Perinatal Risk Factors in Relation to Asthma and Allergic Rhinitis in Children and Adolescents

Se Hwan Hwang, M.D., Ph.D.,[1] Hyesoo Shin, M.D.,[1] Gulnaz Stybayeva, Ph.D.,[2] Do Hyun Kim, M.D., Ph.D.,[3*]

[1]*Department of Otolaryngology-Head and Neck Surgery, Bucheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea.*

[2]*Department of Physiology and Biomedical Engineering, Mayo Clinic, Rochester, MN, USA*

[3]*Department of Otolaryngology-Head and Neck Surgery, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea.*

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ORCID: Se Hwan Hwang, 0000-0002-2838-7820; Hyesoo Shin, 0009-0000-7636-0094; Gulnaz Stybayeva, 0000-0002-1453-245X; Do Hyun Kim, 0000-0002-9248-5572

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***Corresponding author:** Do Hyun Kim, M.D., Ph.D.

Department of Otolaryngology-Head and Neck Surgery, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea.

Address: Banpo-daero 222, Seocho-gu, Seoul 06591, Republic of Korea.

E-mail: dohyuni9292@naver.com, Tel: +82-2-2258-6112, Fax: +82-2-535-1354

Abstract

Objectives: To evaluate the associations between birth-related exposures and postnasal factors and risk for allergic rhinitis and asthma in children and adolescents.

Methods: We conducted a comprehensive search of five literature databases up until May 2023. To estimate the associations between birth-related exposures (birth weight, mode of delivery, prematurity, sex, maternal age, and parental history of allergy) and postnatal factors (birth order, number of siblings, exclusive, and duration of breastfeeding) and allergic disease, we calculated pooled odds ratios with 95% confidence intervals. In addition, we performed subgroup analyses according to allergic disease, birth order, number of siblings, and parental history of allergy. Methodological quality of the included studies was assessed using the Newcastle-Ottawa scale.

Results: This meta-analysis included 31 studies with 218,899 patients. Among the birth-related exposures, low birth weight, maternal age, and prematurity (<37 weeks) showed no significant associations with risk for asthma or allergic rhinitis in childhood or adolescence. On the other hand, male sex, family history of allergy, and cesarean section were related to higher risk for asthma or allergic rhinitis. Among postnatal factors, exclusive breastfeeding, long duration (>6 months) of breastfeeding, birth order second or later, and presence of sibling(s) showed preventive effects against allergic disease in offspring.

Conclusion: The risks for allergic rhinitis and asthma were higher in male patients delivered by cesarean section and with a family history of allergy. By contrast, exclusive and long duration (>6 months) breastfeeding and the presence of sibling(s) reduced the risk of developing respiratory allergic disease.

Keywords: Adolescent; Asthma; Child; Rhinitis, Allergic; Risk factors

HIGHLIGHTS

- Male sex, family history of allergy, and cesarean section were related to higher risk for asthma or allergic rhinitis.
- Exclusive breastfeeding, long duration (>6 months) of breastfeeding showed preventive effects against allergic disease in offspring.
- Birth order second or later, and presence of sibling(s) reduced the risk of developing respiratory allergic disease.

Introduction

There is a common association between asthma and rhinitis involving a predisposition to the development of hypersensitivity reactions to environmental allergens, particularly those present in the air [1]. The increasing prevalence rates of asthma and allergic rhinitis over the past few decades have been well documented [2]. These increases cannot be solely attributed to genetic factors, as environmental changes also significantly contribute to the development of such conditions [3]. There is evidence that exposure during the early stages of life has a significant impact, suggesting that the developing immune system may be more susceptible to improper "programming" during this period [4]. In addition, an atopic phenotype may be programmed *in utero* [5]. The immune system initiates a response to ubiquitous environmental allergens early in development, and there is a possibility of sensitization to allergens even during fetal stages [6]. Therefore, allergen-specific responses of the human immune system may exhibit certain biases from birth and increase with age. Accordingly, assessing and managing pre- and postnatal risk factors with respect to the incidences of asthma and allergic rhinitis in children and adolescents would play an important role in reducing the global health burden of airway disease. Although various studies have been conducted on this topic, as far as we know, no meta-analysis on perinatal risk factors has been reported. Additionally, several conflicting opinions have been reported regarding the effects of several birth-related exposures and postnatal factors on asthma and rhinitis [4,7-36]. Because medical prevention can be more effective than treatment, it is necessary to secure objective and high-level evidence by integrating and analyzing this subject through meta-analysis. It is also important to determine how closely associated each perinatal risk factor is to asthma and rhinitis. Therefore, in this meta-analysis, we investigated the risks for allergic rhinitis and asthma according to a number of birth-related and postnatal factors.

Materials and methods

Study protocol and registration

The necessity for Institutional Review Board (IRB) approval is not mandated by our institution in the case of a systematic review and meta-analysis exclusively reliant on published literature. This systematic review and meta-analysis was prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [37]. This study protocol was prospectively registered in the Open Science Framework (https://osf.io/k7fgy/).

Literature search

Reports were retrieved by searching the PubMed, Scopus, Embase, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) databases until February 2023. The key search Medical Subject Headings (MeSH) terms were as follows: “allergic rhinitis,” “hay fever,” “allergic rhinoconjunctivitis,” “seasonal allergic rhinitis,” “asthma,” “allergic diseases,” “pregnant women,” “pregnant,” “cesarean section,” “c-section,” “delivery mode,” “abdominal deliveries,” “post cesarean section,” “adolescent,” “child,” “breast feeding,” and “risk factors.” Detailed keywords and search methods retrieved from the database are listed in Supplementary Table 1. Two authors independently reviewed and selected candidate studies based on reviewing the title, abstract, and main text. If the two reviewers differed in their decision whether to include a study, it was decided through discussion with a third reviewer.

Selection criteria

The analysis included cross-sectional, cohort, and case–control studies assessing the associations between birth-related exposures (birth weight, mode of delivery, prematurity, sex, maternal age, and parental history of allergy) and postnasal factors (birth order, number of siblings, and exclusiveness and duration of breastfeeding) and risks for allergic rhinitis and asthma in offspring (children and adolescents). In the literature, if allergic rhinitis or asthma

was not specified, it was collectively referred to as 'allergic diseases'. All study designs except case reports and review articles were included. These studies should have relevant data prediction, including risk ratio (odds ratio [OR]) and 95% confidence interval (CI). All studies were performed in human subjects. Articles with insufficient data for statistical analysis were excluded from the study. The selection strategy is summarized in Figure 1.

Data organization and quality assessment

Data were extracted from selected studies and items were organized in a standardized format [38]. We examined the following items: number of patients, sex, nationality, the presence of allergic rhinitis or asthma, and the OR and corresponding 95% CI to evaluate the relations of the risk factors with prevalence of allergic disease [4,7-36,39]. The risk of bias of the studies included in the analysis was assessed using the Newcastle-Ottawa scale.

