Prolonged breastfeeding and protective effects against the development of allergic rhinitis: a systematic review and meta-analysis*

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Rhinology 60: 2, 82 - 91, 2022
https://doi.org/10.4193/Rhin21.274

***Received for publication:**
July 24, 2021
Accepted: September 30, 2021

Abstract

Background: There is insufficient evidence to confirm the protective effects of prolonged breastfeeding against the development of allergic rhinitis (AR).

Methodology: A systematic review and meta-analysis was performed to assess the associations between prolonged breastfeeding and AR symptoms later in life. Comparisons were conducted between breastfeeding durations <6 months and ≥6 months and between <12 months and ≥12 months. Exclusive breastfeeding and nonexclusive breastfeeding were analysed separately. Outcomes were risks of AR development later in life.

Results: Twenty-three observational studies (161,611 children, age 2-18 years, 51.50% male) were included. Two studies (9%) were with high quality. Both exclusive and nonexclusive prolonged breastfeeding (≥6 months) decreased the risk of AR. The long-term (≥12 months) nonexclusive breastfeeding lowered the likelihood of AR compared to the <12 months. The long-term exclusive breastfeeding did not show the same protective effect; however, this result was restricted to only one study.

Conclusions: Exclusive breastfeeding and nonexclusive breastfeeding for ≥6 months may have protective effects against the development of AR up to 18 years of age. The findings should be interpreted with caution given the limitation of low-quality observational studies.

Key words: allergic rhinitis, breastfeeding, prolonged breastfeeding, exclusive breastfeeding, children

Introduction

Allergic rhinitis (AR) is one of the most common atopic diseases worldwide[1]. Genetic and environmental factors during early infancy impact the development of allergic diseases[2-4]. Infant nutrition may influence the development of AR[5-7]. Breast milk consists of immunological components that support the infant's immune system[2]. Immunomodulation induced by maternal antibodies in breast milk is different from infant formula[5,8]. Additionally, the immunomodulatory effect may come from human milk oligosaccharides via the immune and microbiome maturation[9,10]. Understanding the associations of breastfeeding with early-life immune system and susceptibility to AR is essential. However, there is a lack of strong evidence supporting this matter.

The World Health Organization (WHO) recommends exclusive breastfeeding for the first six months of life[11], and breastfeeding should continue with adequate complementary foods for up to two years[11,12]. The European Academy of Allergy and Clinical Immunology (EAACI) advocates exclusive breastfeeding suggesting that infants are breastfed with no other liquids or solid foods for at least four to six months as a preferred natural preventive medicine[13]. Current studies report inconsistent findings of the protective effects of prolonged breastfeeding against the development of AR[7,12,14-17]. Recent meta-analyses are also lacking evidence[14,18,19]. This systematic review aims to assess the associations between the prolonged breastfeeding, for at least

six months, and AR development later in life.

Materials and methods

The study protocol was registered on PROSPERO (reference number CRD42020216311). This systematic review adhered to The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[20]. Systematic searches on PubMed, EMBASE, Web of Science, and CENTRAL electronic databases were conducted from interception until 08 May 2021. ClinicalTrials.gov and WHO International Clinical Trials Registry Platform were searched to collect unpublished data. Manual searches were performed for the references of the included studies and additional sources. The search strategy is displayed in Table S1 (in the Supplement).

Eligibility criteria

Clinical studies with original data that assessed the association between breastfeeding and the development of AR were included. Study design, either observational (cross-sectional, case-control, cohort) or experimental (controlled trial) was accepted. AR could be diagnosed by any means e.g., the International Study of Asthma and Allergy in Children (ISAAC) questionnaire, clinical criteria, and allergy tests. Study participants could be identified by either prospective recruitment or from electronic medical records and health databases. There was no age restriction. Studies which assessed the patients with other allergies were included if the data of AR were reported separately from other allergies. Studies which included only the patients who were breastfed less than six months were excluded. Conference abstracts and non-English publications were excluded.

Study selection process and data extraction

Two review authors (MPH and JS) separately screened the titles and the abstracts of all identified studies based on the predetermined criteria. Full-text articles of the selected titles or abstracts were reviewed following the inclusion and exclusion criteria for the final selection. Two authors (MPH and KSe) independently extracted the data from the eligible studies. If there was incomplete data, the corresponding author of that study was contacted for further supporting information. During the data selection and extraction processes, any disagreements were resolved by discussing with the fourth reviewer (KSn) until reaching a consensus. The extracted data included: first author, year, study design, country, sample size, population, type and duration of breastfeeding, diagnostic tool of AR, control group, confounders, high-risk population, and quality score of the study. Breastfeeding duration in this study was categorized in accordance with the age that the breastfeeding stopped as follows: short-term (<6 months), prolonged breastfeeding (≥6 months), or long-term breastfeeding (≥12 months).

