Relationship between mode of delivery and the development of allergic rhinitis: a systematic review and meta-analysis

Minh P. Hoang[1,2,3], Kachorn Seresirikachorn[1,2], Jompol Samuthpongtorn[1], Wirach Chitsuthipakorn[4,5], Kornkiat Snidvongs[1,2]

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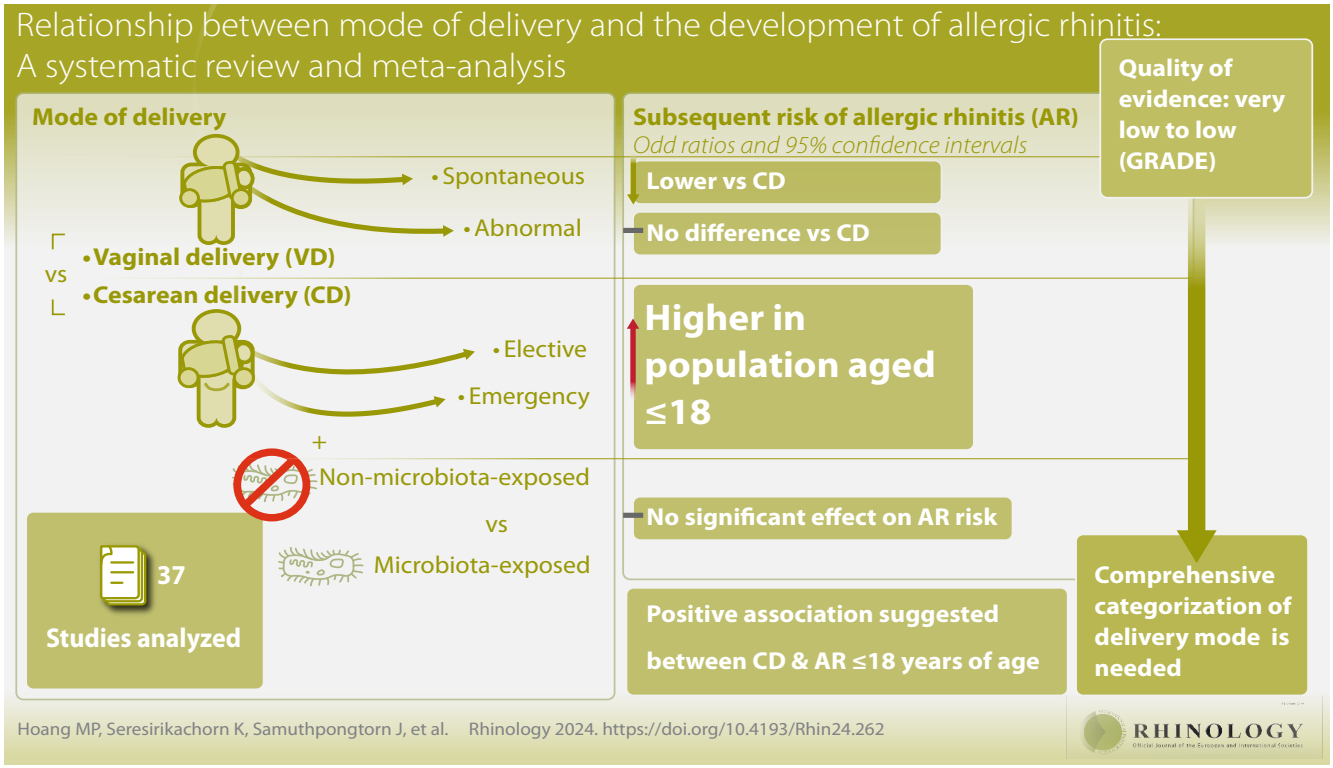

Abstract

Background: Delivery mode can influence infant microbial diversity, cause immune dysregulation, and potentially increase the risk of allergic rhinitis (AR).

Methodology: A systematic review and meta-analysis were performed to assess the association between distinct modes of delivery and the development of AR in childhood and adulthood. The primary comparison was vaginal (VD) versus cesarean delivery (CD). Secondary comparisons were specified CD (elective, emergency) versus specified VD (spontaneous, abnormal) and non-microbiota-exposed versus microbiota-exposed deliveries. The outcomes were subsequent risks of AR presenting as odd ratios and 95% confidence intervals.

Results: Thirty-seven studies were analyzed. Compared to VD, CD, and its specified modes were associated with higher subsequent risks of AR in the population under age 18. The quality of evidence supporting these effects is rated as very low to low following GRADE. Spontaneous VD was associated with lower AR risk compared to CD, but there was no significant difference between abnormal VD and CD. The distinction between non-microbiota-exposed and microbiota-exposed deliveries did not affect AR risk significantly.

Conclusions: The estimated odds ratios demonstrated a positive association between cesarean section and AR up to 18 years of age. A comprehensive categorization of delivery mode is necessary to interpret the existing evidence thoroughly.

Key words: allergy, allergic rhinitis, allergic disease, cesarean section, hygiene hypothesis

Introduction

The incidence of allergic rhinitis (AR), one of the most common inflammatory diseases, has risen over the last decades [1]. This rapid surge sparks an interest in exploring the key drivers that contribute to the onset of AR [2]. Environmental factors may reduce childhood exposure to microorganisms, leading to aberrant microbial metacommunity in early life [3-5]. These changes may raise susceptibility to inflammatory diseases and increase the likelihood of such conditions. During the perinatal period, a child encounters microbial dispersal events from the mother through delivery, skin-to-skin contact, and breastfeeding, which could influence immunological development [5,6].

Increasing evidence suggests that pregnancy-related factors play a significant role in the development of allergic diseases in children [7]. Lately, there has been a growing focus on the biological and physiological effects of delivery mode on the child [8]. However, studies with the same interest showed inconsistent results regarding the association between mode of delivery and subsequent AR later in life [9-45]. The heterogeneity in the classification of cesarean delivery (CD) or confounders (e.g., parental allergy [18], maternal age [35], prematurity [29], intrapartum antibiotic [46], prolonged breastfeeding [31,47], socioeconomic factors) may influence the conclusion. Additionally, factors such as labor conditions or the presence of premature rupture of the membrane (PROM) can shift the gut flora of newborns, potentially affecting their health development [15,36,40,48]. None of the current meta-analyses have a detailed categorization to assess the effect of each delivery mode separately. Moreover, no evidence of delivery mode exists on the development of AR in adults [49-51]. To date, there has been a notable increase in both developed and developing countries, reaching an estimated CD rate of 21.1% in 2015 [52,53]. Hence, it is plausible to revisit the correlation between high CD rates, alternative childbirth delivery options, and the increased incidence of AR. This systematic review aimed to evaluate the relationship between various delivery modes and the development of AR in both children and adults.

Materials and methods

Literature search and study selection

The study protocol was registered on PROSPERO (CRD42021256627). The conduct and reporting of this systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [54]. Systematic searches were performed in PubMed MEDLINE, EMBASE, Web of Science, and Cochrane CENTRAL databases from inception until 3 December 2023. Manual searches were also performed for additional relevant studies from the reference list of the included studies. The search strategy is displayed in Table S1.

Eligibility criteria and study selection process

We included human observational studies (cross-sectional, case-control, birth cohort) assessing the association between mode of delivery and the risk of AR later in life. AR could be defined as physician-diagnosed AR, parent- or self-reported AR, recorded indication for AR on the healthcare databases, or clinical AR with confirmed specific IgE tests. Methods of childbirth were categorized as vaginal (VD) and cesarean delivery. Specified CDs were defined as 1) elective CD and 2) emergency CD. Specified VDs were defined as 1) spontaneous VD and 2) abnormal VD (using assisted maneuvers or instruments). Additionally, we provided a second classification of delivery mode based on the likelihood of exposure to maternal vaginal microbiota as follows: 1) non-microbiota-exposed delivery and 2) microbiota-exposed delivery. Microbiota-exposed delivery refers to VD or CD with PROM in which the membrane ruptures more than 10 minutes before delivery [37]. There was no age limit for reporting outcomes or language restriction. Studies assessing different allergic outcomes were included if data from AR were able to be extracted separately. At least two authors individually screened retrieved titles, abstracts, and full texts. Discrepancies during the study selection process were resolved by discussion with the corresponding author until reaching a consensus.

Data extraction

Two authors independently extracted the data from the eligible studies into a predefined Excel spreadsheet. In the case of incomplete data, the corresponding author of that study was contacted for further supporting information. In the case of several reports of the same data (published articles, post-hoc analysis, abstracts), data were extracted from all sources and presented as one piece of research. Discrepancies during the extraction processes were resolved by discussion with the corresponding author until a consensus was reached.

Quality of the included studies

Two authors individually assessed risk of bias in the included studies using the Newcastle-Ottawa scale (NOS). Discrepancies during the risk of bias assessment were resolved by discussion with the corresponding author until reaching a consensus. The NOS provided three domains, including selection, comparability, and outcome. The maximal score of NOS for cohort or case-control studies and cross-sectional studies is nine and six, respectively. The quality of included studies was categorized using NOS score as follows: high-quality (score 8 to 9), medium-quality (score 5 to 7), and low-quality (score 0 to 4). We used The Grading of Recommendations, Assessment and Evaluation (GRADE) system to rate the certainty of evidence with four judgments: high, moderate, low, and very low [55]. The observational studies started with a low rating until there was a compelling reason for modifying the rating upward [56].

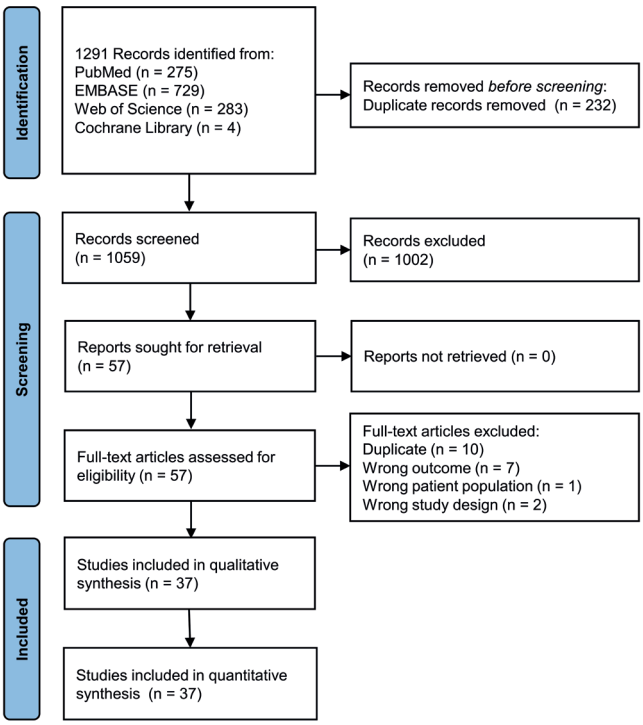

Figure 1. PRISMA flow chart.

Outcome measures and data analysis

The outcomes were the risks of developing AR later in life. Risk data were summarized as odds ratios (ORs) with 95% confidence intervals (CIs). The comparisons were as follows: 1) CD vs. VD; 2) elective CD vs. VD; 3) emergency CD vs. VD; 4) CD vs. spontaneous VD; 5) CD vs. abnormal VD; 6) abnormal VD vs. spontaneous VD; and 7) non-microbiota-exposed delivery vs. microbiota-exposed delivery. In the case of a lack of prevalence, we extracted the reported ORs when available in the included studies. Where both unadjusted OR and adjusted OR were presented, data after adjusting the confounders were pooled into the meta-analysis. If the OR and 95% CI were not provided in the manuscript, data extraction was carried out using figures when available. In the case of multiple time points of the outcome, the relevant estimate for the oldest age of outcome was selected. Data from studies reporting the risks of developing AR as risk ratio (RR) or hazard ratio (HR) were converted into OR before pooling into meta-analysis following the recommended formula [57]:

1) $OR \approx RR$ or HR

if the prevalence of AR is <15% by the end of the follow-up.

2) $OR \approx RR^2$ or $OR \approx \left(\frac{1-0.5\sqrt{HR}}{1-0.5\sqrt{\frac{1}{HR}}}\right)^2$

or if the prevalence of AR is ≥15% by the end of the follow-up.

Where a quantitative synthesis was carried out, the outcome discrepancy among different studies was assessed by calculating the I^2 test. An I^2 of <50% and ≥50% represented low and high heterogeneity. A fixed-effect model was used when the heterogeneity was low. A random-effects model was used if the heterogeneity was high, and all studies were not functionally equivalent. Galbraith plots were performed to assess the heterogeneity and detect potential outliners. Funnel plots with Egger's test were performed to measure small-study effects for quantitative syntheses of at least ten studies. All statistical assessments were conducted using Stata 18.0 (StataCorp, College Station, TX, USA).

Subgroup analysis and meta-regression

We explored the heterogeneities through the analyses of prespecified subgroups as follows:

1) Study design: birth cohort, cross-sectional, and case-control. A birth cohort was defined as a study following up children from birth that enrolled mothers during pregnancy.

2) Regions: Asia, Europe, Africa, North America, South America, Australia.

3) Age of reporting AR outcome: ≤5 years, >5 years, and mixed age [47].

4) Definition of AR: self-reported AR, physician-diagnosed AR, records on health-related databases, and clinical symptoms with specific IgE tests.

5) Exclusion of prematurity: yes versus no. Prematurity was defined as preterm birth (<37 weeks gestational age) [58] and/or low-birth-weight newborns (<2000 to 2500 grams) [59].

6) Available OR: adjusted OR versus unadjusted OR.

7) Proportion of CD among all deliveries: ≤15% versus >15% [53].

We performed the meta-regression with proportion of CD, year of birth, year of publication, the number of potential confounders in the model analysis, and sample size as the continuous moderators.