Statistical analyses

R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria) was used for R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analysis. OR was used as the effect index. The correlation strengths of birth-related exposures and postnasal factors with respiratory allergic disease in offspring were determined by combining OR and 95% CI. The I^2 test was used to assess heterogeneity. If both multivariate and univariate analyses were used to evaluate the risk factors, the OR and relevant 95% CI derived from multivariate analysis were used. The I^2 test accounts for the rate of variability across studies due to heterogeneity with values ranging from 0 to 100 where higher values correspond to increased heterogeneity. In cases where a notable degree of heterogeneity was observed between the outcomes ($I^2 > 50$), a meta-analysis was conducted using a random-effects model. On the other hand, for outcomes without significant heterogeneity ($I^2 < 50$), a fixed-effects model was used for the analysis. All *p*-values are reported as two-tailed values. Furthermore, sensitivity analyses were performed to assess the influence of individual studies

on the overall findings of the meta-analysis. Potential publication bias for each item was identified using a combination of funnel plot and Egger's test. When publication bias was suspected, the funnel plot asymmetry was corrected and confirmed by adding Duval and Tweedie's trim-and-fill method.

Results

In total, 218,899 patients from 31 studies were included in the analysis. Study characteristics and bias assessment are shown in Table 1 and Supplementary Table 2.

Association of birth related exposures with the risk of allergic rhinitis and asthma

Low birth weight (OR = 0.9644 [0.8004; 1.1622]; I^2 = 49.0%), maternal age > 35 years (0.8827 [0.7052; 1.1049]; I^2 = 61.4%), and prematurity (<37 weeks) (OR = 1.0189 [0.9156; 1.1338]; I^2 = 14.9%) had no significant association with the risks for asthma or allergic rhinitis in childhood or adolescence. By contrast, male sex (OR = 1.4985 [1.3961; 1.6084]; I^2 = 56.0%), family history of allergy (OR = 2.3300 [1.9690; 2.7571]; I^2 = 92.2%), and cesarean section (OR = 1.2252 [1.1543; 1.3004]; I^2 = 50.5%) were related to higher risks for asthma or allergic rhinitis (Supplementary Figure 1).

Begg's funnel plot and Egger's test for prematurity (p = 0.563), male sex (p = 0.8109), and family history of allergy (p = 0.0815) suggested that there was no potential publication bias in these studies. However, those tests for cesarean section (p = 0.004629) indicated potential bias in these studies. Nevertheless, the trim-and-fill test revealed a lack of statistical significance in comparisons of observed and adjusted values (1.2252, $p < 0.0001$ vs. 1.1626, $p < 0.0001$). Therefore, we concluded that there was no publication bias in the items included in the analysis. Begg's funnel plot results are presented in Supplementary Figure 2. Analysis of publication bias could not be performed on low birth weight and maternal age > 35 years due to the small number

of included studies (<10).

In subgroup analysis regarding disease type (allergic rhinitis vs. asthma), birth-related exposures (birth weight: allergic rhinitis = 0.8065 [0.6353; 1.0237] vs. asthma = 1.2355 [0.9069; 1.6831], $p = 0.4538$; c-section: allergic rhinitis = 1.2216 [1.1159; 1.3374] vs. asthma = 1.2270 [1.0991; 1.3698], $p = 0.9516$; prematurity: allergic rhinitis = 1.0109 [0.9056; 1.1283] vs. asthma = 1.1418 [0.7096; 1.8372], $p = 0.7941$; sex: allergic rhinitis = 1.5331 [1.4317; 1.6417] vs. asthma = 1.5590 [1.4244; 1.7064], $p = 0.3259$; maternal age: allergic rhinitis = 0.9273 [0.7139; 1.2044] vs. asthma = 0.7289 [0.3877; 1.3707], $p = 0.4901$; parental history of allergy: allergic rhinitis = 2.5807 [2.0509; 3.2474] vs. asthma = 1.9223 [1.2784; 2.8904], $p = 0.2995$) were found to have similar causative or preventive associations with allergic rhinitis and asthma (Supplementary Figure 1).

In subgroup analysis of family history, the risk for allergic disease was higher for maternal than paternal history of allergy (OR = 2.5191 [2.0369; 3.1155] vs. OR = 1.6880 [1.2735; 2.2375], respectively, $p = 0.0262$). By contrast, there were no significant differences in risk for allergic disease between single-parental history of allergy (OR = 2.1035 [1.8149; 2.4380]) and biparental history of allergy (OR = 2.0901 [1.8113; 2.4119], $p = 0.9516$) (Supplementary Figure 1).

Association between postnatal factors and risks for allergic rhinitis and asthma

Exclusive breastfeeding (OR = 0.7573 [0.6564; 0.8738]; $I^2 = 73.7\%$) and long duration (>6 months) of breastfeeding (OR = 0.8584 [0.7907; 0.9319]; $I^2 = 67.3\%$), birth order second or later (0.7925 [0.7526; 0.8344]; $I^2 = 66.3\%$), and presence of sibling(s) (0.7836 [0.7300; 0.8412]; $I^2 = 55.9\%$) were negatively associated with offspring allergic disease (Supplementary Figure 3).

Begg's funnel plot and Egger's test for exclusive breastfeeding ($p = 0.07949$), long duration

(>6 months) of breastfeeding ($p = 0.9796$), and presence of sibling(s) ($p = 0.3667$) showed no publication bias in the studies. However, Egger's test ($p = 0.004675$) and Begg's funnel plot analyses of birth order second or later ($p = 0.03244$) suggested that there may have been publication bias in the included studies.

In subgroup analysis regarding disease type (allergic rhinitis vs. asthma), postnasal factors (exclusive breastfeeding (AR = 0.7471 [0.6317; 0.8836] vs. asthma = 0.7724 [0.5300; 1.1255], $p = 0.8746$) and long duration (>6 months) of breastfeeding (AR = 0.8306 [0.7600; 0.9076] vs. asthma a = 0.9374 [0.8047; 1.0920], $p = 0.1793$) were found to have similar causative or preventive effects on allergic rhinitis and asthma. By contrast, birth order second or later (AR = 0.7369 [0.6796; 0.7989] vs. asthma = 0.8278 [0.6863; 0.9986], $p = 0.0048$) and presence of sibling(s) (AR = 0.7477 [0.6910; 0.8090] vs. asthma = 0.8618 [0.6735; 1.1026], $p = 0.0218$) showed greater preventive effects against allergic rhinitis than asthma (Supplementary Figure 3).

With regard to birth order and number of siblings, there were no significant differences in risk for allergic disease between birth order second and 3rd or later (0.8185 [0.7670; 0.8733] vs. 0.7535 [0.6827; 0.8316], respectively, $p = 0.1701$). In addition, subjects with a single sibling had a reduced risk for allergic disease, which was similar to that of subjects with two or more siblings (0.8341 [0.7515; 0.9257] vs. 0.7659 [0.7020; 0.8357], respectively, $p = 0.2187$) (Supplementary Figure 3).

Sensitivity analyses

Sensitivity analyses were performed to assess differences in congruency estimates. All of the analyzed results were consistent with the above results.