Outcome measures

Risks of developing AR were assessed by analyzing the odds ratio (OR). There were four comparisons evaluated in this meta-analysis: 1) prolonged nonexclusive breastfeeding (≥6 months) versus short-term nonexclusive breastfeeding (<6 months), 2) long-term nonexclusive breastfeeding (≥12 months) versus less than 12 months nonexclusive breastfeeding, 3) prolonged exclusive breastfeeding (≥6 months) versus short-term exclusive breastfeeding (<6 months), and 4) long-term exclusive breastfeeding (≥12 months) versus less than 12 months exclusive breastfeeding. To retrieve data of a single study reporting outcomes with multiple durations of breastfeeding, the risk of AR and new crude OR were calculated at two cut-off timepoints (6 months and 12 months). For studies in which prevalence was unavailable, the available crude OR and adjusted OR were extracted, using the reported value of the most appropriate category. To choose the applicable OR for a single study with multiple ages of outcome, the estimates for the oldest age of outcome were selected.

Quality of included studies

Two authors (MPH and JS) independently evaluated the quality of the included studies following the Newcastle-Ottawa scale (NOS)(21). Three domains were assessed, including selection, comparability, and outcome. The total score of NOS for cohort or case-control studies was nine and for cross-sectional studies was six. The quality of each study was graded according to the NOS score as follows: low-quality (score 0 to 4), medium-quality (score 5 to 7), and high-quality (score 8 to 9). The Grading of Recommendations, Assessment and Evaluation (GRADE) approach was used to evaluate quality of evidence as follows: high, moderate, low, and very low[22]. Data from observational studies were considered low-quality evidence unless there was plausible evidence to be upgraded[23].

Data synthesis and statistical analysis

Data were pooled for meta-analysis. OR and 95% confidence interval (CI) were used for dichotomous data. Discrepancies in the risks of AR among different studies were assessed using heterogeneity (I^2) statistic. An I^2 of <40%, 40-60% and >60% represented low, moderate, and substantial heterogeneity. A fixed-effect model was used when the heterogeneity was low. A random-effects model was used if the heterogeneity was high, for a more conservative estimate of the differences. Funnel plot was used to assess publication bias. Egger's test was used to measure small-study effects for quantitative syntheses of at least ten studies. All statistical assessments were conducted using Review Manager (RevMan) version 5.4 and Stata 16.1 (StataCorp, College Station, TX, USA).

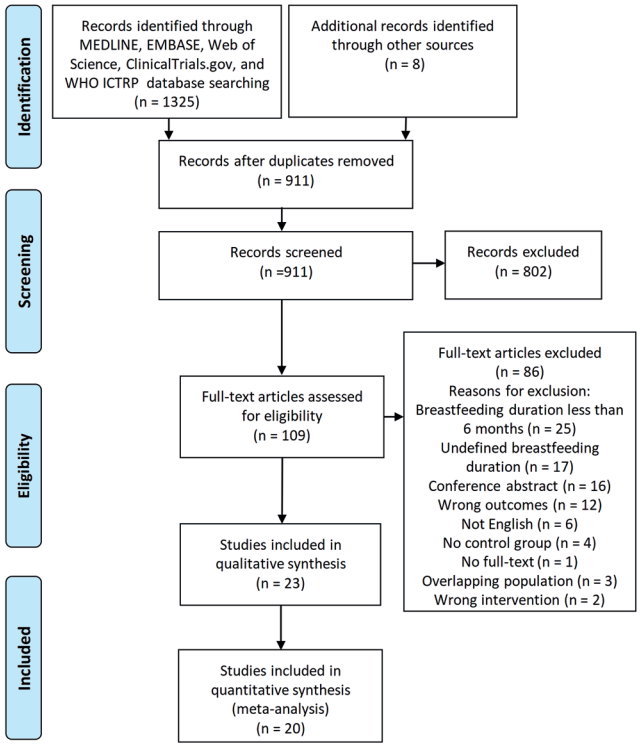

Figure 1. Flow diagram of study selection followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

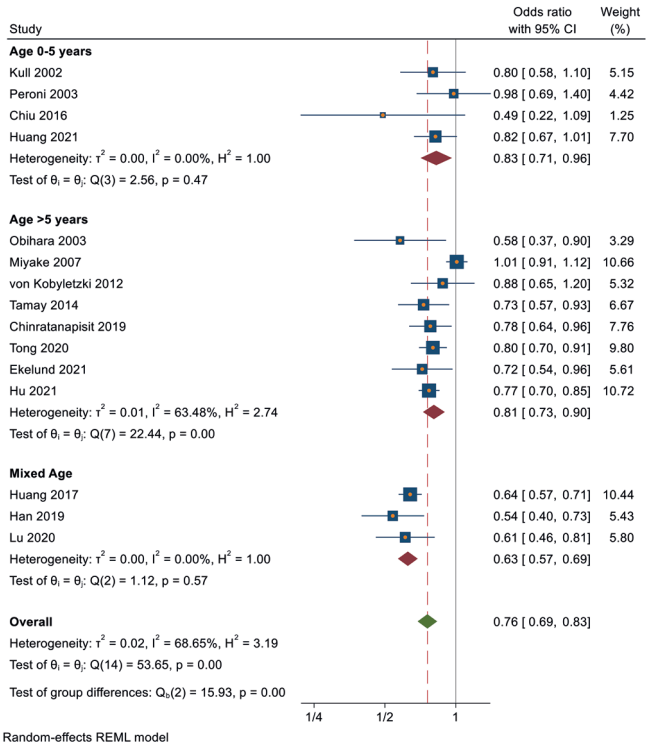

Figure 2. The risk of allergic rhinitis and subgroup analysis by the age of outcome: nonexclusive breastfeeding ≥6 months vs <6 months.