Sensitivity analysis

Sensitivity analyses were the repeats of primary analysis by performing: 1) the meta-analysis excluding studies with the potential source of heterogeneity 2) the meta-analysis that included only those with high and medium quality; 3) the meta-analysis that included only those with high quality; 4) the meta-analysis that included only those with the general population; 5) the meta-analysis that included only those with sample size ≥5000; 6) the meta-analysis that included only those having retention rate (for cohort studies) or responder rate (cross-sectional or case-control studies) >70%; 7) the meta-analysis that included only those having satisfactory adjustment for confounders (any five of maternal age, prematurity, birth order, parental allergy, smoking during pregnancy, socioeconomic factors, and duration of breastfeeding); 8) the meta-analysis that included only

Table 1. Characteristics of the 37 included studies.

First author, Year, [ref]	Study design	Country	n	CD (%)	Assessment of AR	Assessment of atopy	Age at follow-up (years)	AR at follow-up (%)
Montgomery, 2000 [9]	BC	UK	5,519	3.1	Questionnaire (diagnosis at 16 years of age)	No	16-26	29.6
Nafstad, 2000 [10]	BC	Sweden	2,531	11.3	Questionnaire (physicians' diagnosis and symptoms <12 months)	No	4	5.5
Xu, 2001 [11]	BC	Finland	1,953	5.3	Questionnaire (diagnosis)	Yes	31	18
McKeever, 2002 [12]	BC	UK	24,690	17	Hospital database (ICD-8, physicians' diagnosis, and medication)	No	<9.5	4
Bager, 2003 [13]	BC	Denmark	9,722	5.1	Interview (physicians' diagnosis)	No	20-28	14
Negele, 2004 [14]	BC	Germany	2,500	17.4	Questionnaire (physicians' diagnosis and symptoms <6 months)	Yes	2	3.2
Renz-Polster, 2005 [15]	BC	USA	7,872	16.3	Hospital database (physicians' diagnosis)	No	3-10	12.7
Salam, 2006 [16]	BC	USA	3,228	20.7	Questionnaire (diagnosis)	No	8-17	17.3
Mallen, 2008 [17]	CS	UK	567	7.8	Hospital database (physicians' diagnosis)	No	18-25	8.5
Pistiner, 2008 [18]	BC	USA	432	23.6	Interview (physicians' diagnosis and symptoms <12 months)	Yes	9	18.5
Park, 2010 [19]	CS	Korea	279	37.4	ARIA guideline	Yes	<16	28.7
Penaranda, 2012 [21]	CS	Colombia	3,256	NA	Parent-reported ISAAC questionnaire (symptoms <12 months)	No	6-7	30.8
Pyrhonen, 2013 [22]	BC	Finland	2,546	17.3	Questionnaire (diagnosis)	Yes	1-4	3.2
Grabenhenrich, 2015 [20]	BC	Germany	1,314	18.5	ISAAC (symptoms <12 months) and specific serum IgE test	Yes	20	22.1
Li, 2015 [23]	CS	China	20,803	11.7	ISAAC (diagnosis <12 months)	No	5-13	9.8
Brandao, 2016 [24]	CS	Brazil	672	48	ISAAC (symptoms <12 months)	No	6	23.5
Cuppari, 2016 [25]	CS	Italy	917	50.6	Physicians' diagnosis following ARIA guideline	Yes	3-15	10.3
Chu, 2017 [26]	CS	China	12,046	47	Questionnaire (diagnosis and symptoms)	No	5-12	15.3
Lee, 2017 [27,28]	BC	Taiwan	756	26	Questionnaire (physicians' diagnosis and symptoms <6 months) and specific serum IgE test	Yes	6	35.6
Loo, 2017	BC	Singapore	1,077	30.6	Questionnaire (diagnosis)	Yes	5	39.7
Gerlich, 2017 [29]	BC	Germany	801	9.6	Questionnaire (physicians' diagnosis and symptoms <12 months)	Yes	19-24	26.1
Krzych-Falta, 2018 [30]	CS	Poland	3,613	28	ECRHS, ISAAC, and ARIA guideline	Yes	6-44	23.1
Han, 2019 [31]	CS	Korea	1,296	38	Rhinitis symptoms and skin prick test	Yes	4-12	77
Lin, 2019 [32]	BC	Taiwan	628,878	34	Hospital database (ICD-9 code for three ambulatory visits or ICD-9 code for one hospital admission) and INCS prescription	No	6	12.5
Yu, 2019 [33]	CS	China	149,726	41	Questionnaire (physicians' diagnosis)	No	6-17	4.08
Gorris, 2020 [34]	CS	Ecuador	189	38.6	ISAAC (physicians' diagnosis and symptoms)	No	3-12	NA
Lu, 2020 [35]	BC	Taiwan	1,344	36	ISAAC and ARIA guideline (physicians' diagnosis and symptoms <12 months)	Yes	6	59
Mitselou, 2020 [36]	BC	Sweden	1,059,600	16.1	Hospital database (ICD-10)	No	0.2-13	2.11
Richards, 2020 [37]	BC	USA	40,332	27	Hospital database (2 ICD-9 or 10 codes with ≥1-month interval, or 1 ICD-9 or 10 code and 2 INCS or antihistamine prescriptions with ≥1-month interval)	No	10	9.2
Ali, 2021 [40]	BC	Denmark	522	19.7	Questionnaire (diagnosis)	No	4-12	13
Gabryszewski, 2021 [38]	BC	USA	121,577	35	Hospital database (2 ICD-9 or 10 codes with ≥6-month interval)	Yes	>5	17.1
Hu, 2021 [41]	CS	China	10,464	59.6	ISAAC (physicians' diagnosis)	No	6-11	22.7
Meza-Lopez, 2021 [39]	CS	Mexico	1,003	44.2	ISAAC (physicians' diagnosis and symptoms)	No	5-6	4.1
Sigurdardottir, 2021 [42]	BC	Multi-countries	5,572	23.9	ISAAC (physicians' diagnosis and symptoms <12 months)	No	6-10	13.3
Choi, 2023 [43]	CS	Korea	1,446	32.9	ISAAC (physicians' diagnosis and symptoms)	No	9-12	17
Liu, 2023 [44]	CC	China	460	58	Physicians' diagnosis + Serum specfic IgE	Yes	3-18	50
Wang, 2023 [45]	CC	China	2,020	48.4	ISAAC (physicians' diagnosis and symptoms)	No	3-5	20

BC, birth cohort; CS, cross-sectional study; CC, case-control study; CD, cesarean delivery; AR, allergic rhinitis; ICD, International Classification of Diseases; ISAAC, The International Study of Asthma and Allergies in Childhood Questionnaires; ECRHS, The European Community Respiratory Health Survey; ARIA, Allergic Rhinitis and its Impact on Asthma; INCS, intranasal corticosteroids sprays.

Table 2. Certainty of the evidence (GRADE) of risk of allergic and mode of delivery.

Comparisons	Studies (n)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Sample size	Effect size OR (95% CI)	Quality
CD vs. VD	37	Certain	Serious inconsistency	No serious indirectness	No serious imprecision	Uncertain	2,132,087	1.15 (1.11, 1.21)	+ - - - Very Low
Elective CD vs. VD	4	Uncertain	No serious inconsistency	No serious indirectness	No serious imprecision	Uncertain	1,000,842	1.15 (1.04, 1.26)	++ - - Low
Emergency CD vs. VD	4	Uncertain	No serious inconsistency	No serious indirectness	No serious imprecision	Uncertain	998,892	1.13 (1.07, 1.19)	++ - - Low
CD vs. spontaneous VD	4	Uncertain	No serious inconsistency	No serious indirectness	No serious imprecision	Uncertain	663,340	1.09 (1.01, 1.19)	++ - - Low
CD vs. spontaneous VD	4	Uncertain	No serious inconsistency	No serious indirectness	No serious imprecision	Uncertain	663,340	1.09 (1.01, 1.19)	++ - - Low
CD vs. abnormal VD	2	Uncertain	No serious inconsistency	No serious indirectness	No serious imprecision	Uncertain	7,290	0.96 (0.79, 1.18)	++ - - Low
Abnormal VD vs. spontaneous VD	3	Uncertain	No serious inconsistency	No serious indirectness	No serious imprecision	Uncertain	30,407	1.10 (0.94, 1.28)	++ - - Low
Non-microbiota-exposed vs. microbiota-exposed delivery	3	Uncertain	Serious inconsistency	No serious indirectness	Serious imprecision	Uncertain	24,614	1.25 (0.88, 1.77)	+ - - - Very Low

CD, cesarean delivery; VD, vaginal delivery; OR, odds ration; CI, confidence interval.

studies with age of outcome ≥18 years; 9) the meta-analysis that included only studies with participants were born in 2000s.

Results

Study selection

The systematic search identified 1291 studies. After removing duplicated records and title and abstract screening, fifty-seven studies were assessed for eligibility; 37 were included in qualitative and quantitative analysis: 21 birth-cohort studies [9-16,18,20,22,27-29,32,35-38,40,42], 14 cross-sectional studies [17,19,21,23-26,30,31,33,34,39,41,43], and two case-control studies [44,45]. Figure 1 presents the PRISMA flowchart of study selection process.

Study characteristics

There were 2,132,087 participants included in the analysis. The included studies were from four continents: Asia (n=830,595), Europe (n=1,122,931), North America (173,441), and South America (n=5120). Six studies assessed the age of outcome under five [10,14,22,28,32,45]. A self-reported questionnaire was the most common epidemiological tool for diagnosing AR, and it was used in 23 studies [9-11,13,14,16,18,21-24,26,28-30,33,34,39-43,45]. Physician-diagnosed allergic rhinitis [19,25,35], records on healthcare databases [12,15,17,32,36-38], and specific IgE tests [20,27,31,44] were used to define AR in 3, 7, and 4 studies, respectively. Eight studies excluded subjects with a history of prematurity [10,14-16,18,25,26,33,42]. Thirty studies had a CD rate of over 15% [12,15-22,24-28,30-45]. Twenty-three studies had regression adjustment to control the confounding [9,11,14-16,18,19,21-24,26-29,31,33-35,41-43,45]. Characteristics of the included studies are presented in Table 1 and Table S2.

Cesarean delivery versus vaginal delivery

Thirty-seven studies assessed the risk of AR between CD and VD (9-45). The pooled data showed a significantly higher risk of AR in participants born through cesarean delivery compared to those born vaginally (OR 1.15; 95% CI 1.11, 1.21; p<0.01) (Figure 2, Figure S1). The GRADE rating was very low quality due to high heterogeneity (I^2 of 51%) and a high risk of bias (Table 2). Galbraith plot analysis indicated that five studies [12,16,33,37,41] were the potential source of heterogeneity of estimated risk of AR (Figure S2).

Subgroup analysis

Subgroup analyses were performed to explore the plausibility of heterogeneity. Region (p=0.01) and exclusion of prematurity (p<0.01) were the two potential confounders. Participants born by CD in South America had a significantly higher risk of developing AR (OR of 1.46; 95% CI 1.22, 1.75; I^2 of 0%) compared to other regions [21,24,34,39]. Study populations exposed to CD without a history of prematurity had a significantly higher risk of AR (OR of 1.26; 95% CI 1.17, 1.36; I^2 of 19%) than those having exposure with CD with inclusion of preterm births or lacked clear descriptions (OR of 1.11; 95% CI 1.07, 1.16; I^2 of 36%). There was no association in other subgroup analyses, including by study design, age of AR outcome, definition of AR, available OR, and proportion of CD (Figure 2, Figures S3-9).

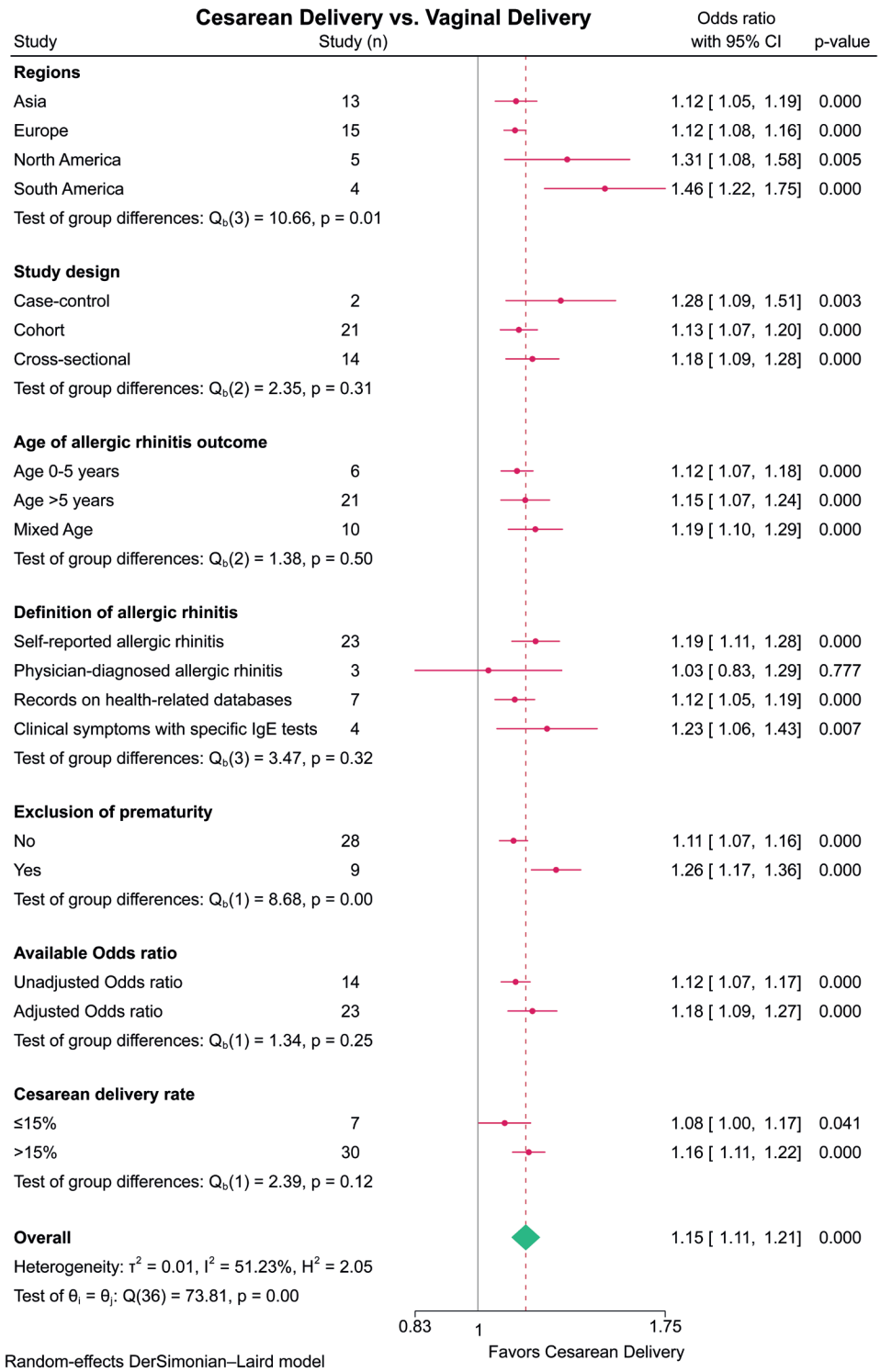

Figure 2. The risk of allergic rhinitis and subgroup analyses: cesarean delivery vs. vaginal delivery. AR, allergic rhinitis; OR, odds ratio.