Discussion

Through meta-analysis, we were able to perform odd ratio analysis by statistically integrating a larger number of patients, thus providing more objective and high-level evidence. Also, we can check how large the odd ratio is for each factor. Among birth-related exposures, family history of allergy showed the highest odds ratio for asthma or allergic rhinitis, followed by male sex and cesarean section. Among family history of allergies, maternal history of allergy was especially important. Among postnatal factors, exclusive breastfeeding was most negatively associated, followed by presence of sibling(s), birth order second or later, and long duration (>6 months) of breastfeeding. Presence of sibling(s) and birth order were particularly more negatively associated with allergic rhinitis. There were reports that allergic rhinitis and asthma were related to low birth weight, high maternal age and prematurity [14,17,21]. However, as shown in the results of this analysis, low birth weight had a low relation with allergic rhinitis, and asthma had a high relationship. When this was integrated overall, it was possible to conclude that there was no relationship. There were mixed reports in the case of elderly mothers and prematurity, but through this analysis, it was concluded that the relationship with allergic disease was not clear.

In subgroup analysis, birth order second or later and presence of sibling(s) showed greater preventive effects against allergic rhinitis than asthma. However, all birth-related exposures (birth weight, birth by cesarean section, prematurity, sex, maternal age, parental history of allergy) and other postnasal factors (exclusive or long duration [>6 months] of breastfeeding) were found to have similar causative or preventive effects on allergic rhinitis and asthma.

Allergic rhinitis and asthma were suggested to be influenced by both genetic and environmental factors [40]. Allergic rhinitis and asthma are prevalent allergic diseases with similar etiologies, which frequently occur concomitantly in the same family [41]. Genetic susceptibility to allergic

diseases has been reported, which explains why a family history of the disease can be an important risk factor for the occurrence of allergy in children [42]. Recently, however, the different entities of these two diseases have been discussed more actively, away from the concept of “one-airway-one-disease" [43]. In this study, we confirmed that interactions with siblings were more closely related to allergic rhinitis than asthma. Children who experience familial infections or have exposure to gut commensals are prone to encountering microorganisms for extended periods and potentially in greater quantities, thereby facilitating appropriate immune conditioning. In addition, heightened levels of household crowding have been associated with elevated antigen exposure, potentially contributing to the observed protective influence of crowding [4,35]. It was inferred that continuous exposure to allergens contributes more to the occurrence of allergic rhinitis than asthma, and additional research on this issue is required.

In this study, the risks for allergic rhinitis and asthma were higher in boys during childhood. However, there have been reports that the proportion of females with these allergic diseases increases with age [44]. This may be due to genetic susceptibility and environmental exposure, but it has also been suggested that the influence of hormones, such as estrogen and progesterone, may make women more vulnerable to allergic diseases [44].

A multidisciplinary review yielded identical findings regarding the relations between breastfeeding and the subsequent development of allergic diseases [45]. The plausibility of the allergy-preventive impact of breastfeeding has been investigated using various approaches, including analyzing traces of food proteins ingested by lactating mothers that promote tolerance to these foods, as well as eliminating microbes that trigger inflammatory responses [46].

The effects of cesarean delivery have been compared to those of vaginal delivery, considering factors such as the absence of vaginal compression on the chest of the neonate and reduced

stress during cesarean delivery. The stress and labor during vaginal delivery stimulate the release of catecholamines, cortisol, and pulmonary surfactant, which contribute significantly to normal postnatal lung development [47]. Furthermore, it has been postulated that cesarean section, by not exposing the neonate to maternal vaginal microflora, could potentially impede maturation of the immune system, possibly impacting the balance between Th1 and Th2 lymphocytes in early life [48]. Caesarean section rates, both for medical necessity and nonmedical reasons, continue to increase worldwide [49]. In addition, caesarean section could affect lactogenesis, which makes breastfeeding less likely or may delay the onset of breastfeeding [50]. Therefore, as caesarean section for nonmedical reasons and duration and extent of breastfeeding could affect the development of asthma and allergic rhinitis in children, these points should be included as important components of maternal education.

This study had several limitations. Primarily, the majority of investigations that have examined the associations between pre- or postnatal factors and respiratory allergic status in children and adolescents have relied on retrospective or cross-sectional designs, lacking the inclusion of explicit clinical criteria for maternal or medical decision-making regarding caesarean section, preterm birth, maternal age, breastfeeding, and other relevant factors. Therefore, conclusions regarding cause-and-effect relations are limited. Additional clinical studies that assess the effects of pre- or postnatal factors on respiratory allergic state are needed to overcome this issue. Second, it is necessary to consider that variation in publication domains, duration of study, and approaches employed to address confounding variables may contribute to potential disparities between the reported results and the true underlying status. Furthermore, our analysis encompassed certain enrolled investigations that relied on self-reported diagnoses of allergic rhinitis or asthma, potentially leading to disparity from actual prevalence and consequently diminishing the generalizability of our findings. It is essential to acknowledge that any deviations or inaccuracies present within individual studies could have influenced our overall

analysis. Nevertheless, given the robustness of the association between pre- or postnatal factors and respiratory allergic state development, our findings suggest that future randomized trials that explore the potential roles of these factors on respiratory allergic state are warranted.

In summary, allergic rhinitis and asthma showed increased incidence rates among individuals delivered by cesarean section, identified as male at birth, and those with a familial background of allergies. On the other hand, exclusive and long-duration (>6 months) breastfeeding and the presence of siblings were potential protective factors against the development of allergic rhinitis and asthma in children and adolescents.

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Table 1. Characteristics of Included Studies.

Study (year)	Study design	Sample Size	Age (year; mean, range, or standard deviation)	Time line (year; mean, range, or standard deviation)	Sex (Male/Female)	Nation	Allergic disease diagnosis	Comparison
Nafstad 2000	Cohort	2531	4	4	1298/1233	Sweden	Physician based	Allergic disease (AR vs asthma), delivary mode (C section vs vaginal delivery), any family member allergy history, single parent allergy history (mother vs father), parent allergy history (single vs both history), gender (male vs female), maternal age at birth (older than 35 vs less than 35), birth order (second vs third or later), number of sibiling (2 vs 3 or more)
Montgomery 2001	Cohort	5519	26	27	NA	UK	Survey based	Any family member allergy history, parent allergy history (single vs both history), birth order (Second vs third or later), number of sibiling (2 vs 3 or more), exclusive breastfeeding, duration of breastfeeding more than 6 month, delivary mode (C section vs vaginal delivery)
Xu 2001	Cohort	11635	31	31	NA	Finland	Physician based	Delivary mode (C section vs vaginal delivery)
McKeever 2002	Cohort	29238	2.9 (0-11)	2	NA	UK	Physician based	Allergic disease (AR vs asthma), delivary mode (C section vs vaginal delivery)
Bager 2003	Cohort	9722	25 (20-28)	25	0/9722	Denmark	Physician based	Allergic disease (AR vs asthma), delivary mode (C section vs vaginal delivery), Maternal age at birth older than 35, premature (<37 weeks), number of sibiling (2 vs 3 or more)
Negele 2004	Cohort	2500	2	2	1205/1295	Germany	Physician based	Allergic disease (AR vs asthma), delivary mode (C section vs vaginal delivery)