Subgroup analysis

Subgroup analyses were performed to explore the heterogeneity by the following characteristics: study design (case-control, cross-sectional, cohort, experimental), age of AR outcome (≤5 years, >5 years)[24], adjustment for confounding factors that affect the maturity of the immune system after breastfeeding (adequate adjustment, inadequate adjustment), region of the study (Asia, Europe, Africa, North America, South America, Australia), study quality (low, medium, high), AR diagnostic tool (confirmed by specific IgE tests, not confirmed by specific IgE tests), and available OR (unadjusted OR, adjusted OR). Adjustment for confounding factors was rated as adequate if a study adjusted any three of the five potential confounders (parental atopy, birth weight, smoking during pregnancy, socioeconomic status, and race/ethnicity)[16,25].

Results

Study selection

The literature search yielded 911 studies. One hundred and nine studies were selected for full-text review. Twenty-three observational studies (nine cohort studies[6,26-33] and 14 cross-sectional studies[12,34-46]) were included for qualitative synthesis, of which 20 studies[12,26-28,30-32,34-46] were included in meta-analysis. A PRISMA flowchart is illustrated in Figure 1.

Study characteristics

There were 161,611 children below 18 (age 2-18 years, 51.50% male) included in the analysis. The included studies were from three continents: Asia (n=106,693), Europe (n=54,057), and Africa (n=861). Characteristics of the included studies are presented in Table 1. Seven studies assessed children under five[26,29,31,34,37,38,46]. There were four studies that included specific populations: one study assessed rhinitis population[12], two studies assessed population with HLA-conferred susceptibility to type 1 diabetes[29,33], and one study assessed population with maternal history of asthma which was considered as a high-risk for developing AR[30]. The ISAAC questionnaire was the most common epidemiological tool for diagnosing AR used in 18 studies[6,27-29,31-42,44,46]. A skin prick test was used to define AR in three studies[12,30,38]. Atopic sensitization was investigated by specific IgE tests in nine studies[6,12,27,29-31,34,38,46]. Seventeen out of 23 studies had adequate adjustment for confounding variables[6,12,27,28,30-36,40-44,46].

Nonexclusive breastfeeding ≥6 months and its impact on the development of AR

Eighteen studies assessed the effect of prolonged nonexclusive breastfeeding (≥6 months)[6,12,26,28,29,31-36,39-44,46]. One study[33] used hazard ratio (HR) and found no association with the risk of seasonal AR. Bion et al.[6] assessed the effects of multiple breast-

Table 1. Characteristics of the included studies.