Meta-regression

Meta-regression did not find any interaction between the priori-defined covariates (proportion of CD, year of birth, year of publication, the number of potential confounders in the model analysis, and sample size) and the likelihood of AR in comparing CD and VD (Figures S10-14). A funnel plot and Egger's test with p=0.11 indicated no publication bias for the meta-analysis (Figure S15).

Sensitivity analysis

Sensitivity analyses showed a higher likelihood of developing AR in participants born through CD compared to those born

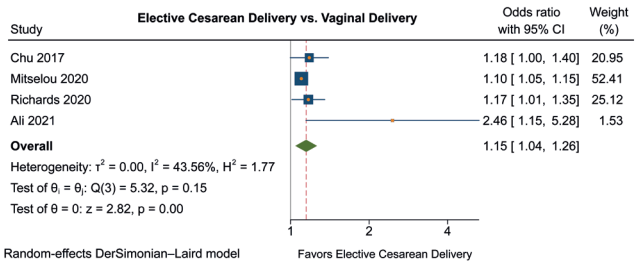

Figure 3. The risk of allergic rhinitis: elective cesarean delivery vs. vaginal delivery.

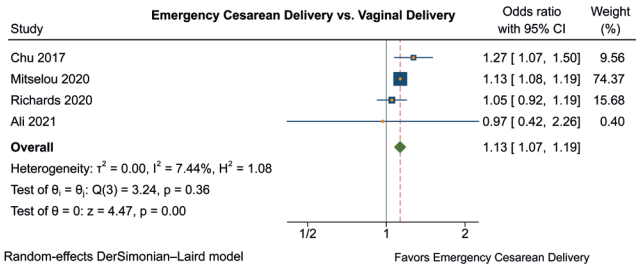

Figure 4. The risk of allergic rhinitis: emergency cesarean delivery vs. vaginal delivery.

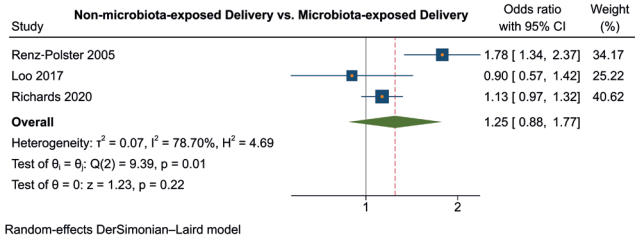

Figure 5. The risk of allergic rhinitis: non-microbiota-exposed delivery vs. microbiota-exposed delivery.

vaginally, except for studies with age of outcome ≥18 years (OR of 1.15; 95% CI 0.98, 1.36; I2 of 0%) (Table 3).

Elective cesarean delivery versus vaginal delivery

Four studies assessed the risk of AR between elective CD and VD [26,36,37,40]. The pooled data showed a significantly higher risk of AR in participants born through elective cesarean delivery compared to those born vaginally (OR 1.15; 95% CI 1.04, 1.26; p<0.01; I^2 of 44%) (Figure 3). The GRADE rating was low quality (Table 2).

Emergency cesarean delivery versus vaginal delivery

Four studies assessed the risk of AR between emergency CD and VD [26,36,37,40]. The pooled data showed a significantly higher risk of AR in participants born through emergency CD compared to those born vaginally (OR 1.13; 95% CI 1.07, 1.19; p<0.01; I^2 of 0%) (Figure 4). The GRADE rating was low quality (Table 2).

Cesarean delivery versus spontaneous vaginal delivery

Four studies assessed the risk of AR between CD and spontaneous VD [12,13,29,32]. The pooled data showed a significantly higher risk of AR in participants born through CD compared to those who experienced spontaneous VD (OR 1.09; 95% CI 1.01, 1.19; p<0.01; I^2 of 19%) (Figure S16). The GRADE rating was low quality (Table 2).

Cesarean delivery versus abnormal vaginal delivery

Two studies assessed the risk of AR between CD and abnormal VD [12,13]. The pooled data did not show a significantly higher risk of AR in participants born through cesarean delivery compared to those who experienced abnormal VD (OR 0.96; 95% CI 0.79, 1.18; p=0.72; I^2 of 0%) (Figure S17). The GRADE rating was low quality (Table 2).

Abnormal vaginal delivery versus spontaneous vaginal delivery

Three studies assessed the risk of AR between abnormal and spontaneous VD [12,13,29]. The pooled data did not show a significantly higher risk of AR in participants born through abnormal VD compared to those who experienced spontaneous VD (OR 1.10; 95% CI 0.94, 1.28; p=0.24; I^2 of 0%) (Figure S18). The GRADE rating was low quality (Table 2).

Non-microbiota-exposed versus microbiota-exposed delivery

Three studies assessed the risk of AR between non-microbiota-exposed and microbiota-exposed delivery [15,28,37]. The pooled data did not show a significantly higher risk of AR in participants having non-microbiota-exposed delivery compared to those having microbiota-exposed delivery (OR 1.25; 95% CI 0.88, 1.77; p=0.22; I^2 of 79%) (Figure 5). The GRADE rating was very low quality due to high heterogeneity (Table 2).

Risk of bias assessment

There were 13 (35%) studies with low quality, 18 (49%) with medium quality, and six (16%) with high quality (Tables S2-S4). The cross-sectional studies had low score in ascertainment of exposure due to recall bias. All twenty-one cohort studies had moderate-to-high quality.

Discussion

In the newborn, T-helper (Th)2 is the predominant phenotype of the T cells. Following birth, infants maintain a prevalent Th2 immune response, transitioning to a balanced Th1 response by the end of the first year. However, allergic infants have a prolonged Th2 skewing, and their ability to develop Th1 function is delayed [60]. The prenatal and postnatal environment factors, combined with aeroallergens, microbial exposure, diets, and psychosocial influences, can affect the Th1/Th2 ratio, increasing

Table 3. Sensitivity analyses of risk of allergic rhinitis: cesarean delivery vs. vaginal delivery.

	Studies (n)	Relative OR (95% CI)	P values	I^2 (%)
Removing 5 studies with the potential source of heterogeneity	32	1.16 (1.12, 1.21)	<0.01	20
High- and medium-quality studies	26	1.16 (1.10, 1.22)	<0.01	47
High-quality studies	6	1.07 (1.01, 1.14)	0.03	36
Studies with general population	30	1.14 (1.09, 1.20)	<0.01	56
Studies with sample size ≥5000	13	1.12 (1.07, 1.18)	<0.01	70
Studies with retention rate or responder rate ≥70%	21	1.14 (1.09, 1.20)	0.01	45
Studies with satisfactory adjustment for confounders	16	1.12 (1.04, 1.21)	<0.01	57
Studies with age of outcome ≥18 years	6	1.15 (0.98, 1.36)	0.09	0
Participants were born in 2000s	19	1.13 (1.08, 1.19)	<0.01	55

OR, odds ratio; CI, confidence interval.

the risk of atopy in early life [47]. Infants receive one of their initial microbial exposures during delivery [5]. Therefore, delivery mode may present a challenge in a critical phase of developing the immune system of newborns. Recent findings indicate that babies born via CD often exhibit decreased levels of natural killer (NK) cells and diminished interleukin (IL)-12 production while having elevated levels of IL-13 and interferon (IFN)-γ [25]. Mode of delivery can shape the acquisition and structure of the initial gut microbiota in newborns [61]. Growing evidence highlights differences in gut microbiota between infants born vaginally and those delivered via CD, attributable to distinct transfers of maternal microbiomes during childbirth [62-64]. Although delivery mode may impact the microbiomes and immune system development, its relationships with the subsequent allergic conditions have been inconsistent. Cesarean section predisposes to the development of asthma and food allergy but not atopic dermatitis in childhood [49,65,66].

This systematic review and meta-analysis showed the association between the CD and the likelihood of developing AR later in life. Interestingly, our pooled data had lower OR with lower heterogeneity than recent meta-analyses with the same interest [50,51]. A significantly larger number of included studies and a greater balance regarding the weight of individual effect size may be a plausible reason for the difference. The incidence of AR continues steadily until the age of five, at which point there is a noticeable increase. On the contrary, some children affected by the atopic march may experience symptoms persisting over several years, while for others, these symptoms may resolve as they get older [67]. Hence, we aim to examine whether there are any subgroup variations in the onset of AR between the ages of ≤5 years and >5 years. Consequently, an increasing trend of AR related to CD was observed in both groups without significant differences. However, the studies assessing the incidence of AR after 18 years of age unsuccessfully showed the relationship between CD and AR according to the sensitivity analysis, suggesting that long-term follow-up cohorts should be conducted to prove the impact of CD (Table 3).

Many genetic and environmental factors and study settings may drive the effect of CD on the risk of AR [42], leading to non-trivial heterogeneity of our result. Subgroup analyses revealed two potential confounders, including region and exclusion of prematurity. South American continent had the highest OR compared to other regions; however, the results should be interpreted with caution since all studies in this region have cross-sectional designs [21,24,34,39]. Prematurity, represented by low birthweight and being born before full term, along with an underdeveloped gastrointestinal tract or immune system, could increase the likelihood of allergic diseases [29]. On the contrary, studies limited to full-term births demonstrated a notably higher likelihood of AR associated with CD compared to those including preterm births or lacked clear descriptions. The variations in how prematurity is defined across different studies and settings create challenges for the conclusion, indicating the need for additional investigation. The number of potential covariates in the regression model analysis did not significantly affect the likelihood of AR risk related to CD (Figure 1, Table 3, Figure S13). Although numerous theories attempt to link atopic disease risk with intricate lifestyle and socioeconomic factors that directly or indirectly interfere with microbial exposure [5,68], it remains challenging to consolidate all these aspects into a single formula for universal assessment.

Recent studies assessing the relationship between the delivery mode and AR susceptibility show a higher incidence of AR compared to publications in the 2000s (Table 1). Unlike expectation, the rate of CD was not proportionally related to the likelihood of AR (Figures S9-10). Again, this finding was confirmed by the meta-regressions in which continuous variables (year of birth, year of publication) were considered potential covariates (Figures S11-12). Our evidence suggested that CD increases the risk of AR, with its positive effect staying consistent over time.

It has been argued that certain CD occurs after the rupture of the protective amniotic membranes, which permits the ascent of maternal vaginal microflora into the amniotic fluid [15]. In cases of CD with PROM, mother-to-child microbial transmission happens during the intrauterine period. Consequently, the gut flora of infants in CD with PROM is comparable to that in VD. Irrespective of the microbial-transfer hypothesis, the current finding indicated a null association with AR when comparing deliveries exposed and not exposed to maternal microbiota (Figure 5, Table 2). Therefore, it seems that the sole influence of delivery mode on microbial diversity is inadequately accountable for allergic conditions in offspring.

Compared to VD, elective and emergency CDs in our study were statistically significantly associated with a higher risk of AR. This effect was also observed when comparing CD to spontaneous VD overall. Stress experienced during pregnancy may impact health development, potentially affecting the development of allergic diseases [69]. Moreover, prenatal stress appears to be linked to elevated rates of both elective and emergency CDs [70]. Abnormal VD, including assisted birth types, exhibits higher levels of stress hormones for both mother and child compared to regular spontaneous VD or CD [71]. Despite the absence of increased AR risks following abnormal VD compared to spontaneous VD or CD in our results, the pooled data were limited by a modest number of studies and participants, highlighting the need for further research in this area.

A strength of our study was that the large number of studies and participants allowed us to elaborate on the thorough analysis of different delivery modes excluded in previous meta-analyses. Only one previous meta-analysis assessed the effect of elective and emergency CD compared to VD on the risk of AR in children [50]. Our study is the first meta-analysis providing stringent definitions of delivery mode while also scrutinizing their impacts separately. Definition of vaginal delivery lacked information to determine perinatal microbiota-exposed conditions across studies. Many research investigations relied on parent-reported AR status assessed through questionnaires, with some using the validated International Study of Asthma and Allergies in Childhood questionnaire. Although subgroup analysis based on the definition of AR revealed no significant difference in the probability of AR development across studies using various subjective and objective diagnostic methods, the physician-diagnosed AR group failed to show a positive relationship between CD and AR. Given that this group is likely one of the most reliable groups regarding AR definition, more detailed investigations are needed. We also assessed the impact of delivery modes on the risks of developing AR at different ages and time points up to 44 years, along with the GRADE approach to rate the quality of evidence. Sensitivity analyses by removing medium- and low-quality studies did not alter the outcome, suggesting the uncertain risk of bias.