Polster 2005	Cohort	7872	3-10	3-10	4001/3871	USA	Physician based	Gender (male vs female), allergic disease (AR vs asthma), delivary mode (C section vs vaginal delivery), birth order (second vs third or later), number of sibiling (2 vs 3 or more)
Salam 2006	Cohort	2653	10.5±2.2	10.5	NA	USA	Survey based	Delivary mode (C section vs vaginal delivery), allergic disease (AR vs asthma),
Miyake 2007	Cross-sectional	24077	6-15	6-15	12161/11916	Japan	Survey based	Allergic disease (AR vs asthma), exclusive breastfeeding, duration of breastfeeding more than 6 months
Westergaard 2007	Cross-sectional	31145	15-43	15-43	All women	Denmark	Physician based	Birth order (Second vs third or later), number of sibiling (2 vs 3 or more)
Ehlayel 2008	Cross-sectional	1278	0-5	0-5	632/646	UK	Physician based	Allergic disease (AR vs asthma), exclusive breastfeeding
Mallen 2008	Cross-sectional	567	18-25	18-25	NA	UK	Physician based	Allergic disease (AR vs asthma), delivary mode (C section vs vaginal delivery), Premature (<37 weeks)
Pistiner 2008	Cohort	432	7.4 (6.5-10.1)	9	237/195	USA	Physician based	Allergic disease (AR vs asthma), delivary mode (C section vs vaginal delivery)
Park 2010	Cross-sectional	279	4.6±3.8	4.6±3.8	180/99	Korea	Physician based	Allergic disease (AR vs asthma), delivary mode (C section vs vaginal delivery)
Valdivia 2010	Case-control	366	4.02 (2-7)	2-7	172/197	Peru	Physician based	Exclusive breastfeeding, low birth weight (<2500 g), Premature (<37 weeks)
Jelding-Dannemand 2015	Cohort	335	7	7	NA	Denmark	Physician based	Allergic disease (AR vs asthma), exclusive breastfeeding
Li 2015	Cross-sectional	20803	9.19	9.19	10803/10000	China	Survey based	Exclusive breastfeeding, delivary mode (C section vs vaginal delivery), gender (male vs female), premature (<37 weeks)
Bion 2016	Cohort	2140	10-18	10	NA	UK	Survey based	Allergic disease (AR vs asthma), exclusive breastfeeding, duration of breastfeeding more than 6 months
Brandão 2016	Cross-sectional	672	6	6	336/336	Brazil	Survey based	Allergic disease (AR vs asthma), delivary mode (C section vs vaginal delivery)

Chu 2017	Cross-sectional	12639	7-10	7-10	NA	China	Survey based	Delivary mode (C section vs vaginal delivery)
Bedolla-Barajas 2018	Cross-sectional	1003	6-7	6-7	474/529	Mexico	Survey based	Allergic disease (AR vs asthma), any family member allergy history, parent allergy history (single vs both history), gender (male vs female)
Krzych-Fałta 2018	Cross-sectional	18617	NA	6-44	8606/10011	Poland	Physician based	Delivary mode (C section vs vaginal delivery), any family member allergy history
Han 2019	Cohort	1374	4-12	4-12	941/433	Korea	Physician based	Duration of breastfeeding more than 6 months, delivary mode (C section vs vaginal delivery), number of sibiling (2 vs 3 or more)
Kim 2019	Cohort	175	3	3	78/97	Korea	Survey based	Delivary mode (C section vs vaginal delivery), any family member allergy history, parent allergy history (single vs both history), low birth weight (<2500 g), Premature (<37 weeks), gender (male vs female)
Gorris 2020	Cross-sectional	189	8.2±2.7	8.2±2.7	101/88	Austria	Physician based	Allergic disease (AR vs asthma), exclusive breastfeeding, delivary mode (C section vs vaginal delivery), any family member allergy history, single parent allergy history (mother vs father), parent allergy history (single vs both history), Premature (<37 weeks), gender (male vs female)
Lu 2020	Cohort	1344	6.4	6.4	763/581	Taiwan	Physician based	Delivary mode (C section vs vaginal delivery), any family member allergy history, single parent allergy history (mother vs father), parent allergy history (single vs both history), maternal age at birth older than 35, premature (<37 weeks), birth order (second vs third or later), number of sibiling (2 vs 3 or more), gender (male vs female)
Tong 2020	Cross-sectional	5550	6-12	8.79±1.7	2993/2557	China	Physician based	Duration of breastfeeding more than 6 months, any family member allergy history, Maternal age at birth older than 35, gender (male vs female)
Hu 2021	Cohort	10464	6-12	9.2±2.2	5464/5000	China	Survey based	Allergic disease (AR vs asthma), duration of breastfeeding more than 6 months, delivary mode

								(C section vs vaginal delivery), any family member allergy history, low birth weight (<2500 g), premature (<37 weeks), gende (male vs female)
Meza-Lopez 2021	Cross-sectional	1003	6-7	6-7	477/526	Mexico	Survey based	Delivary mode (C section vs vaginal delivery)
Tong 2022	Cross-sectional	10757	6-12	8.91±1.78	5809/4948	China	Survey based	Duration of breastfeeding more than 6 months, delivary mode (C section vs vaginal delivery), any family member allergy history, Maternal age at birth older than 35, gender (male vs female)
Wang 2022	Case-control	2020	5.18±0.99	5.18±0.99	225/179	China	Survey based	Duration of breastfeeding more than 6 months, delivary mode (C section vs vaginal delivery), any family member allergy history, single parent allergy history (mother vs father), parent allergy history (single vs both history), low birth weight (<2500 g), premature (<37 weeks)

NA; Nor available, AR; allergic rhinitis, C section; Cesarean section

Figure Legends

Figure 1. Flow diagram of the article-selection process.

Supplementary Table 1. Search Strategies.

Supplementary Table 2. Risk of Bias Assessment.

Supplementary Figure 1. Odd ratios of birth-related exposures with risks for allergic rhinitis and asthma. (A) Low birth weight. (B) Maternal age > 35 years. (C) Prematurity (<37 weeks). (D) Male sex. (E) Family history of allergy. (F) Birth by cesarean section.

Supplementary Figure 2. Begg's funnel plot. (A) Prematurity. (B) Male sex. (C) Family history of allergy. (D) Birth by cesarean section. (E) Exclusive breastfeeding. (F) Long duration (>6 months) of breastfeeding. (G) Presence of sibling(s). (H) Birth order.

Supplementary Figure 3. Odds ratios of postnatal factors with risks for allergic rhinitis and asthma. (A) Exclusive breastfeeding. (B) Long duration (>6 months) of breastfeeding. (C) Birth order second or later. (D) Presence of sibling(s).