First author, Year	Country	Design	Sample size	Male/ Female	Type of BF	AR Diagnostic Tools	Age of outcome	Odds ratio (95% CI)		NOS score QOS
								≥6 vs <6 (months)	≥12 vs <12 (months)	
Kull[26], 2002	Sweden	Cohort	4,089	2,065/2,024	NBF	Question-naire	Age 2	0.80 (0.58, 1.09)	NA	7, Medium
Peroni[34], 2003	Italy	Cross sectional	1,042	734/668	NBF	ISAAC	Age 3-5	1.02 (0.75, 1.54)	NA	4, Low
Obihara[35], 2005	South Africa	Cross sectional	861	687/654	NBF	ISAAC	Age 6-14	0.58 (0.37, 0.90)*	0.50 (0.29, 0.89)*	5, Medium
Miyake[36], 2007	Japan	Cross sectional	24,077	12,016/ 12,161	NBF	ISAAC	Age 6-14	1.01 (0.91, 1.11)*	NA	
					EBF			NA	1.02 (0.88, 1.17)*	
Ehlaye[37], 2008	Qatar	Cross sectional	1,278	632/646	EBF	ISAAC	Age 0-5	0.56 (0.44, 0.71)	NA	3, Low
Kramer[27], 2009	Belarus	Cohort	13,889	7,181/6,708	EBF	ISAAC	Age 6.5	0.80 (0.47, 1.38)*	NA	8, High
Siriaksorn[38], 2011	Thailand	Cross sectional	2,301	1,289/1,012	EBF	ISAAC, SPT	Age 3-5	0.17 (0.03, 0.88)	NA	4, Low
von Kobyletzki [28], 2012	Sweden	Cohort	3,125	1,579/1,546	NBF	ISAAC	Age 6-7	0.88 (0.65, 1.20)	NA	6, Medium
Nwaru[29], 2013	Finland	Cohort	3,781	1,993/1,788	NBF	ISAAC	Age 5	NA	NA	7, Medium
Tamay[39], 2014	Turkey	Cross sectional	9,807	4,972/4,835	NBF	ISAAC	Age 6-7	0.73 (0.57, 0.93)	NA	4, Low
Jelding-Danne-mand[30], 2015	Den-mark	Cohort	389	160/229	EBF	ISAAC, SPT	Age 7	0.30 (0.07, 1.28)	NA	8, High
Bion [a][6], 2016	UK	Cohort	1,536	786/750	NBF	ISAAC	Age 18	NA	NA	8, High
Bion [b][6], 2016	UK	Cohort	957	495/462	NBF	ISAAC	Age 10	NA	NA	8, High
Chiu[31], 2016	Taiwan	Cohort	186	83/103	NBF	ISAAC	Age 4	0.49 (0.22, 1.09)	NA	7, Medium
					EBF			NA	NA	
Huang[40], 2017	China	Cross sectional	13,289	6,536/6,753	NBF	ISAAC	Age 4-6	0.80 (0.71, 0.91)*	NA	5, Medium
					EBF			0.56 (0.45, 0.69)*	NA	
Chinratanapi-sit[41], 2019	Thailand	Cross sectional	6,291	3,278/3,013	NBF	GAN/ISAAC	Age 6-7	0.78 (0.64, 0.96)	NA	4, Low
Han[12], 2019	Korea	Cross sectional	1,374	941/433	NBF	Rhinitis symptoms, SPT	Age 4-12	0.54 (0.40, 0.73)	0.49 (0.36, 0.68)	5, Medium
Li[45], 2020	China	Cross sectional	2,126	1,093/1033	EBF	ATS-DLD-78-C	Age 6-11	0.63 (0.48, 0.82)*	NA	2, Low
Lu[42], 2020	China	Cross sectional	39,782	20,633/ 19,149	NBF	ISAAC	Age 3-6	0.61 (0.46, 0.81)	NA	4, Low
Tong[43], 2020	China	Cross sectional	5,550	2,993/2,557	NBF	Question-naire	Age 6-12	0.80 (0.70, 0.91)	NA	4, Low
Ekelund[32], 2021	Norway	Cohort	6,796	3,379/3,417	NBF	ISAAC	Age 6	0.77 (0.58, 1.04)	NA	7, Medium
Hu[44], 2021	China	Cross sectional	10,464	5,464/5,000	NBF	ISAAC	Age 6-11	0.77 (0.70, 0.85)	NA	3, Low
Huang[46], 2021	Taiwan	Cross sectional	3,192	1,725/1,467	NBF	ISAAC	Age <6	0.82 (0.67, 1.01)	NA	4, Low
Hummel[33], 2021	Multi-coun-tries	Cohort	8615	4390/4225	NBF	Physicians' diagnosis	Age 8.3 (IQR: 2.8-10.2)	Hazard ratio 0.87 (0.70, 1.08)	Hazard ratio 0.91 (0.70, 1.19)	7, Medium

Table 2. Subgroup analyses of nonexclusive breastfeeding for ≥6 months vs <6 months and risk of allergic rhinitis.

Subgroup	Studies (n)	Odds ratio (95% CI)	P value
Study design			
Cohort	5	0.76 (0.66, 0.88)	0.92
Cross-sectional	10	0.76 (0.69, 0.85)	
Age of outcome			
≤5 years	4	0.83 (0.71, 0.96)	<0.01
>5 years	8	0.81 (0.73, 0.90)	
Mixed Age	3	0.63 (0.57, 0.69)	
Adjustment for confounders			
Adequate adjustment	13	0.76 (0.68, 0.84)	1.00
Inadequate adjustment	2	0.76 (0.62, 0.92)	
Region			
Africa	1	0.58 (0.37, 0.90)	0.36
Asia	9	0.74 (0.65, 0.85)	
Europe	5	0.80 (0.70, 0.91)	
Quality of study			
Medium quality	8	0.73 (0.61, 0.87)	0.49
Low quality	7	0.78 (0.73, 0.83)	
AR diagnostic tools			
Specific IgE tests	1	0.54 (0.40, 0.73)	0.02
No specific IgE tests	14	0.77 (0.71, 0.85)	
Available Odds ratio			
Adjusted	10	0.77 (0.73, 0.82)	0.57
Unadjusted	6	0.72 (0.57, 0.91)	

Abbreviations: CI, Confidence interval

Table 3. Subgroup analyses of exclusive breastfeeding for ≥6 months vs <6 months and risk of allergic rhinitis.

Subgroup	Studies (n)	Odds ratio (95% CI)	P value
Study design			
Cohort	2	0.71 (0.43, 1.18)	0.40
Cross-sectional	4	0.57 (0.49, 0.66)	
Age of outcome			
≤5 years	2	0.55 (0.43, 0.69)	0.51
>5 years	3	0.65 (0.51, 0.82)	
Mixed Age	1	0.54 (0.42, 0.69)	
Adjustment for confounders			
Adequate adjustment	3	0.57 (0.46, 0.71)	0.88
Inadequate adjustment	3	0.58 (0.49, 0.70)	
Region			
Asia	4	0.57 (0.49, 0.66)	0.40
Europe	2	0.71 (0.43, 1.18)	
Quality of study			
High quality	2	0.71 (0.43, 1.18)	0.63
Medium quality	1	0.54 (0.42, 0.69)	
Low quality	3	0.58 (0.49, 0.70)	
AR diagnostic tools			
Specific IgE tests	2	0.24 (0.08, 0.71)	0.11
No specific IgE tests	4	0.59 (0.51, 0.67)	
Available Odds ratio			
Adjusted	3	0.60 (0.46, 0.77)	0.77
Unadjusted	3	0.57 (0.48, 0.67)	

