI, confidence interval; Ref, reference; RR, risk ratio. [a]Adjusted for sex, parity, multiple pregnancies, in vitro fertilization, maternal smoking, maternal alcohol consumption, maternal age at delivery, paternal age at delivery, maternal education attainment, paternal education attainment, place of birth and residence, and maternal complications.

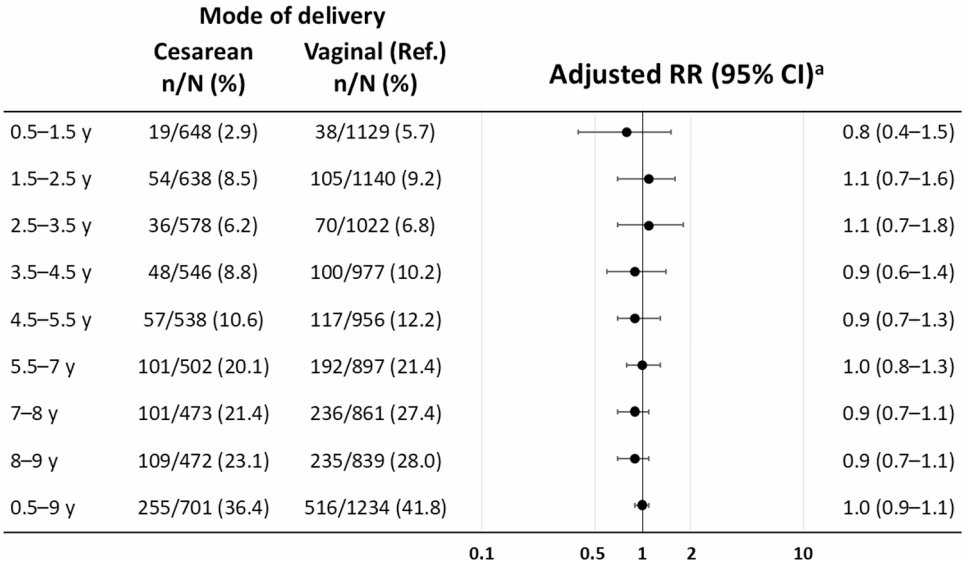

Fig. 5. Adjusted RRs for associations between cesarean delivery and Allergic rhinoconjunctivitis from ages 0.5 to 9. CI, confidence interval; Ref, reference; RR, risk ratio. [a]Adjusted for sex, parity, multiple pregnancies, in vitro fertilization, maternal smoking, maternal alcohol consumption, maternal age at delivery, paternal age at delivery, maternal education attainment, paternal education attainment, place of birth and residence, and maternal complications.

predisposition, environmental influences, and immune system responses[27]. The delivery method is only one of these factors. Therefore, in Japan, it is possible that the delivery method does not have a strong direct impact on the development of allergies. Fourth, the difficulty in diagnosing allergies may have influenced our results. This study relied on a parental questionnaire and did not collect detailed information on the methods used for diagnosis. Previous studies have demonstrated inconsistent findings according to the diagnostic method used for food allergy[28].

This study comprehensively and longitudinally followed allergic diseases, namely atopic dermatitis, food allergy, and bronchial asthma, which is a notable strength. However, several limitations to this study should

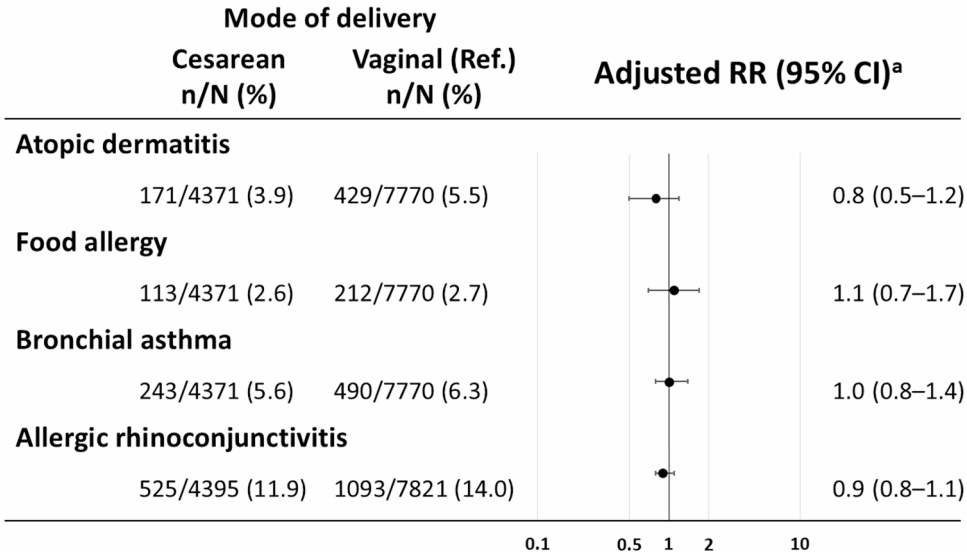

Fig. 6. Adjusted RRs for associations between cesarean delivery and childhood allergic diseases using GEE analysis. CI, confidence interval; GEE, generalized estimating equation; Ref, reference; RR, risk ratio. [a]Adjusted for sex, parity, multiple pregnancies, in vitro fertilization, maternal smoking, maternal alcohol consumption, maternal age at delivery, paternal age at delivery, maternal education attainment, paternal education attainment, place of birth and residence, and maternal complications.

be acknowledged. First, the sample size of the study was relatively small. Although the Longitudinal Survey of Babies in the 21 st Century originally included a large sample size, only a subset could be linked to the PRN. Consequently, caution is warranted when interpreting the results because the population in this cohort may have a higher risk for cesarean delivery than the general population. Second, the disease outcomes were obtained using retrospective parental reporting by questionnaires. This methodology precluded our ability to assess the diagnostic accuracy of the conditions. In particular, the high number of reported asthma treatments based on parental questionnaires before the age of 3.5 years underscores the potential for misclassification, given the difficulty of reliably diagnosing asthma in very young children. Similarly, the diagnosis of food allergy or allergic rhinoconjunctivitis based solely on parental reports without supporting data such as sensitization tests or failed food challenges raises concerns regarding diagnostic accuracy. These issues represent a limitation of our methodology, and our findings should therefore be interpreted with caution in this context. Third, although we adjusted for several potential confounding factors in the statistical model, we could not account for certain variables, such as chorioamnionitis and parental history of allergic disease. Whether parental allergic conditions affect the likelihood of cesarean delivery remains unclear, but these factors could affect study outcomes. Therefore, we could not exclude the possibility that the absence of this information may have affected our findings.

Conclusions

A longitudinal survey in Japan did not show a clear association between cesarean delivery and childhood allergic diseases. This finding is inconsistent with the results of systematic reviews that analyzed this association. Further studies with larger samples are required to validate our findings and to determine how they differ from other studies.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Author contributions
KT contributed to the study design, data analysis and interpretation, and writing the first draft and revision of the manuscript. NM and TY contributed to the study design, data analysis and interpretation, and revision of the manuscript. TM, HM, and TY contributed to data collection, providing important intellectual content, and revision of the manuscript. All the authors mentioned above approved the final manuscript.

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Declarations

Competing interests
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