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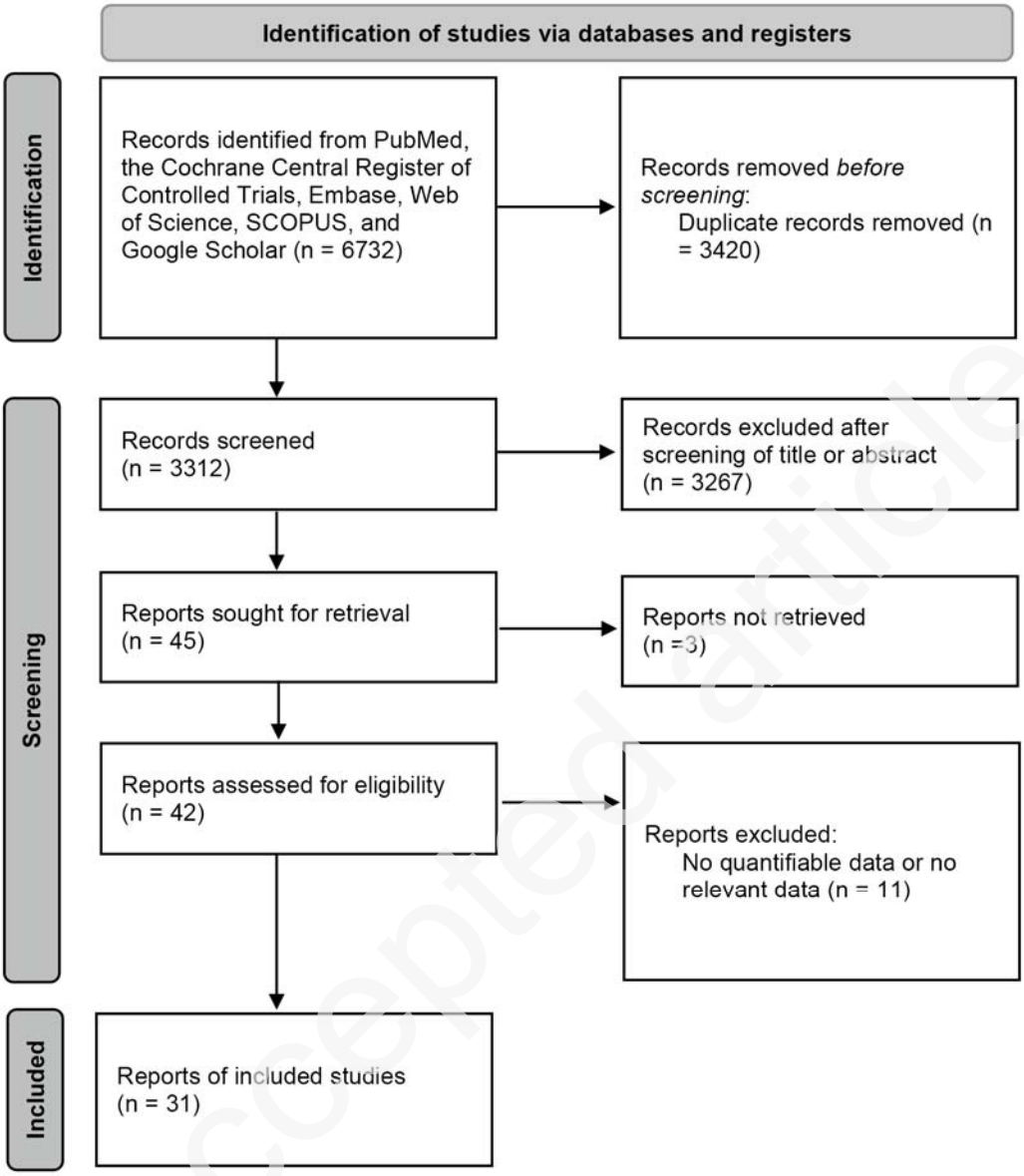
http://www.textcheck.com/certificate/BdyOwT

Figure 1.



Supplementary Table 1. Search Strategies.

Database	Search	Search terms/queries
PubMed	#1	"Child"[Mesh] OR "Child"[TW] OR "Children"[TW]
	#2	"Child, Preschool"[Mesh]
	#3	"Child, Preschoo"[TW] OR "Preschool Child"[TW] OR "Children, Preschool"[TW] OR "Preschool Childrenl"[TW]
	#4	"Adolescent"[Mesh]
	#5	"Adolescent"[TW] OR "Adolescents"[TW] OR "Adolescence"[TW] OR "Teens"[TW] OR "Teen"[TW] OR "Teenagers"[TW] OR "Teenager"[TW] OR "Youth"[TW] OR "Youths"[TW] OR "Adolescents, Female"[TW] OR "Adolescent, Female"[TW] OR "Female Adolescent"[TW] OR "Female Adolescents"[TW] OR "Adolescents, Male"[TW] OR "Adolescent, Male"[TW] OR "Male Adolescent"[TW] OR "Male Adolescents"[TW]
	#6 Combine	#1 OR #2 OR #3 OR #4 OR #5
	#7	"Asthma"[Mesh]
	#8	"Asthma"[TW] OR "Asthmas"[TW] OR "Bronchial Asthma"[TW] OR "Asthma, Bronchial"[TW]
	#9	"Rhinitis, Allergic"[Mesh]
	#10	"Rhinitis, Allergic"[TW] OR "Allergic Rhinitides"[TW] OR "Rhinitides, Allergic"[TW] OR "Allergic Rhinitis"[TW] OR "allergic rhinoconjunctivitis"[TW]
	#11	"Rhinitis, Allergic, Seasonal"[Mesh]
	#12	"Rhinitis, Allergic, Seasonal"[TW] OR "Seasonal Allergic Rhinitis"[TW] OR "Allergic Rhinitides, Seasonal"[TW] OR "Allergic Rhinitis, Seasonal"[TW] OR "Rhinitides, Seasonal Allergic"[TW] OR "Rhinitis, Seasonal Allergic"[TW] OR "Seasonal Allergic Rhinitides"[TW] OR "Pollen Allergy"[TW] OR "Allergies, Pollen"[TW] OR "Allergy, Pollen"[TW] OR "Pollen Allergies"[TW] OR "Pollinosis"[TW] OR "Pollinoses"[TW] OR "Hay Fever"[TW] OR "Fever, Hay"[TW] OR "Hayfever"[TW]
	#13 Combine	#7 OR #8 OR #9 OR #10 OR #11 OR #12
	#14	"Delivery, Obstetric"[Mesh]
	#15	"Delivery, Obstetric"[TW] OR "Deliveries, Obstetric"[TW] OR "Obstetric Deliveries"[TW] OR "Obstetric Delivery"[TW] OR "Delivery"[TW] OR "Delivery mode"[TW] OR "vaginal delivery"[TW]
	#16	"Cesarean Section"[Mesh]
	#17	"Cesarean Section"[TW] OR "Cesarean Sections"[TW] OR "Delivery, Abdominal"[TW] OR "Abdominal Deliveries"[TW] OR "Deliveries, Abdominal"[TW] OR "Caesarean Section"[TW] OR "Caesarean Sections"[TW] OR "Abdominal Delivery"[TW] OR "C-Section (OB)"[TW] OR "C Section (OB)"[TW] OR "C-Sections (OB)"[TW] OR "Postcesarean Section"[TW] OR "C-section"[TW]
	#18	"allergy history"[TW] OR "family member allergy history"[TW] OR "single parent allergy history"[TW] OR "parent allergy history"[TW]