Abbreviations: CI, Confidence interval

feeding durations without reporting the raw data for recalculating the crude odds ratio. Nwaru et al.[29] used inappropriate cut-off timepoints (five and 9.5 months) of breastfeeding duration in which data were unable to be pooled in the meta-analysis. The pooled data from 15 studies (n=126,708) showed a significant association between nonexclusive breastfeeding for at least six months and its protective effects against the development of AR (OR 0.76; 95% CI 0.69, 0.83; p<0.01)[12,26-28,31,34-36,38-43,46] (Figure 2). The GRADE rating was very low quality due to substantial heterogeneity (I^2 of 69%) and high risk of bias (Table 4).

Nonexclusive breastfeeding ≥12 months and its impact on the development of AR

Four studies assessed the effect of long-term nonexclusive breastfeeding (≥12 months)[12,33,35,36]. One study[33] reported the association with the risk of developing seasonal AR using hazard model but the data was not convertible. The pooled data from three cross-sectional studies (26,312 children) showed a significant association between nonexclusive breastfeeding for at least 12 months and its protective effects against the development of AR (OR 0.63; 95% CI 0.41, 0.97; p<0.01)[12,35,36] (Figure 3). The GRADE rating was very low quality due to substantial heterogeneity (I^2 of 82%, Table 4).

Exclusive breastfeeding ≥6 months and its impact on the development of AR

Seven observational studies assessed the sole protective effects of prolonged exclusive breastfeeding (≥6 months) vs <6 months[27,30,31,37,38,40,45]. Only two studies[27,40] followed the definition of exclusive breastfeeding by the WHO. Three studies[30,31,37] modified the definition while the other two[38,45] did not mention the definition of exclusive breastfeeding (Table S2 in the Supplement). Data of exclusive breastfeeding could not be extracted separately from mixed types of breastfeeding in one study[31]. The pooled data of six studies (33,272 children) showed statistically significant protective effects against AR in children who

Footnote Table 1: * recalculated crude odds ratio.

Abbreviations: BF, Breastfeeding; NBF, Nonexclusive breastfeeding; EBF, Exclusive breastfeeding; ISAAC, International Study of Asthma and Allergies in Childhood questionnaire; GAN, The Global Asthma Network; ATS-DLD-78-C, American Thoracic Society's Division of Lung Diseases; NOS, The Newcastle-Ottawa Scale; SPT, Skin prick test; CI, Confidence interval.

Table 4. Certainty of the evidence (GRADE).

Outcomes AR ≤18 years	Studies (n)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Sample size	Effect size OR (95% CI)	Quality
Nonexclusive breastfeeding									
≥6 vs <6 months	15	Certain	Serious inconsistency	No serious indirectness	No serious imprecision	Uncertain	126,708	0.76 (0.69, 0.83)	+ - - - Very low
≥12 vs <12 months	3	Uncertain	Serious inconsistency	No serious indirectness	Serious imprecision	Uncertain	26,312	0.63 (0.41, 0.97)	+ - - - Very low
Exclusive breastfeeding									
≥6 vs <6 months	6	Uncertain	No serious inconsistency	No serious indirectness	No serious imprecision	Uncertain	33,272	0.60 (0.50, 0.85)	+ + - - Low
≥12 vs <12 months	1	Certain	No serious inconsistency	No serious indirectness	No serious imprecision	Uncertain	11,916	0.89 (0.77, 1.04)	+ - - - Very low

AR, Allergic rhinitis; OR, Odds ratio; CI, Confidence interval.

were exclusively breastfed for ≥6 months (OR 0.58; 95% CI 0.50, 0.66; p<0.01; I^2=0%)[27,30,37,38,40,45] (Figure 4). The GRADE rating was low quality (Table 4).

Exclusive breastfeeding ≥12 months and its impact on the development of AR

One study assessed the sole protective effects against AR in exclusively breastfed children for ≥12 months vs <12 months[36]. Exclusive breastfeeding for ≥12 months was not associated with a lower likelihood of developing AR (OR 0.89; 95% CI 0.77, 1.04; p=0.14). The GRADE rating was very low quality due to high risk of bias (Table 4).

Subgroup analysis

Subgroup analyses were performed to explore the plausibility of heterogeneity (Tables 2-3, Figures S1-12 in the Supplement). Subgroup analysis by AR diagnostic criteria (p=0.02, Table 2) showed significant associations of prolonged nonexclusive breastfeeding (≥6 months). The protective effects were greater when the included studies used specific IgE tests (OR 0.54; 95% CI 0.40, 0.73) than other tests (OR 0.77; 95%CI 0.71, 0.85), p=0.02. Subgroup analysis by the age of AR outcome also showed the difference (p<0.01), though the difference in three subgroups was due to the subgroup of mixed age. There was no difference between the subgroup of age 0-5 and age >5 years old for both nonexclusive (Figure 2) and exclusive breastfeeding ≥6 months (Figure 4). There were no associations demonstrated in other subgroup analyses, including by study design, adjustment for confounding factors, study quality, and available OR.