The limitation of our study was the inconsistency in methodology that impacted and influenced the quality of evidence. The discrepancy of methodology in study design may cause bias and inconsistent conclusions. Furthermore, the definition of microbiota-exposed delivery was not regularly used in assessing events of VD and CD, toning down the quality of evidence. We suggest that a rigorous assessment of maternal microbiota exposure during delivery, long-term follow-up, and specific categorization of delivery mode should be applied in future studies.

Conclusion

Overall, most estimated odd ratios were consistent with a positive association between cesarean delivery and allergic rhinitis in childhood. Early-life environmental exposures that affect microbial colonization may influence the risk of allergic rhinitis. Further studies focusing on non-microbiota-exposed versus microbiota-exposed delivery are needed.

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Authors' contributions

MPH: study design, search, study selection, data collection, data analysis, drafting the article, and final approval. KSe: search, study selection, data collection, revising the article, and final approval. JS: data collection, revising the article, and final approval. WC: data collection, revising the article, and final approval. KSn: conception, study design, data analysis, drafting the article, and final approval.

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Conflicts of interest

Kornkiat Snidvongs has served on the speaker's bureau for Organon and Menarini. All other authors declare no conflicts of interest.

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Kornkiat Snidvongs
Department of Otolaryngology
Faculty of Medicine
Chulalongkorn University
1873 Rama 4 Road
Pathumwan
Bangkok 10330
Thailand

Tel: (+66) 2-256-4103
Fax: (+66) 2-252-7787
E-mail: drkornkiat@yahoo.com

Minh P. Hoang[1,2,3], Kachorn Seresirikachorn[1,2], Jompol Samuthpongtorn[1], Wirach Chitsuthipakorn[4,5], Kornkiat Snidvongs[1,2]

[1] Department of Otolaryngology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
[2] Endoscopic Nasal and Sinus Surgery Excellence Center, King Chulalongkorn Memorial Hospital, Bangkok, Thailand
[3] Department of Otolaryngology, Hue University of Medicine and Pharmacy, Hue University, Hue, Vietnam
[4] Center of Excellence in Otolaryngology-Head & Neck Surgery, Rajavithi Hospital, Bangkok, Thailand
[5] Department of Otolaryngology, College of Medicine, Rangsit University, Bangkok, Thailand

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SUPPLEMENTARY MATERIAL

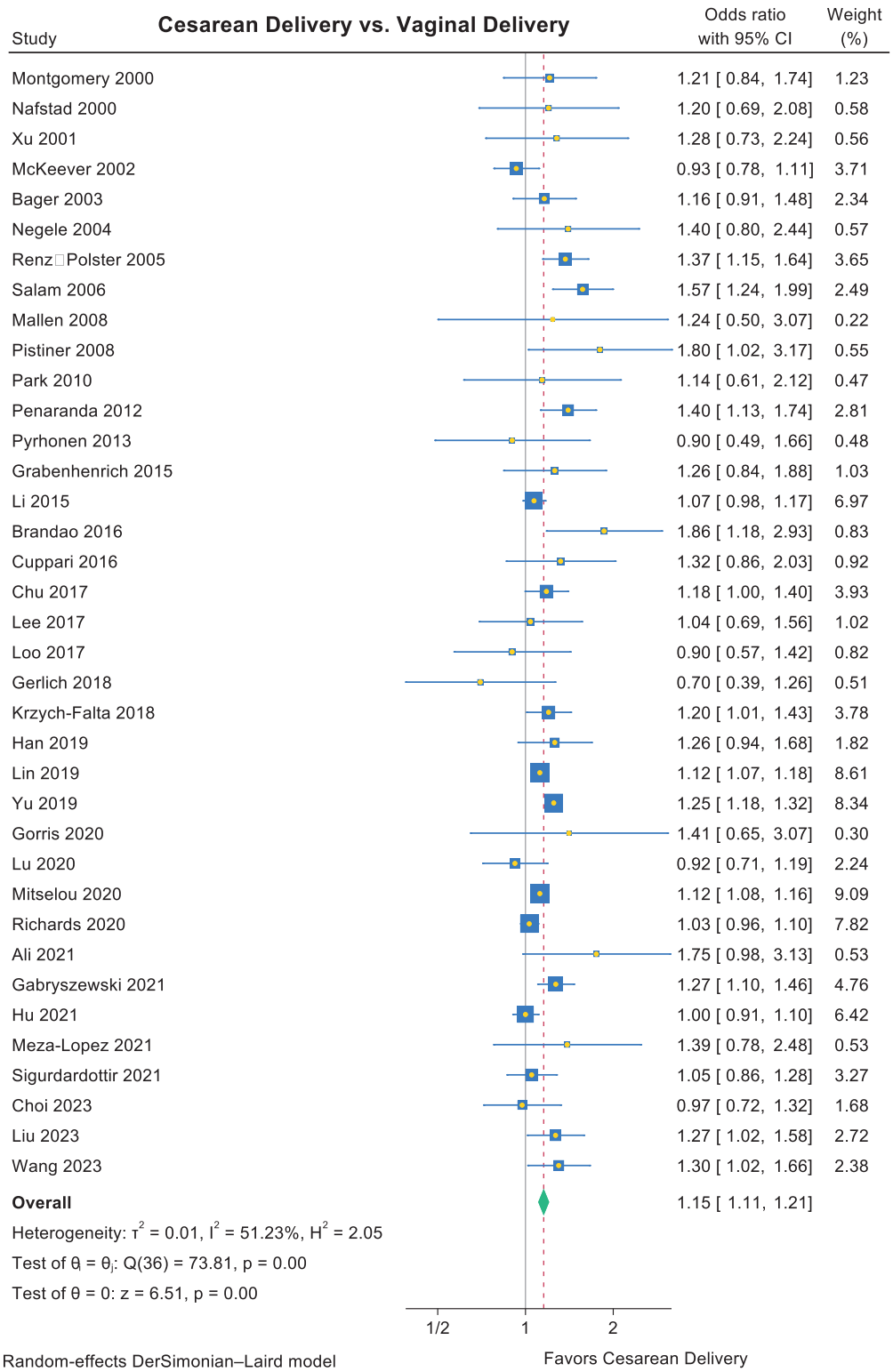

Figure S1. Risk of allergic rhinitis: cesarean delivery vs. vaginal delivery

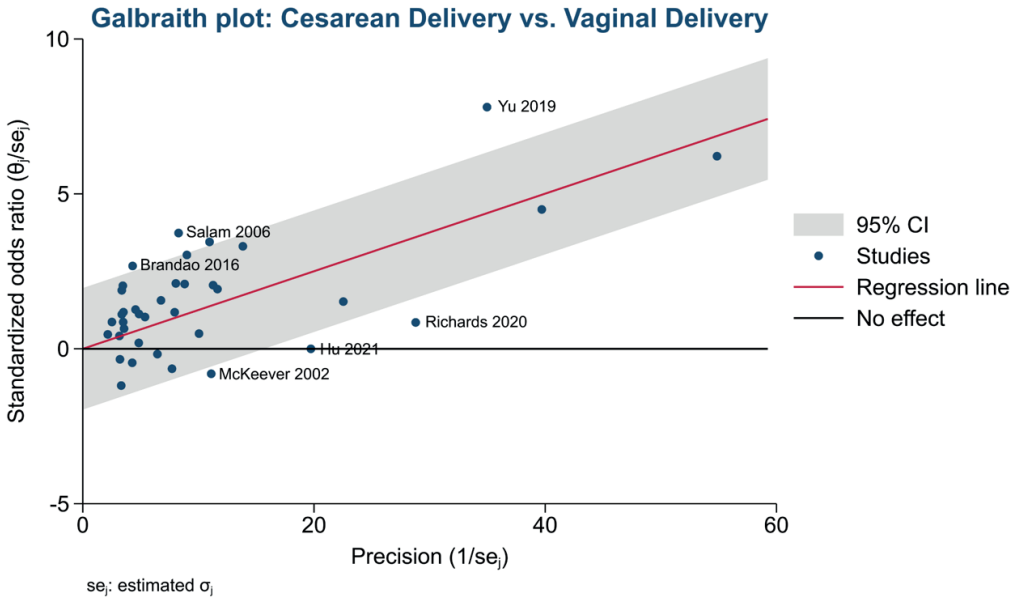

Figure S2. Galbraith plot analysis indicated that four studies were the potential source of heterogeneity of estimated risk of allergic rhinitis: cesarean delivery vs. vaginal delivery

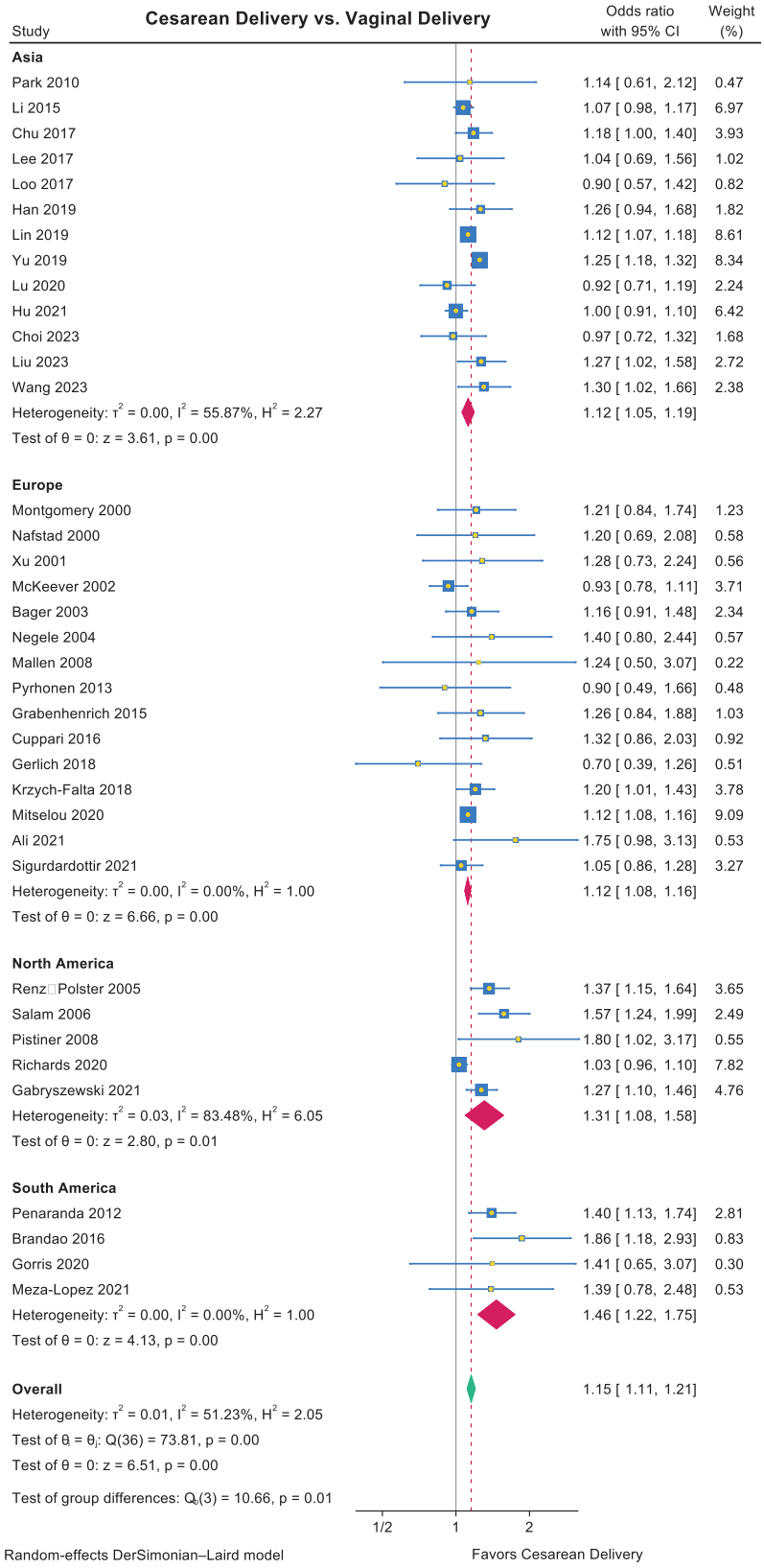

Figure S3. Risk of allergic rhinitis and subgroup by study design: cesarean delivery vs. vaginal delivery