	#19	"Maternal Age"[Mesh]
	#20	"Maternal Age"[TW] OR "Age, Maternal"[TW] OR "Ages, Maternal"[TW] OR "Maternal Ages"[TW]
	#21	"Birth Order"[Mesh]
	#22	"Birth Order"[TW] OR "Birth Orders"[TW] OR "First Birth"[TW] OR "Birth, First"[TW] OR "Births, First"[TW] OR "First Births"[TW]
	#23	"Siblings"[Mesh]
	#24	"Siblings"[TW] OR "Sibling"[TW] OR "Sisters"[TW] OR "Sister"[TW] OR "Brothers"[TW] OR "Brother"[TW] OR "number of sibling"[TW]
	#25	"Breast Feeding"[Mesh]
	#26	"Breast Feeding"[TW] OR "Breastfed"[TW] OR "Breastfeeding"[TW] OR "Breast Fed"[TW] OR "Milk Sharing"[TW] OR "Sharing, Milk"[TW] OR "Breast Feeding, Exclusive"[TW] OR "Exclusive Breast Feeding"[TW] OR "Breastfeeding, Exclusive"[TW] OR "Exclusive Breastfeeding"[TW] OR "Wet Nursing"[TW] OR "exclusive breastfeeding "[TW] OR "duration of breastfeeding"[TW]
	#27	"Premature Birth"[Mesh]
	#28	"Premature Birth"[TW] OR "Birth, Premature"[TW] OR "Births, Premature"[TW] OR "Premature Births"[TW] OR "Preterm Birth"[TW] OR "Birth, Preterm"[TW] OR "Births, Preterm"[TW] OR "Preterm Births"[TW]
	#29 Combine	#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28
	#30 Combine	#6 AND #13 AND #29

Database	Search	Search terms/queries
EMBASE	#1	"child"/exp OR "Child":ti,ab,kw,de OR "Children":ti,ab,kw,de
	#2	"preschool child"/exp
	#3	"Child, Preschoo":ti,ab,kw,de OR "Preschool Child":ti,ab,kw,de OR "Children, Preschool":ti,ab,kw,de OR "Preschool Childrenl":ti,ab,kw,de
	#4	"adolescent"/exp
	#5	"Adolescent":ti,ab,kw,de OR "Adolescents":ti,ab,kw,de OR "Adolescence":ti,ab,kw,de OR "Teens":ti,ab,kw,de OR "Teen":ti,ab,kw,de OR "Teenagers":ti,ab,kw,de OR "Teenager":ti,ab,kw,de OR "Youth":ti,ab,kw,de OR "Youths":ti,ab,kw,de OR "Adolescents, Female":ti,ab,kw,de OR "Adolescent, Female":ti,ab,kw,de OR "Female Adolescent":ti,ab,kw,de OR "Female Adolescents":ti,ab,kw,de OR "Adolescents, Male":ti,ab,kw,de OR "Adolescent, Male":ti,ab,kw,de OR "Male Adolescent":ti,ab,kw,de OR "Male Adolescents":ti,ab,kw,de
	#6 Combine	#1 OR #2 OR #3 OR #4 OR #5
	#7	"asthma"/exp
	#8	"Asthma":ti,ab,kw,de OR "Asthmas":ti,ab,kw,de OR "Bronchial Asthma":ti,ab,kw,de OR "Asthma, Bronchial":ti,ab,kw,de

	#9	"allergic rhinitis"/exp
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	#11	"pollen allergy"/exp
	#12	"Rhinitis, Allergic, Seasonal":ti,ab,kw,de OR "Seasonal Allergic Rhinitis":ti,ab,kw,de OR "Allergic Rhinitides, Seasonal":ti,ab,kw,de OR "Allergic Rhinitis, Seasonal":ti,ab,kw,de OR "Rhinitides, Seasonal Allergic":ti,ab,kw,de OR "Rhinitis, Seasonal Allergic":ti,ab,kw,de OR "Seasonal Allergic Rhinitides":ti,ab,kw,de OR "Pollen Allergy":ti,ab,kw,de OR "Allergies, Pollen":ti,ab,kw,de OR "Allergy, Pollen":ti,ab,kw,de OR "Pollen Allergies":ti,ab,kw,de OR "Pollinosis":ti,ab,kw,de OR "Pollinoses":ti,ab,kw,de OR "Hay Fever":ti,ab,kw,de OR "Fever, Hay":ti,ab,kw,de OR "Hayfever":ti,ab,kw,de
	#13 Combine	#7 OR #8 OR #9 OR #10 OR #11 OR #12
	#14	"obstetric delivery"/exp
	#15	"Delivery, Obstetric":ti,ab,kw,de OR "Deliveries, Obstetric":ti,ab,kw,de OR "Obstetric Deliveries":ti,ab,kw,de OR "Obstetric Delivery":ti,ab,kw,de OR "Delivery":ti,ab,kw,de OR "Delivery mode":ti,ab,kw,de OR "vaginal delivery":ti,ab,kw,de
	#16	"cesarean section"/exp
	#17	"Cesarean Section":ti,ab,kw,de OR "Cesarean Sections":ti,ab,kw,de OR "Delivery, Abdominal":ti,ab,kw,de OR "Abdominal Deliveries":ti,ab,kw,de OR "Deliveries, Abdominal":ti,ab,kw,de OR "Caesarean Section":ti,ab,kw,de OR "Caesarean Sections":ti,ab,kw,de OR "Abdominal Delivery":ti,ab,kw,de OR "C-Section (OB)":ti,ab,kw,de OR "C Section (OB)":ti,ab,kw,de OR "C-Sections (OB)":ti,ab,kw,de OR "Postcesarean Section":ti,ab,kw,de OR "C-section":ti,ab,kw,de
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		"Breastfeeding, Exclusive":ti,ab,kw,de OR "Exclusive Breastfeeding":ti,ab,kw,de OR "Wet Nursing":ti,ab,kw,de OR "exclusive breastfeeding ":ti,ab,kw,de OR "duration of breastfeeding":ti,ab,kw,de
	#27	"prematurity"/exp
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	#29 Combine	#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28
	#30 Combine	#6 AND #13 AND #29