Risk of bias assessment

Quality of included studies

There were 10 (43%) studies with low quality, 11 (48%) with medium quality, and two (9%) with high quality (Table 1, Tables S3-S4 in the Supplement). The cross-sectional studies had a low score in ascertainment of exposure due to recall bias. All eight cohort studies had moderate-to-high quality.

Quality assessment of outcomes

A funnel plot and Egger's test with p=0.17 indicated no publication bias for the meta-analysis of nonexclusive breastfeeding for at least six months (Figure S18 in the Supplement).

Sensitivity analysis

When there were only observational studies with mixed populations included for qualitative synthesis and meta-analyses, there was a concern whether the study inclusion should be restricted by the study's quality and the general population, or the model selection impacted the results. A sensitivity analysis was performed by undertaking the meta-analysis twice: 1) the meta-analysis that included all studies; 2) the meta-analysis that included only those with medium and high quality; 3) the meta-analysis that included only those with general population. After removing low-quality studies, according to the NOS score, both sensitivity analyses in nonexclusive breastfeeding (OR of 0.73; 95% CI 0.61, 0.87; I^2=78%) and exclusive breastfeeding (OR 0.57; 95% CI 0.46, 0.71; I^2=18%) for at least six months did not impact the total effects (Figures S13-S14 in the Supplement). Similarly, omission of studies with high-risk populations did not change the total effects in both nonexclusive breastfeeding (OR of 0.77; 95% CI 0.71, 0.85; I^2=65%) and exclusive breastfeeding (OR of 0.58; 95% CI 0.51, 0.67; I^2=4%) (Figures S15-S16 in the Supplement). The random-effects model did not impact the total effect of exclusive breastfeeding for at least six months. However, the protective effect was not displayed up to 5 years of age (Figure S17 in the Supplement).

Discussion

Breastfeeding has many benefits for children, including protections against many diseases (e.g., infectious diseases,

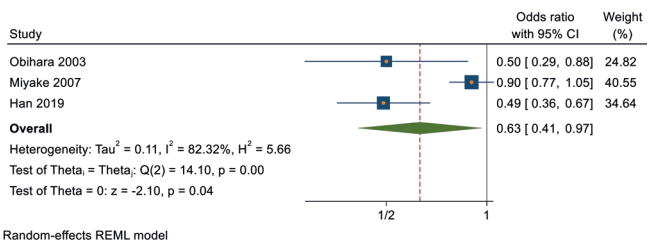

Figure 3. The risk of allergic rhinitis: nonexclusive breastfeeding ≥12 months vs <12 months.

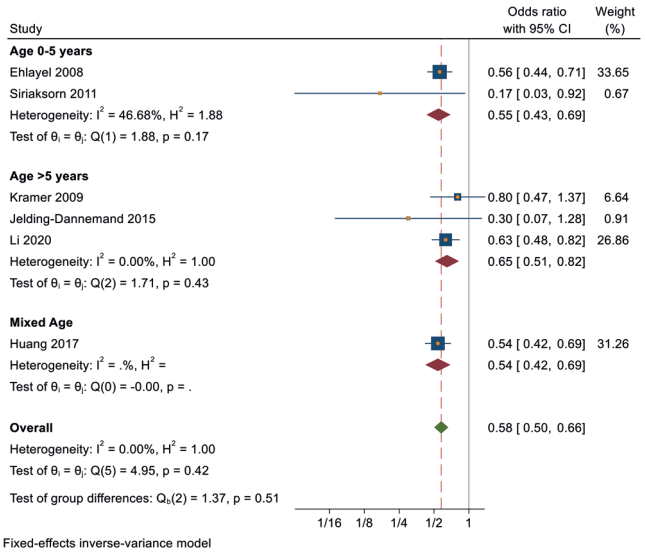

Figure 4. The risk of allergic rhinitis and subgroup analysis by the age of outcome: exclusive breastfeeding ≥6 months vs <6 months.

autoimmune diseases, and obesity[47]). It also benefits mothers, such as helping decrease the incidence of breast cancer and diabetes and helping space pregnancies in nursing women[47]. Active compounds found in breast milk can mature the adaptive immunity[31]. Interferon-gamma in breast milk stimulates the T helper 1 (Th1) inflammatory response and suppresses the Th2 allergic response[48]. Other immunological compounds such as long-chain polyunsaturated fatty acids and osteoprotegerin can promote antigen-specific tolerance, the Th1 and Th2 response, and regulate the Th1/Th2 balance[48]. Breastfeeding intensifies innate immunity by regulating the gut microbiome diversity which is thought to mediate the Th1/Th2 balance[31]. Short-chain fatty acids are microbiota-generated metabolites that can influence peripheral T cells, especially regulatory T (Treg) cells, by inhibiting histone deacetylases. Short-chain fatty acids can adjust the frequency and function of Treg in vivo[49]. Breastfed neonates have a two-fold higher proportion of Treg cells and decreased inflammatory cytokine production compared to those who received formula milk[8]. With these immunological effects, breastfeeding may have benefits on protection against allergic diseases.