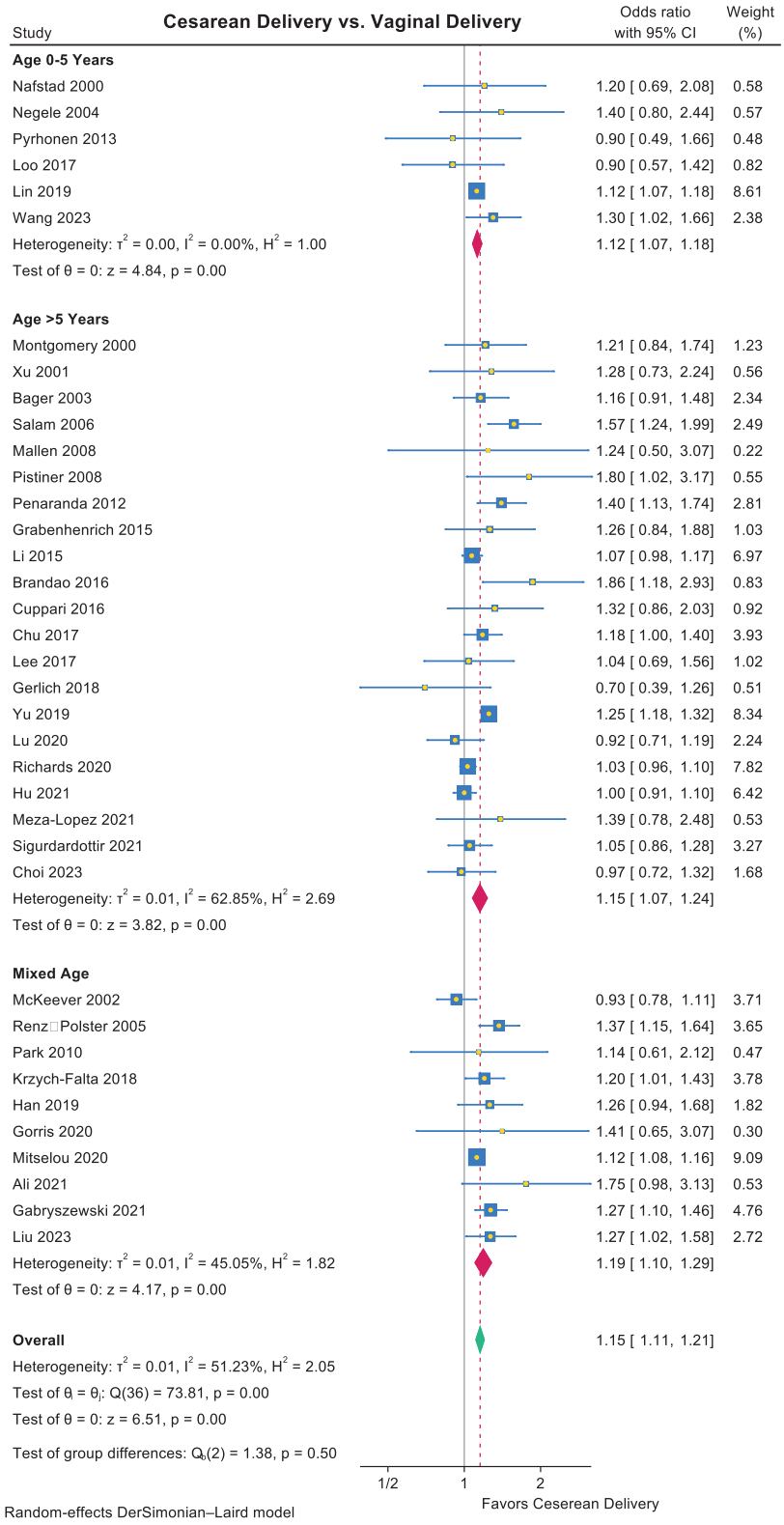

Figure S4. Risk of allergic rhinitis and subgroup by affluence of country: cesarean delivery vs. vaginal delivery

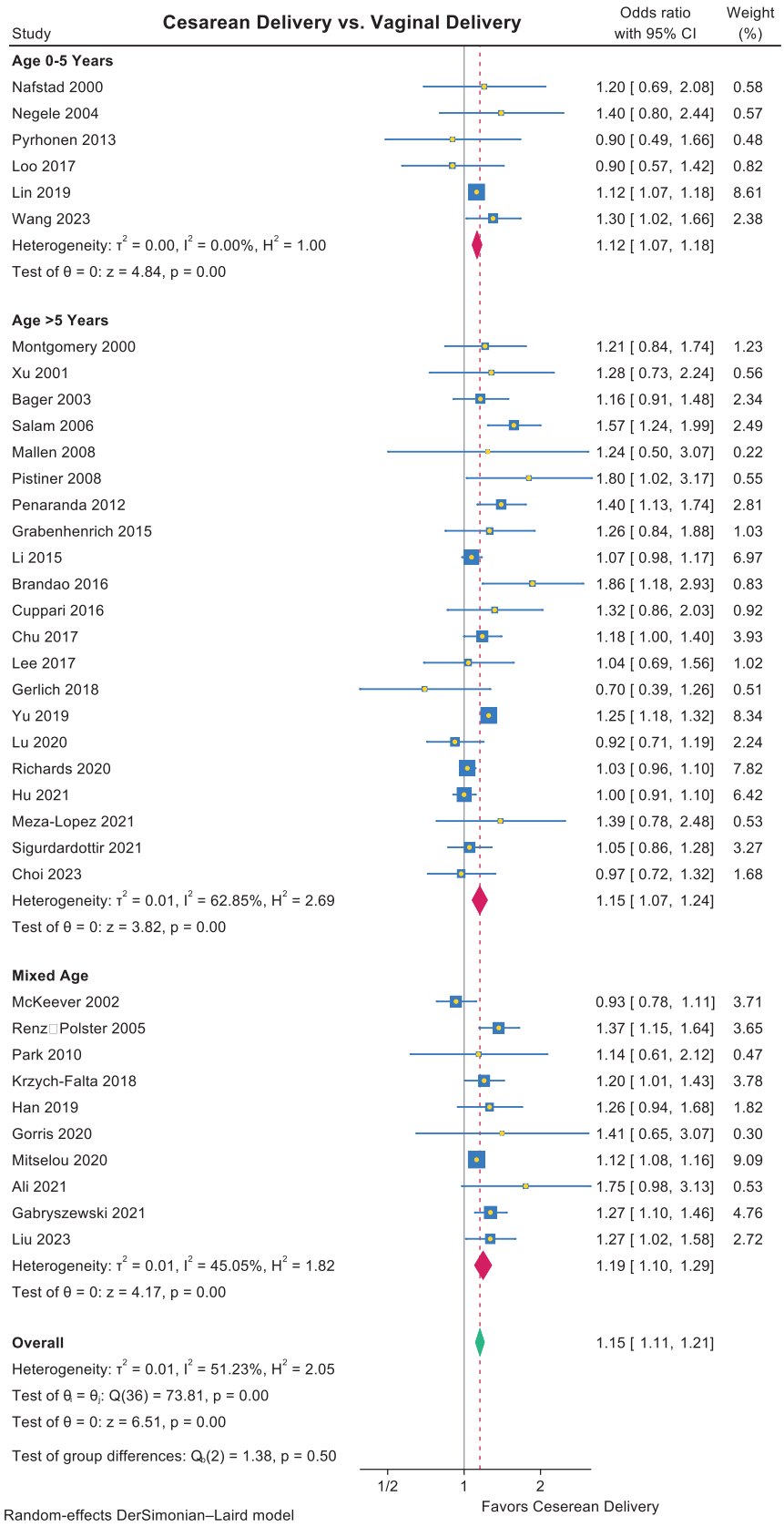

Figure S5. Risk of allergic rhinitis and subgroup by age of outcome: cesarean delivery vs. vaginal delivery

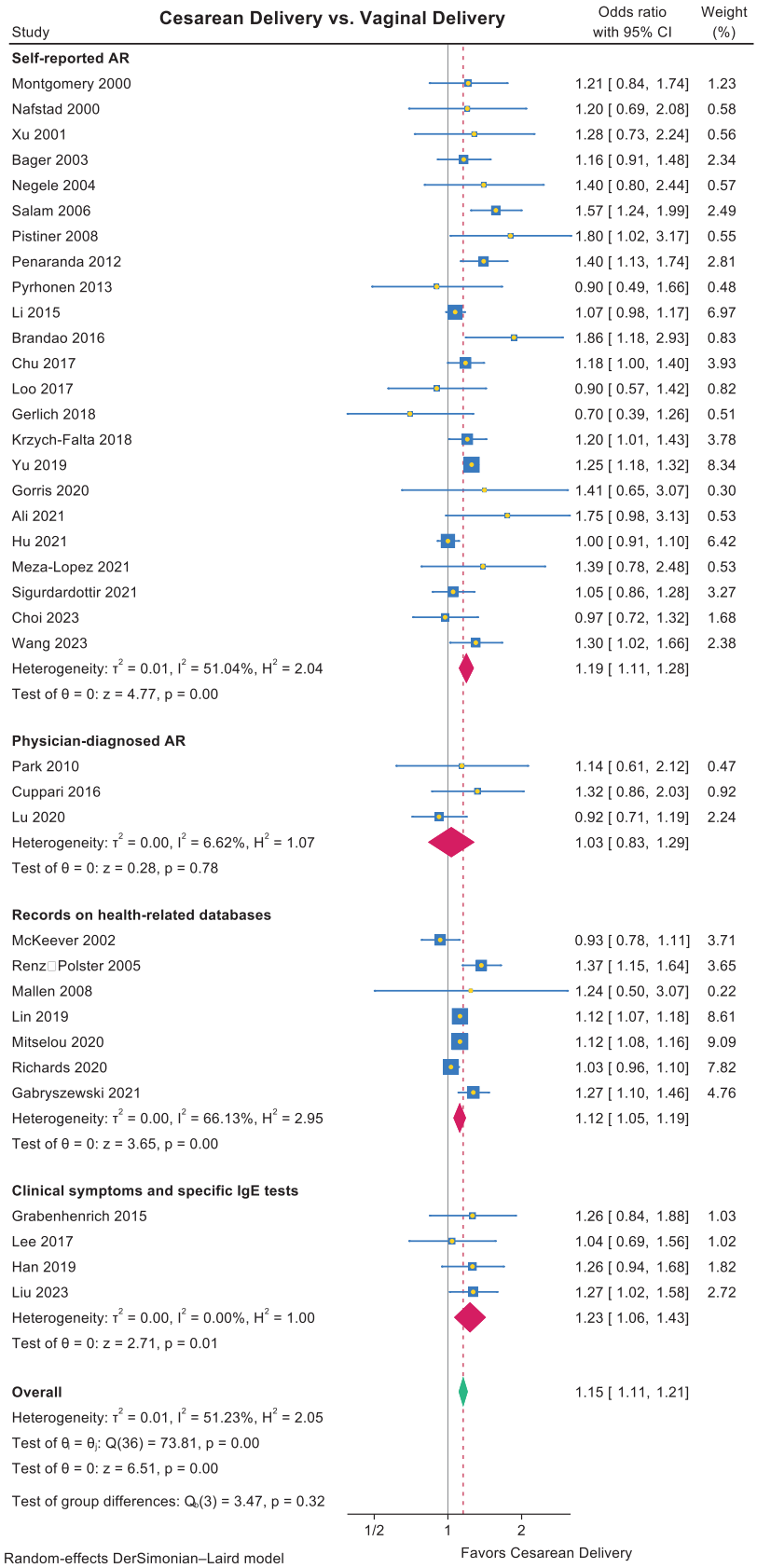

Figure S6. Risk of allergic rhinitis and subgroup by definition of AR: cesarean delivery vs. vaginal delivery

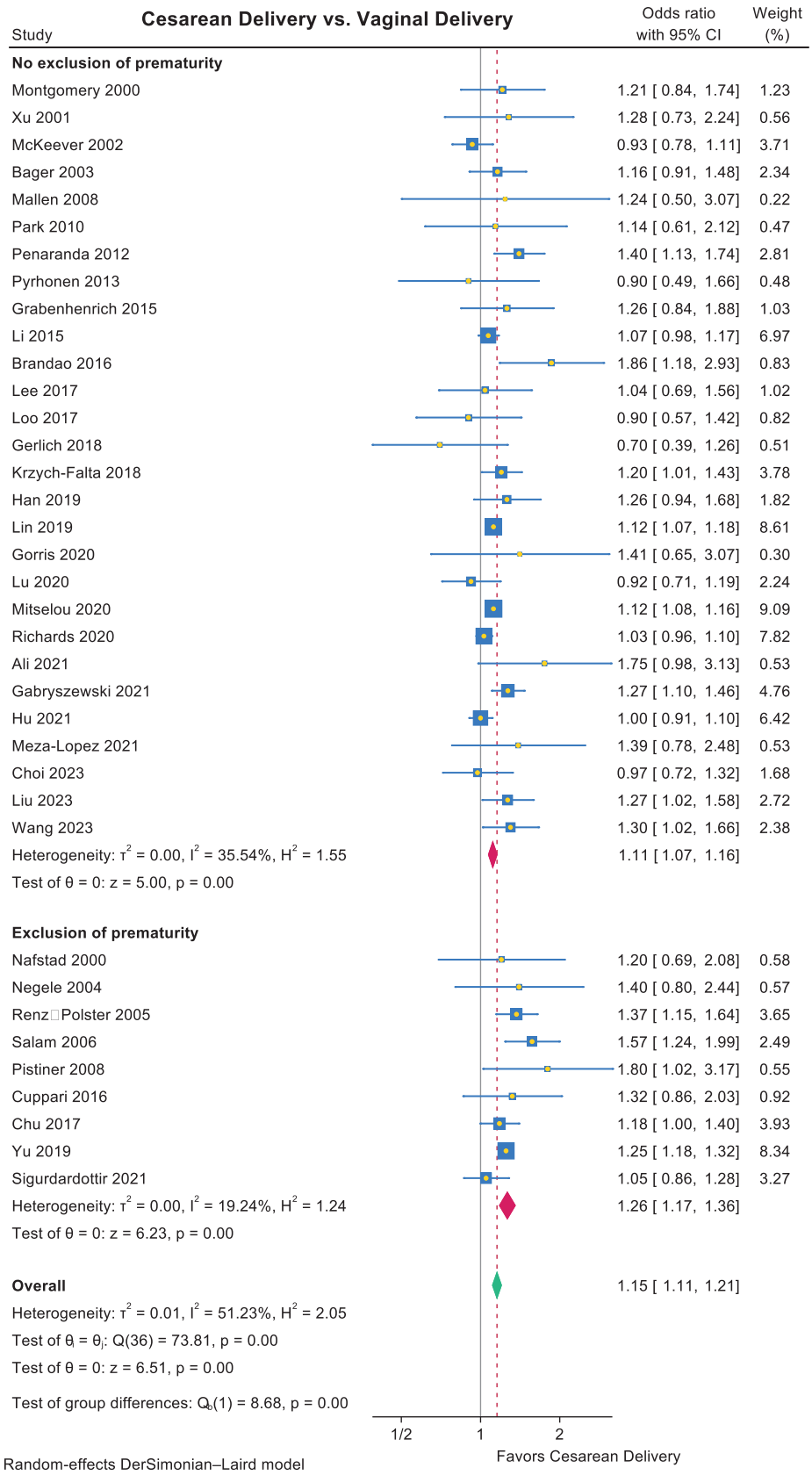

Figure S7. Risk of allergic rhinitis and subgroup by exclusion of prematurity: cesarean delivery vs. vaginal delivery