Database	Search	Search terms/queries
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	#2	[mh "Child, Preschool"]
	#3	"Child, Preschoo":ti,ab,kw OR "Preschool Child":ti,ab,kw OR "Children, Preschool":ti,ab,kw OR "Preschool Childrenl":ti,ab,kw
	#4	[mh "Adolescent"]
	#5	"Adolescent":ti,ab,kw OR "Adolescents":ti,ab,kw OR "Adolescence":ti,ab,kw OR "Teens":ti,ab,kw OR "Teen":ti,ab,kw OR "Teenagers":ti,ab,kw OR "Teenager":ti,ab,kw OR "Youth":ti,ab,kw OR "Youths":ti,ab,kw OR "Adolescents, Female":ti,ab,kw OR "Adolescent, Female":ti,ab,kw OR "Female Adolescent":ti,ab,kw OR "Female Adolescents":ti,ab,kw OR "Adolescents, Male":ti,ab,kw OR "Adolescent, Male":ti,ab,kw OR "Male Adolescent":ti,ab,kw OR "Male Adolescents":ti,ab,kw
	#6 Combine	#1 OR #2 OR #3 OR #4 OR #5
	#7	[mh "Asthma"]
	#8	"Asthma":ti,ab,kw OR "Asthmas":ti,ab,kw OR "Bronchial Asthma":ti,ab,kw OR "Asthma, Bronchial":ti,ab,kw
	#9	[mh "Rhinitis, Allergic"]
	#10	"Rhinitis, Allergic":ti,ab,kw OR "Allergic Rhinitides":ti,ab,kw OR "Rhinitides, Allergic":ti,ab,kw OR "Allergic Rhinitis":ti,ab,kw OR "allergic rhinoconjunctivitis":ti,ab,kw
	#11	[mh "Rhinitis, Allergic, Seasonal"]
	#12	"Rhinitis, Allergic, Seasonal":ti,ab,kw OR "Seasonal Allergic Rhinitis":ti,ab,kw OR "Allergic Rhinitides, Seasonal":ti,ab,kw OR "Allergic Rhinitis, Seasonal":ti,ab,kw OR "Rhinitides, Seasonal Allergic":ti,ab,kw OR "Rhinitis, Seasonal Allergic":ti,ab,kw OR "Seasonal Allergic Rhinitides":ti,ab,kw OR "Pollen Allergy":ti,ab,kw OR "Allergies, Pollen":ti,ab,kw OR "Allergy, Pollen":ti,ab,kw OR "Pollen Allergies":ti,ab,kw OR "Pollinosis":ti,ab,kw OR "Pollinoses":ti,ab,kw OR "Hay Fever":ti,ab,kw OR "Fever, Hay":ti,ab,kw OR "Hayfever":ti,ab,kw

	#13 Combine	#7 OR #8 OR #9 OR #10 OR #11 OR #12
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	#16	[mh "Cesarean Section"]
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	#18	"allergy history":ti,ab,kw OR "family member allergy history":ti,ab,kw OR "single parent allergy history":ti,ab,kw OR "parent allergy history":ti,ab,kw
	#19	[mh "Maternal Age"]
	#20	"Maternal Age":ti,ab,kw OR "Age, Maternal":ti,ab,kw OR "Ages, Maternal":ti,ab,kw OR "Maternal Ages":ti,ab,kw
	#21	[mh "Birth Order"]
	#22	"Birth Order":ti,ab,kw OR "Birth Orders":ti,ab,kw OR "First Birth":ti,ab,kw OR "Birth, First":ti,ab,kw OR "Births, First":ti,ab,kw OR "First Births":ti,ab,kw
	#23	[mh "Siblings"]
	#24	"Siblings":ti,ab,kw OR "Sibling":ti,ab,kw OR "Sisters":ti,ab,kw OR "Sister":ti,ab,kw OR "Brothers":ti,ab,kw OR "Brother":ti,ab,kw OR "number of sibling":ti,ab,kw
	#25	[mh "Breast Feeding"]
	#26	"Breast Feeding":ti,ab,kw OR "Breastfed":ti,ab,kw OR "Breastfeeding":ti,ab,kw OR "Breast Fed":ti,ab,kw OR "Milk Sharing":ti,ab,kw OR "Sharing, Milk":ti,ab,kw OR "Breast Feeding, Exclusive":ti,ab,kw OR "Exclusive Breast Feeding":ti,ab,kw OR "Breastfeeding, Exclusive":ti,ab,kw OR "Exclusive Breastfeeding":ti,ab,kw OR "Wet Nursing":ti,ab,kw OR "exclusive breastfeeding ":ti,ab,kw OR "duration of breastfeeding":ti,ab,kw
	#27	[mh "Premature Birth"]
	#28	"Premature Birth":ti,ab,kw OR "Birth, Premature":ti,ab,kw OR "Births, Premature":ti,ab,kw OR "Premature Births":ti,ab,kw OR "Preterm Birth":ti,ab,kw OR "Birth, Preterm":ti,ab,kw OR "Births, Preterm":ti,ab,kw OR "Preterm Births":ti,ab,kw
	#29 Combine	#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28
	#30 Combine	#6 AND #13 AND #29

Database	Search	Search terms/queries
Web of Science	#1	TS=("Child" OR "Children" OR "Preschool Child" OR "Adolescent" OR "Teenager" OR "Teen")
	#2	TS=("Asthma" OR "Allergic Rhinitis" OR "Allergic Rhinitides" OR "allergic rhinoconjunctivitis" OR "Seasonal Allergic Rhinitis" OR "Seasonal Allergic Rhinitides" OR "Hay Fever")
	#3	TS=("Obstetric Delivery" OR "Obstetric Deliveries" OR "Delivery" OR "Cesarean Section" OR "C-section" OR "allergy history" OR "Maternal Age" OR "Maternal Ages" OR "Birth Order" OR "First Birth" OR "Siblings" OR "Sister" OR "Brother" OR "number of sibling" OR "Breast Feeding" OR "Premature Birth" OR "Preterm Birth")
	#4 Combine	#1 AND #2 AND #3

Database	Search	Search terms/queries
Google Scholar	#1	("Child" OR "Children" OR "Adolescent")
	#2	("Asthma" OR "Allergic Rhinitis" OR "allergic rhinoconjunctivitis" OR "Hay Fever")
	#3	("Cesarean Section" OR "Maternal Age" OR "Birth Order" OR "Siblings" OR "Breast Feeding" OR "Premature Birth")
	#4 Combine	("Child" OR "Children" OR "Adolescent") AND ("Asthma" OR "Allergic Rhinitis" OR "allergic rhinoconjunctivitis" OR "Hay Fever") AND ("Cesarean Section" OR "Maternal Age" OR "Birth Order" OR "Siblings" OR "Breast Feeding" OR "Premature Birth")

Supplementary Table 2. Risk of Bias Assessment.

Study (year)	Selection[a]				Comparability[b]		Exposure[c]			The Newcastle-Ottawa Scale
	1	2	3	4	5A	5B	6	7	8	
Nafstad 2000	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	**7**
Montgomery 2001	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	**7**
Xu 2001	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	**6**
McKeever 2002	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	**6**
Bager 2003	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	**7**
Negele 2004	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	**7**
Polster 2005	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	**6**
Salam 2006	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	**7**
Miyake 2007	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	**7**
Westergaard 2007	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	**6**
Ehlayel 2008	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	**7**
Mallen 2008	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	**6**
Pistiner 2008	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	**6**
Park 2010	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	**7**

Valdivia 2010	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	**7**
Jelding-Dannemand 2015	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	**6**
Li 2015	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	**7**
Bion 2016	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	**6**
Brandão 2016	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	**7**
Chu 2017	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	**6**
Bedolla-Barajas 2018	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	**7**
Krzych-Fałta 2018	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	**7**
Han 2019	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	**7**
Kim 2019	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	**7**
Gorris 2020	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	**7**
Lu 2020	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	**6**
Tong 2020	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	**7**
Hu 2021	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	**6**
Meza-Lopez 2021	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	**7**
Tong 2022	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	**7**
Wang 2022	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	**7**