This systematic review and meta-analysis demonstrated the protective effect of prolonged breastfeeding (≥6 months) against the development of AR when compared to short-term breastfeeding (<6 months). The likelihood of developing AR was lower in children who were exclusively breastfed for at least six months compared to those with prolonged nonexclusive breastfeeding. The non-overlapping of the two odds ratios indicated statistical significance. The authors would like to stress that prolonged breastfeeding was generally defined as breastfed for greater than 6 months. Therefore, the number of manuscripts including breastfeeding for 12 months is certainly inferior in number and quality compared to the ones that analysed breastfeeding at 6 months. Long-term nonexclusive breastfeeding (at least 12 months) also had a significant impact in reducing the risk of AR. All three included studies in this meta-analysis were from Asia, representing the shorter breastfeeding duration in Europe[47].

The protective effects continued up to 18 years. In this study, subgroup analysis by age of AR outcome (≤5 years, >5 years) was performed to assess the atopic march at five years of age. The progression of atopic disorders from atopic dermatitis and food allergy to allergic rhinitis and asthma develops at certain ages[24]. Some children with atopic march may persist for several years, whereas others may resolve with increasing age. We therefore would like to assess if there was any subgroup difference between the age of AR outcome of 5 years and 18 years.

To date, there have been three meta-analyses assessing the effects of breastfeeding on the development of AR[14,18,19]. Mimouni et al.[18] pooled data from six prospective studies and showed that breastfeeding for at least three months had a protective effect against AR in children under five years of age. Lodge et al.[14] extracted data from 16 studies with different cut-off timepoints for breastfeeding duration and mixed types of breastfeeding. They found similar findings, but the protective effects did not continue after five years of age[14]. In 2018, a comprehensive meta-analysis used different timepoints for exclusive breastfeeding and did not show any associations between exclusive breastfeeding and the development of AR[19]. None of the three previous meta-analyses followed the WHO guidelines in choosing the timepoints for breastmilk duration. Classifications of breastfeeding duration were not clearly defined in the earlier meta-analyses. The pooled data from unclear classifications may affect the results. Instead of 'more vs less' or 'ever vs never', the more specific term such as '≥6 months vs <6 months' may result in more accurate data.

In the first years of life, most nasal symptoms are related to viral infection rather than allergy[50]. Although epidemiological tools, such as the ISAAC questionnaire, cannot distinguish these two conditions[51], the current epidemiological knowledge of pediatric AR is derived from ISAAC questionnaire[52]. In this review, the core ISAAC questions for diagnosis of AR were modified and

used in different self-reported questionnaires and surveys. How the prevalence of allergic rhinitis was defined among included studies was heterogeneous, leading to a limitation of our review. Kim et al.[53] found that the omission of a detailed anamnesis and IgE testing resulted in low accuracy of the ISAAC survey. Zacharasiewicz et al.[54] noted that only fifty percent of rhinitis symptoms are contributable to atopy. The variability has been announced worldwide without a clear explanation[55]. Our subgroup analysis by AR diagnostic criteria indicated the difference in protective effects between specific IgE tests and epidemiologic tools. For future studies, the combination of allergy testing and epidemiological tools for diagnosing AR should be considered. Specific IgE tests detect allergen sensitization after environmental exposures and contribute to the early prevention of allergic diseases.

The strengths of our meta-analysis were that we focused on the duration of breastfeeding and analyzed the nonexclusive breastfeeding separately from exclusive breastfeeding to explore the sole effect of each type. Both types of prolonged breastfeeding (>6 months) reduced the likelihood of developing AR. Sensitivity analyses by removing low-quality studies did not change the effect, indicating uncertain risk of bias. Subgroup analysis by recalculated crude OR did not show any significant difference in the protective effect of breastfeeding. Furthermore, subgroup analysis by adjustment for confounding factors following the criteria of Kramer[16] did not suggest a well-designed study with assessment for many essential confounders.

The limitation of this study was the low to medium quality of the included studies. The overall quality of evidence was low. Most included studies had bias on ascertainment of exposure. The inconsistency in methodology influenced the quality of evidence. Reverse causation may happen when a child with a family history with atopy or early allergic signs tends to receive prolonged breastfeeding. A few studies explored the effect of reverse causation and had conflicting results. Jelding-Dannemand et al.[30] found that the onset of allergic diseases and SPT before finishing the exclusive breastfeeding did not change the results. On the other hand, Kusunoki et al.[56] demonstrated a longer breastfeeding duration in a population with high risk of allergic diseases compared to those with low risk. The incidence of allergic rhinitis may be affected by many factors. The discrepancy in the definition of exclusive breastfeeding and the criteria for AR diagnosis may cause bias. In addition, recall bias of breastfeeding duration and solid food introduction causes inconsistent conclusions. Large population-based prospective cohorts using an appropriate methodology for AR diagnostic criteria and ascertainment of breast milk consumption such as secure records, structured interviews, written self-report are required. Rigorous assessment and long-term follow-up in further studies strengthen the evidence of our study. Despite the low- to very low-quality of evidence following GRADE, this meta-analysis highlights the benefits of breastfeeding for at least six months on AR prevention.