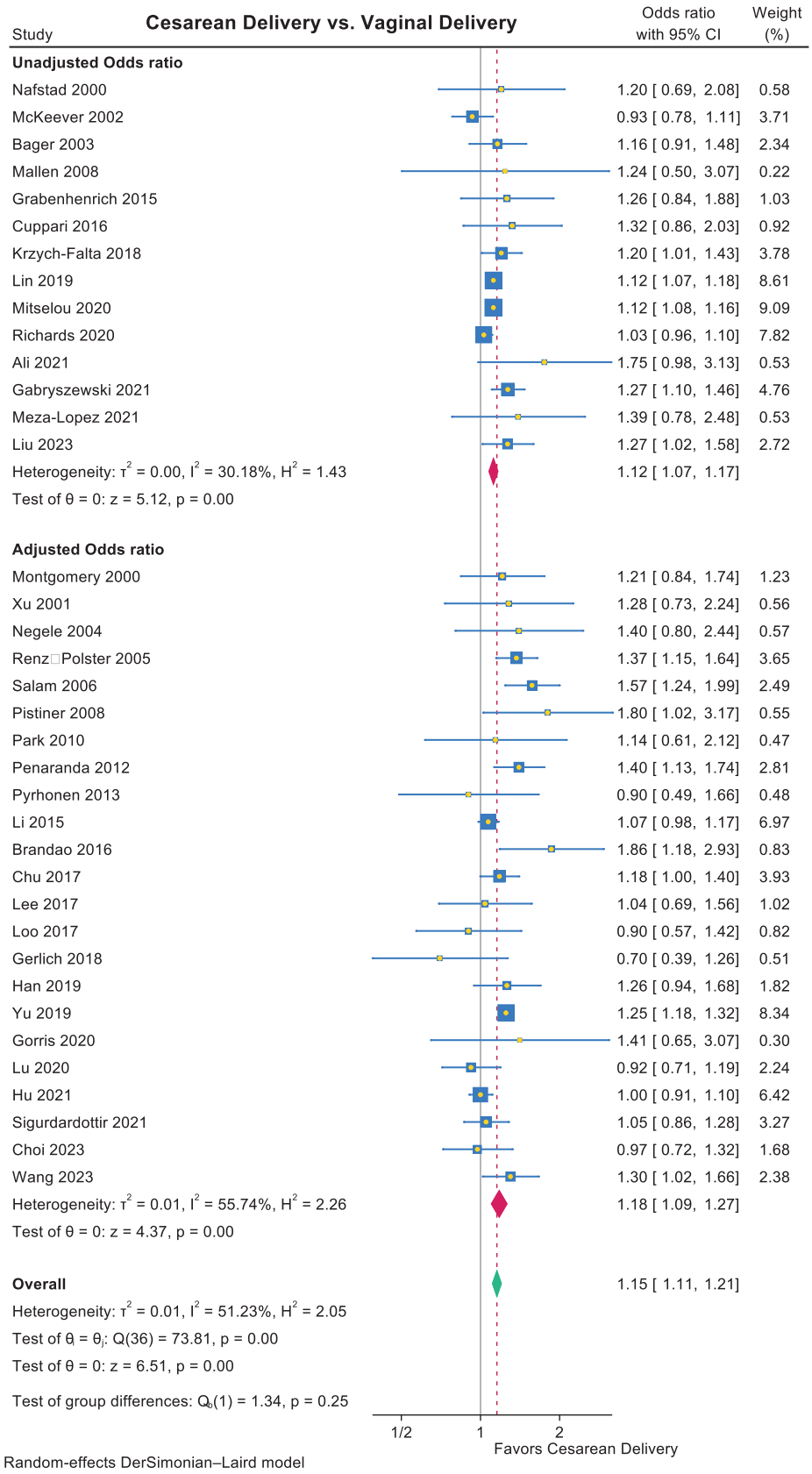

Figure S8. Risk of allergic rhinitis and subgroup by available OR: cesarean delivery vs. vaginal delivery

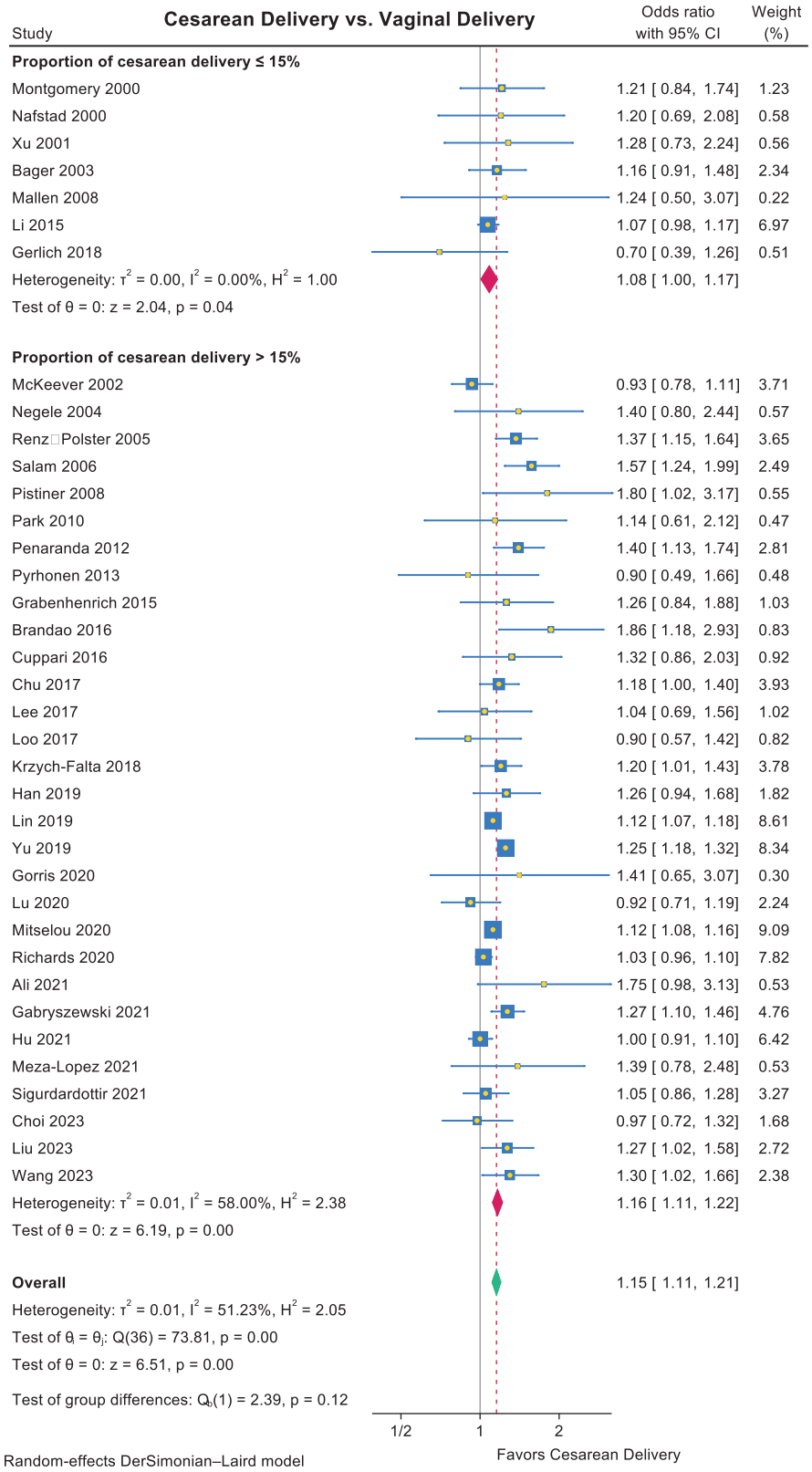

Figure S9. Risk of allergic rhinitis and subgroup by proportion of cesarean delivery: cesarean delivery vs. vaginal delivery

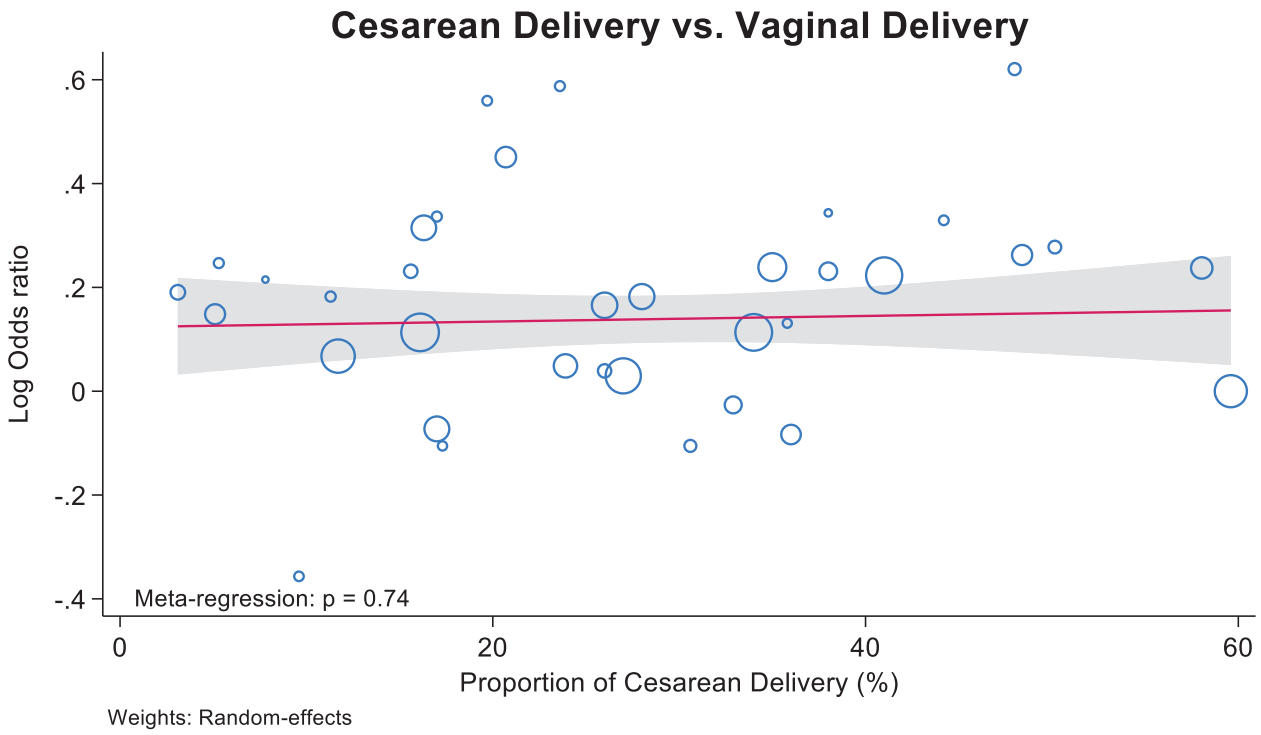

Figure S10. Bubble plot with random-effects meta-regression line of the log odds ratio of risk of AR: cesarean delivery vs. vaginal delivery and proportion of Cesarean delivery

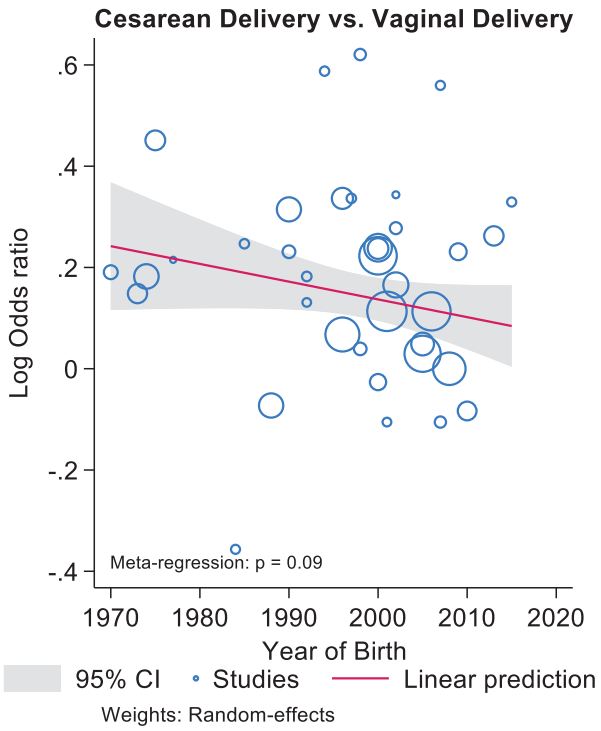

Figure S11. Bubble plot with random-effects meta-regression line of the log odds ratio of risk of AR: cesarean delivery vs. vaginal delivery and participants' year of birth.