A star rating system was used to indicate the quality of a study, with a maximum of nine stars. A study could be awarded a maximum of one star for each

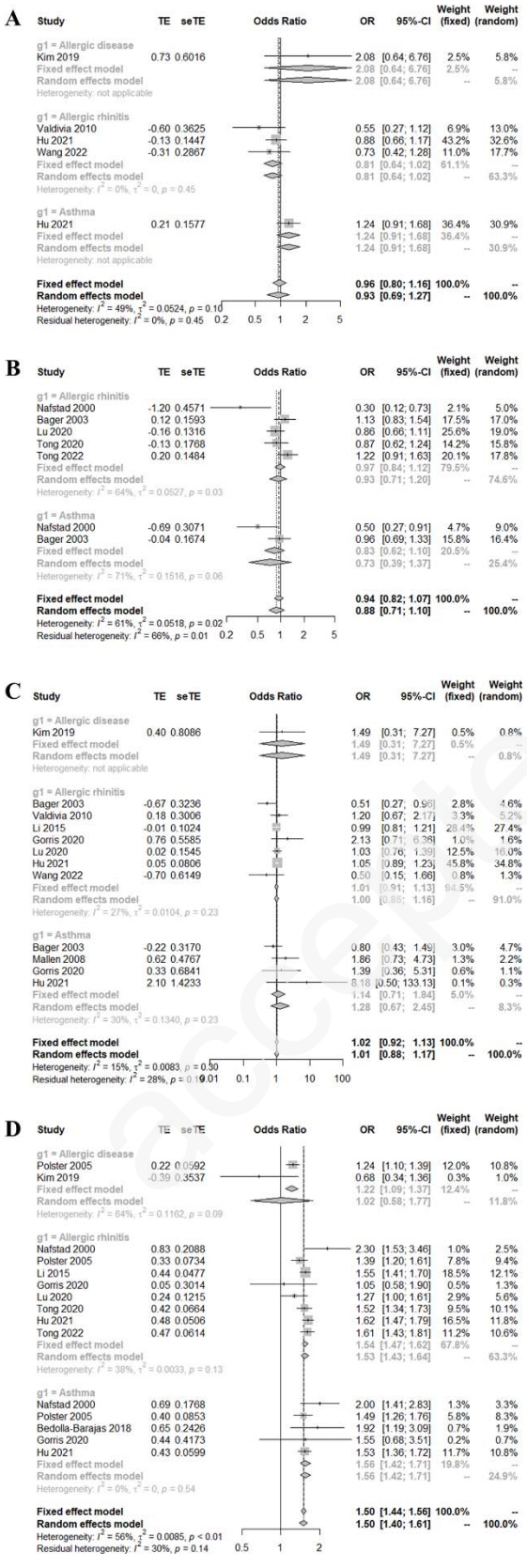
numbered item within the selection and exposure categories

a: Selection (4 items): adequacy of case definition; representativeness of the cases; selection of controls; and definition of controls.

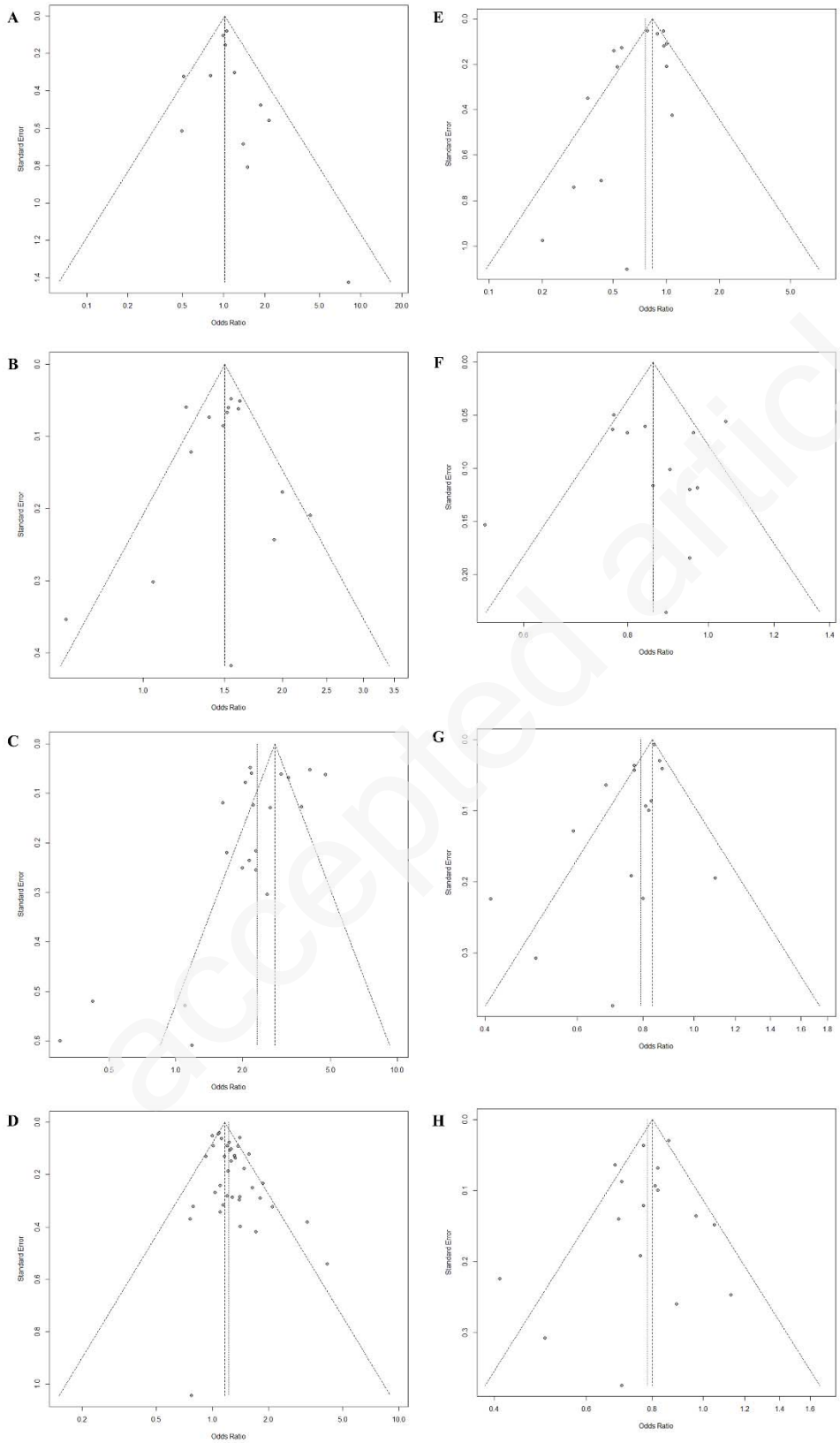
b:. Comparability (1 item): comparability of cases and controls on the basis of the design or analysis.

c:. Exposure (3 items): ascertainment of exposure; same method of ascertainment for cases and controls; and non-response rate (same rate for both groups).

Supplementary Figure 1.



Supplementary Figure 2.



Supplementary Figure 3.