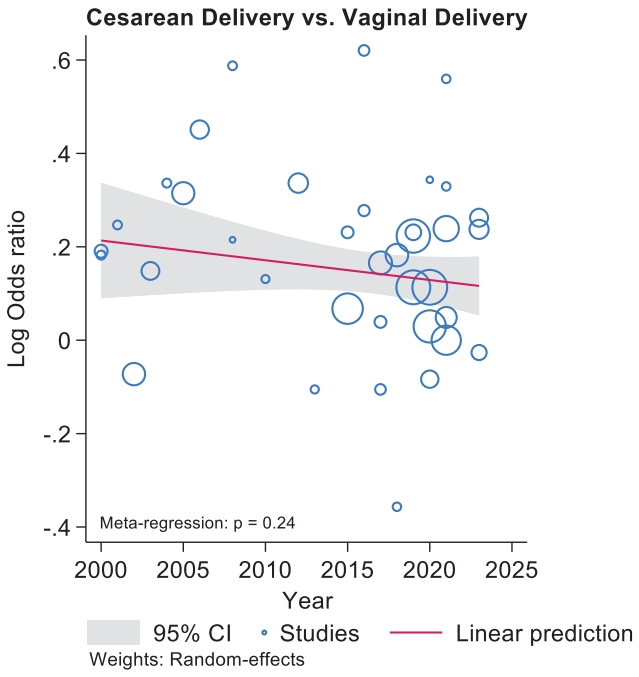

Figure S12. Bubble plot with random-effects meta-regression line of the log odds ratio of risk of AR: cesarean delivery vs. vaginal delivery and year of publication.

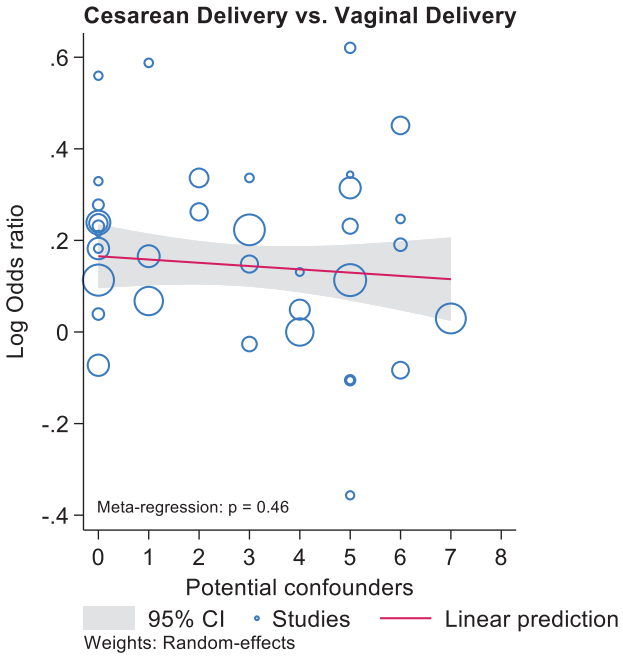

Figure S13. Bubble plot with random-effects meta-regression line of the log odds ratio of risk of AR: cesarean delivery vs. vaginal delivery and number of adjusted potential confounders

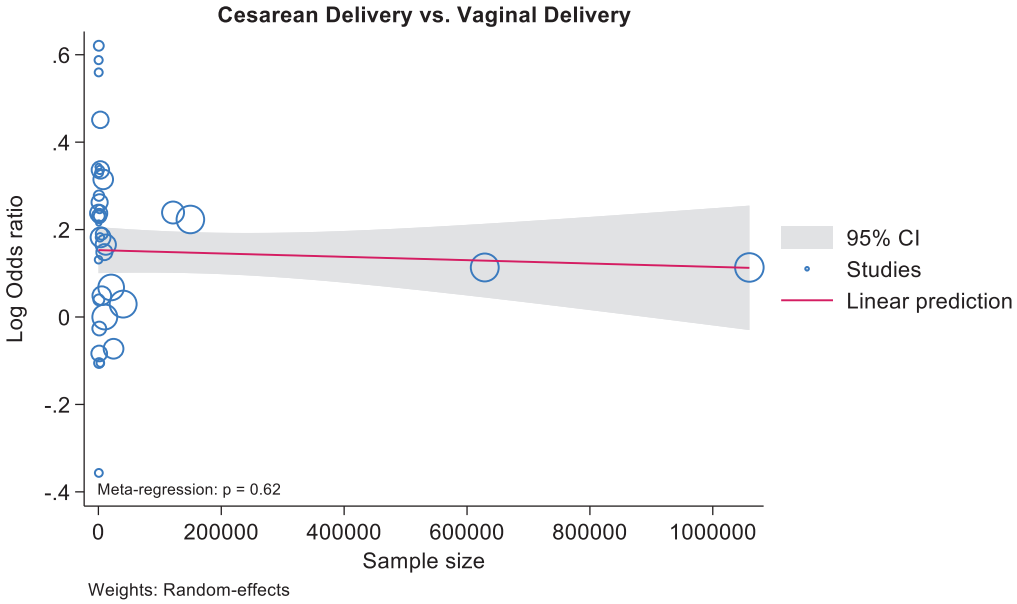

Figure S14. Bubble plot with random-effects meta-regression line of the log odds ratio of risk of AR: cesarean delivery vs. vaginal delivery and sample size

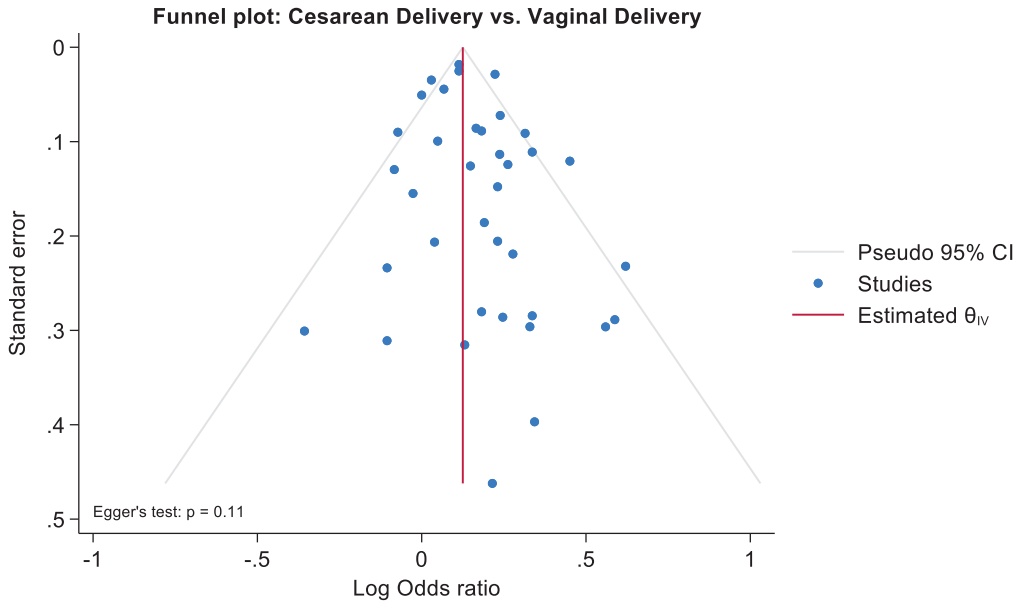

Figure S15. Funnel plot with the log odds ratio of risk of AR: cesarean delivery vs. vaginal delivery

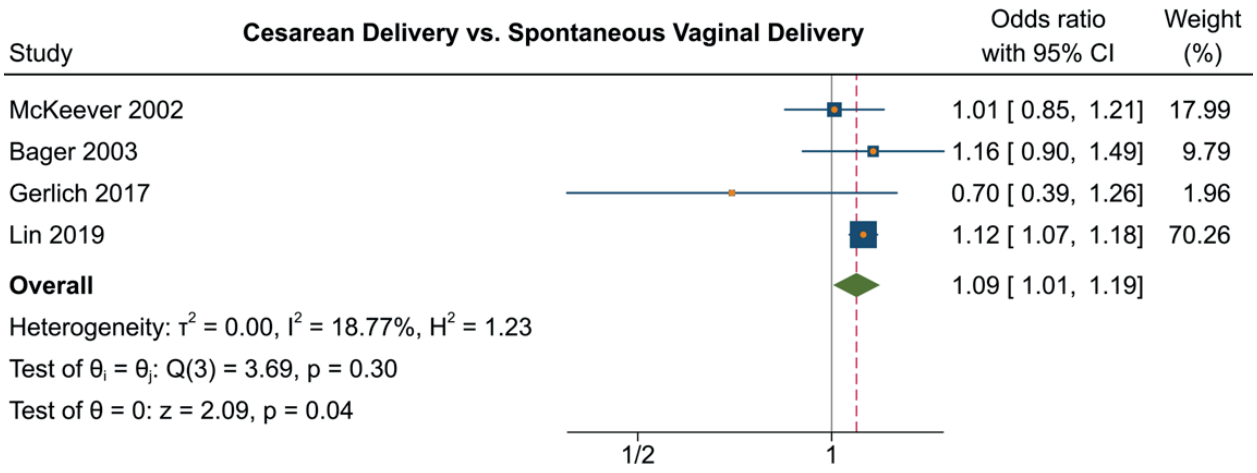

Figure S16. The risk of allergic rhinitis: ceserean delivery vs. spongtaneous vaginal delivery

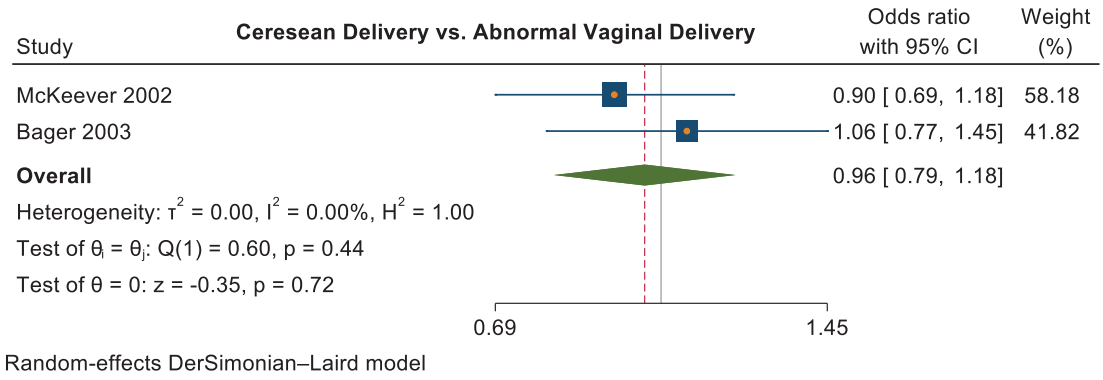

Figure S17. The risk of allergic rhinitis: cesarean delivery vs. abnormal vaginal delivery

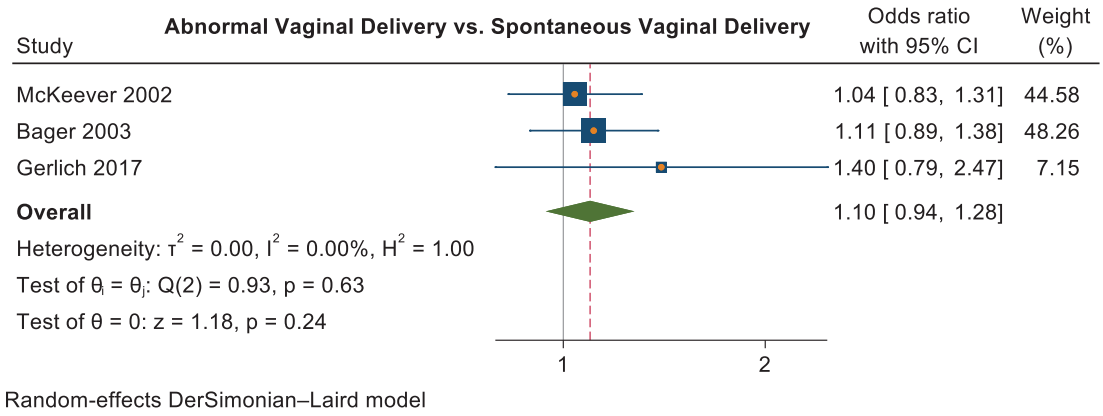

Figure S18. The risk of allergic rhinitis: abnormal vaginal delivery vs. spontaneous vaginal delivery

Table S1. Search strategy.

PubMed MEDLINE (269)	EMBASE (633)
#1 "delivery, obstetric" [Mesh]	#1 exp delivery, obstetric/
#2 "cesarean section" [Mesh]	#2 exp cesarean section/
#3 "cesarean section*" [All Fields]	#3 cesarean section*.mp.
#4 "delivery abdominal" [All Fields]	#4 delivery abdominal.mp.
#5 "abdominal deliver*" [All Fields]	#5 abdominal deliver*.mp.
#6 "C section*" [All Fields]	#6 C section*.mp.
#7 "postcesarean section" [All Fields]	#7 postcesarean section.mp.
#8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	#8 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7
#9 "delivery" [All Fields]	#9 delivery.mp.
#10 "birth" [All Fields]	#10 birth.mp.
#11 "perinatal" [All Fields]	#11 perinatal.mp.
#12 "obstetric complications" [All Fields]	#12 obstetric complications.mp. or exp Obstetric Labor Complications/
#13 "pregnancy complications" [All Fields]	#13 pregnancy complications.mp. or exp Pregnancy Complications/
#14 #10 OR #11 OR #12 OR #13	#14 #10 OR #11 OR #12 OR #13
#15 #9 AND #14	#15 #9 AND #14
#16 #15 NOT #8	#16 #15 NOT #8
#17 "Rhinitis, Allergic, Seasonal" [Mesh]	#17 exp Rhinitis, Allergic, Seasonal/
#18 "Rhinitis, Allergic, Perennial" [Mesh]	#18 exp Rhinitis, Allergic, Perennial/
#19 "Allergic rhinitis" [All fields]	#19 exp Rhinitis, Allergic/
#20 "Hay fever" [All fields]	#20 Hay fever.mp.
#21 "Allergic rhinoconjunctivitis" [All fields]	#21 conjunctivitis, allergic/ or allergic rhinoconjunctivitis.mp.
#22 "Atopic disease*" [All fields]	#22 allergic disease*.mp.
#23 "Allergic disease*" [All fields]	#23 atopic disease*.mp.
#24 #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23	#24 #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23
#25 #8 AND #24	#25 #8 AND #24
#26 #16 AND 24	#26 #16 AND #24
#27 #25 OR #26	#27 #25 OR #26
Web of Science (268), CENTRAL (4)	
#1 TS= ("allergic rhinitis" OR "hay fever" OR "allergic disease" OR "atopic disease" OR "allergic rhinoconjunctivitis")	
#2 TS= ("cesarean section" OR "C section*" OR "cesarean delivery" OR "mode of delivery" OR "abdominal delivery")	
#3 TS= ("delivery" AND ("birth" OR "perinatal" OR "obstetric complications" OR "pregnancy complications"))	
#4 #3 NOT #2	
#5 #1 AND #2	
#6 #1 AND #4	
#7 #5 OR #6	

Table S2. Characteristics of the included studies and relative estimates of measure effect.

First author, Year	Year of births	Affluence of country	Population	Female (%)	Source of delivery	Type of CD	Type of VD	Original effect measure	Adjusted OR (yes/no)	Confounder(s) for adjustment	OR (95% CI)	Exclusion of prematurity	Loss to follow-up >30%
Nafstad, 2000	<2000	Affluent	Normal	48.7	Hospital records	Unclassified	Unclassified	OR	No	None	1.2 (0.7-2.1)	Yes	Yes
Montgomery, 2000	<2000	Affluent	Normal	NA	Health records	Unclassified	Unclassified	OR	Yes	ABCDFG	1.21 (0.84-1.74)	No	Yes
Xu, 2001	<2000	Affluent	Normal	NA	Hospital records	Unclassified	Unclassified	OR	Yes	ABCDEF	1.28 (0.73-2.24)	No	No
McKeever, 2002	<2000	Affluent	Normal	NA	Hospital records	Unclassified	Unclassified-SpontaneousAb-normal	IRR	No No No	None None None	0.93 (0.78-1.11)† 1.01 (0.85-1.21) 0.90 (0.69-1.18)† 1.11 (0.89-1.38)†*	No	No
Bager, 2003	<2000	Affluent	Female	100	Hospital records	Unclassified	Unclassified-SpontaneousAb-normal	OR	No Yes No No	None ABC None None	1.16 (0.91-1.49)† 1.16 (0.90-1.49) 0.90 (0.69-1.18)† 1.11 (0.89-1.38)†*	No	No
Negele, 2004	<2000	Affluent	Normal	48	Health records	Unclassified	Unclassified	OR	Yes	ACG	1.40 (0.80-2.44)	Yes	No
Renz- Polster, 2005	<2000	Affluent	Normal	49	Health records	Unclassified	Unclassified	OR	Yes Yes	ACDEF ACDEF	1.37 (1.14-1.63) 1.78 (1.34-2.37)**	Yes	No
Salam, 2006	<2000	Affluent	Normal	51.5	Health records	Unclassified	Unclassified	OR	Yes	ABCDEF	1.57 (1.24-1.99)	Yes	Yes
Mallen, 2008	<2000	Affluent	Normal	NA	Health records	Unclassified	Unclassified	OR	No	None	1.36 (0.51-3.65)	No	Yes
Pistiner, 2008	<2000	Affluent	Parental allergy	45	Health records	Unclassified	Unclassified	OR	Yes	B	1.80 (1.00-3.10)	Yes	No
Park, 2010	<2000	Affluent	Normal	35	Questionnaire	Unclassified	Unclassified	OR	Yes	ABDG	1.14 (0.61-2.10)	No	No
Penaranda, 2012	<2000	Non-affluent	Normal	56.2	Questionnaire	Unclassified	Unclassified	OR	Yes	EF	1.40 (1.10-1.70)	No	No
Pyrhonen, 2013	≥2000	Affluent	Normal	49.4	Questionnaire	Unclassified	Unclassified	OR	Yes	BCDEG	0.90 (0.47-1.59)	No	Yes
Grabenhenrich, 2015	<2000	Affluent	Normal	47.9	Questionnaire	Unclassified	Unclassified	HR	No	None	1.26 (0.84-1.88)†	No	No
Li, 2015	<2000	Non-affluent	Normal	50.4	Questionnaire	Unclassified	Unclassified	OR	Yes	F	1.07 (1.00-1.19)	No	No
Brandao, 2016	<2000	Non-affluent	Normal	50	Health records	Unclassified	Unclassified	OR	Yes	BCEFG	1.86 (1.18-2.93)	No	No
Cuppari, 2016	≥2000	Affluent	Normal	48.1	Health records	Unclassified	Unclassified	OR	No	None	1.32 (0.86-2.03)†	No	Yes

Table S2 continued. Characteristics of the included studies and relative estimates of measure effect.

First author, Year	Year of births	Affluence of country	Population	Female (%)	Source of delivery	Type of CD	Type of VD	Original effect measure	Adjusted OR (yes/no)	Confounder(s) for adjust-ment	OR (95% CI)	Exclusion of prematurity	Loss to follow-up >30%
Chu, 2017	≥2000	Non-affluent	Normal	47	Questionnaire	Elective	Unclassified	OR	Yes	E	1.18 (1.00-1.40)	Yes	No
Lee, 2017	≥2000	Affluent	Normal	46.8	Health records	Unclassified	Unclassified	OR	Yes	BEG	1.04 (0.69-1.55)	No	Yes
Loo, 2017	≥2000	Affluent	Normal	NA	Health records	CD without PROM	Unclassified	OR	Yes	ABCDF	0.90 (0.60-1.50)**	No	No
Gerlich, 2018	<2000	Affluent	Normal	56.8	Health records	Unclassified	SpontaneousAb-normal	OR	Yes Yes	ABDEF ABDEF	0.70 (0.40-1.30) 1.40 (0.80-2.50)*	No No	Yes
Krzych-Falta, 2018	≥2000	Affluent	Normal	53.8	Questionnaire	Unclassified	Unclassified	OR	No	None	1.20 (1.01-1.43)	No	Yes
Han, 2019	≥2000	Affluent	Rhinitis	33	Questionnaire	Unclassified	Unclassified	OR	Yes	BCDFG	1.26 (0.93-1.66)	No	No
Lin, 2019	≥2000	Affluent	Normal	47.7	Health records	Unclassified	Spontaneous	OR	No	None	1.12 (1.06-1.17)	No	No
Yu, 2019	≥2000	Non-affluent	Normal	46.3	Questionnaire	Unclassified	Unclassified	OR	Yes	CFG	1.25 (1.18-1.32)	Yes	Yes
Gorris, 2020	≥2000	Non-affluent	Normal	41.6	Questionnaire	Unclassified	Unclassified	OR	Yes	BDEFG	1.41 (0.65-3.08)	No	Yes
Lu, 2020	≥2000	Affluent	Normal	43.2	Health records	Unclassified	Unclassified	OR	Yes	ABCDEF	0.92 (0.71-1.18)	No	No
Mitselou, 2020	≥2000	Affluent	Normal	48.9	Health records	Unclassified Elective Emergency	Unclassified	HR HR HR	Yes Yes Yes	ABDEF ABDEF ABDEF	1.14 (1.10-1.18) 1.10 (1.05-1.15) 1.13 (1.08-1.19)	No	No
Richard, 2020	≥2000	Affluent	Normal	48.8	Health records	Unclassified Elective Emergency CD without PROM	Unclassified	RR RR RR RR	Yes Yes Yes Yes	ABCDEFG ABCDEFG ABCDEFG ABCDEFG	1.03 (0.96-1.10) 1.17 (1.01-1.35) 1.05 (0.92-1.19) 1.13 (0.97-1.32)**	No	Yes
Ali, 2021	≥2000	Affluent	Asthmatic mothers	46.4	Health records	Unclassified Elective Emergency	Unclassified	OR	No Yes Yes	None AE ACE	1.27 (1.10-1.46)† 2.46 (1.46-5.30) 0.97 (0.42-2.27)	No	Yes
Gabryszewski, 2021	≥2000	Affluent	Normal	49	Health records	Unclassified	Unclassified	HR	Yes	None	1.27 (1.10-1.46)†	No	No
Hu, 2021	≥2000	Non-affluent	Normal	47.8	Questionnaire	Unclassified	Unclassified	OR	Yes	CDFG	1.00 (0.91-1.11)	No	No
Meza-Lopez, 2021	≥2000	Non-affluent	Normal	52.4	Questionnaire	Unclassified	Unclassified	OR	No	None	1.39 (0.78-2.49)	No	No
Sigurdardottir, 2021	≥2000	Affluent	Normal	48	Questionnaire	Unclassified	Unclassified	OR	Yes	CDEG	1.05 (0.86-1.27)	No	Yes

Table S2 continued. Characteristics of the included studies and relative estimates of measure effect.

First author, Year	Year of births	Affluence of country	Population	Female (%)	Source of delivery	Type of CD	Type of VD	Original effect measure	Adjusted OR (yes/no)	Confounder(s) for adjustment	OR (95% CI)	Exclusion of prematurity	Loss to follow-up >30%
Choi, 2023	≥2000	Affluent	Normal	49.9	Questionnaire	Unclassified	Unclassified	OR	Yes	DEF	0.97 (0.69-1.27)	No	No
Liu, 2023	≥2000	Non-affluent	Normal	47.2	Questionnaire	Unclassified	Unclassified	OR	No	None	1.27 (1.01-1.58)	No	No
Wang, 2023	≥2000	Non-affluent	Normal		Questionnaire	Unclassified	Unclassified	OR	Yes	DE	1.30 (1.02-1.66)	No	No

Footnote: † recalculated odds ratio; * abnormal VD vs. spontaneous VD; ** non-microbiota-exposed delivery vs. microbiota-exposed delivery

Abbreviation: CD, cesarean delivery; VD, vaginal delivery; PROM, premature rupture of membranes; OR, odds ratio; RR, risk ratio; IRR, incidence rate ratio; HR, hazard ratio; CI, confidence interval; NA, not available; A, maternal age; B, prematurity; C, birth order; D, parental allergy; E, smoking during pregnancy; F, socioeconomic factors; G, duration of breastfeeding.

Table S3. Newcastle-Ottawa assessment for Cohort studies.

Reference	(1) Representative exposed cohort	(2) Selection of the non-exposed cohort	(3) Ascertainment of exposure	(4) Demonstration that outcome of interest was not present at start of study	(5) Comparability of cohorts on the basis of the design or analysis	(6) Assessment of the outcome	(7) Was follow-up long enough for outcomes to occur	(8) Adequacy of follow up of cohorts	Total
Nafstad 2000	1	1	1	1	1	0	0	0	5
Montgomery 2000	1	1	1	1	1	0	1	0	6
Xu 2001	0	0	1	1	2	0	1	0	5
McKeever 2002	1	1	1	1	0	1	0	1	6
Bager 2003	1	1	1	0	1	0	1	1	6
Negele 2004	1	1	1	1	2	0	0	1	7
Renz-Polster 2005	1	1	1	1	2	0	0	1	7
Salam 2006	1	1	0	0	2	0	1	1	6
Pistiner 2008	1	1	1	1	1	0	1	1	7
Pyrhonen 2013	1	1	1	1	2	0	0	1	7
Grabenhenrich 2015	1	1	1	1	2	1	1	1	9
Lee 2017	1	1	1	1	1	1	0	0	6
Loo 2017	1	1	1	1	2	1	0	1	8
Gerlich 2018	1	1	0	0	2	0	1	0	5
Lin 2019	1	1	1	1	0	1	0	1	6
Lu 2020	1	1	1	1	2	1	0	1	8
Mitselou 2020	1	1	1	1	2	1	0	1	8
Richards 2020	1	1	1	1	2	1	1	0	8
Ali 2021	0	1	1	0	1	1	1	0	5
Gabryszewski 2021	1	1	1	1	1	0	0	1	6
Sigurdardottir 2021	1	1	1	1	2	1	1	0	8

Table S4. Newcastle-Ottawa assessment for Case-control studies.

Reference	(1) Representative exposed cohort	(2) Selection of the non-exposed cohort	(3) Ascertainment of exposure	(4) Demonstration that outcome of interest was not present at start of study	(5) Comparability of cohorts on the basis of the design or analysis	(6) Assessment of the outcome	(7) Was follow-up long enough for outcomes to occur	(8) Adequacy of follow up of cohorts	Total
Liu 2023	1	1	0	1	0	0	1	0	4
Wang 2023	0	1	1	0	0	1	1	0	4

Table S5. Newcastle-Ottawa assessment for Cross-sectional studies.

Reference	(1) Representative exposed cohort	(2) Selection of the non-exposed cohort	(3) Ascertainment of exposure	(4) Comparability of cohorts on the basis of the design or analysis	(5) Assessment of the outcome	Total
Mallen 2008	0	0	1	1	0	2
Park 2010	0	0	1	2	1	4
Penaranda 2012	1	1	1	1	0	4
Li 2015	1	1	1	1	0	4
Brandao 2016	1	1	1	2	0	5
Cuppari 2016	1	1	1	0	1	4
Chu 2017	1	1	1	2	0	5
Krzych-Falta 2018	1	1	0	0	1	3
Han 2019	1	1	0	2	1	5
Yu 2019	1	1	0	1	0	3
Gorris 2020	0	0	1	2	0	3
Hu 2021	1	1	0	1	0	3
Meza-Lopez 2021	1	1	0	1	0	3
Choi 2023	1	1	0	1	1	4