Conclusion

Prolonged breastfeeding (at least six months) provided protection against allergic rhinitis. This finding is in accordance with the World Health Organization recommendation that every infant should be breastfed for at least six months. Breastfed children may receive essential benefits such as prevention of uncommunicable diseases like allergic rhinitis. The overall quality of evidence was low so these findings should be interpreted with caution. Most included studies had a limitation on ascertainment of exposure. Recall bias and poor methodology of observational studies may influence these protective effects of prolonged breastfeeding.

Funding

This is an unfunded project.

Authorship contribution

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

Conflict of interest

Kornkiat Snidvongs received Honoraria for speaking at symposia from Organon, Mylan, and Menarini. Minh P. Hoang, Jompol Samuthpongtorn, and Kachorn Seresirikachorn declare that they have no conflict of interest.

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This manuscript contains online supplementary material

SUPPLEMENTARY MATERIAL

Table S1. Search strategies.

PubMed MEDLINE	EMBASE
#1 "Breast Feeding"[Mesh] #2 "Milk, Human"[Mesh] #3 Breast[All Fields] AND Feed*[All Fields] #4 Breast-fe*[All Fields] #5 Infant fe* [All Fields] #6 Infant nutrition* [All Fields] #7 Human milk feeding [All Fields] #8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	#1 exp breast feeding/ #2 exp breast milk/ #3 Breast AND Feed* #4 Breast-fe*.mp. #5 Infant fe*.mp. #6 Infant nutrition*.mp. #7 Human milk feeding [All fields] #8 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7
#9 "Rhinitis, Allergic, Seasonal"[Mesh] #10 "Rhinitis, Allergic, Perennial"[Mesh] #11 Allergic rhinitis [All fields] #12 Hay fever [All fields] #13 Allergic rhinoconjunctivitis [All fields] #14 #9 OR #10 OR #11 OR #12 OR #13	#9 exp allergic rhinitis/ #10 allergic rhinitis.mp. #11 hay fever.mp. #12 allergic rhinoconjunctivitis #13 9 OR 10 OR 11 OR 12
#8 AND #14	#8 AND #13
Web of Science (283), CENTRAL (135), ClinicalTrials.gov (3), WHO International Clinical Trials Registry Platform (6)	
#1 ("breastfeeding" OR "human milk" OR ("breast" AND "feeding") OR "infant feeding" OR "infant nutrition" OR "human milk feeding" OR "breastfed")	
#2 ("allergic rhinitis" OR "seasonal allergic rhinitis" OR "perennial allergic rhinitis" OR "hayfever" OR "hay fever" OR "allergic rhinoconjunctivitis"	
#3 #1 AND #2	

Table S2. Definition of exclusive breastfeeding,

First Author, Year	Definition	Cut-off breastfeeding duration
Miyake, 2007	NA	<1, 1- 3, 4 -11, and 12+ months
Ehlayel, 2008	Bread-fed only	6 months
Kramer, 2009	Receiving no solids, nonbreast milk, or water or other liquids (other than vitamins or medications) at all visits	3 months, 6 months
Siriaksorn, 2011	NA	6 months
Jelding-Dannemand, 2015	Receiving hypoallergenic formula for less than 7 days before establishing breastfeeding and not receiving supplementation with formula	6 months
Chiu, 2016	Receiving breast milk only without additional foods or drinks except water	6 months
Huang, 2017	Feeding solely by the mother's breast milk without introducing other foods or liquids	3 months, 6 months
Li, 2020	NA	4 months, 6 months

Abbreviation: NA, not applicable

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
Kull (2002)	1	1	-	1	1	1	1	1	7
Kramer (2009)	1	1	1	1	1	1	1	1	8
von Vobyletzki (2012)	1	1	1	1	1	-	1	1	7
Nwaru (2013)	1	1	-	-	2	1	1	1	7
Jelding-Dannemand (2015)	1	1	1	1	1	1	1	1	8
Bion (2016)	1	1	-	1	1	1	1	1	7
Chiu (2016)	-	1	1	1	1	1	1	1	7
Ekelund (2021)	1	1	1	1	1	-	1	1	7
Hummel (2021)	1	1	1	1	1	-	1	1	7

Table S4. 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
Peroni (2003)	1	1	-	1	1	4
Obihara (2005)	1	1	-	2	1	5
Miyake (2007)	1	1	-	1	1	4
Ehlayel (2008)	1	1	-	-	1	3
Siriaksorn (2011)	1	1	-	1	1	4
Tamay (2014)	1	1	-	1	1	4
Huang (2017)	1	1	-	2	1	5
Chinratanapisit (2019)	1	1	-	1	1	4
Han (2019)	1	-	1	2	1	5
Li (2020)	-	1	-	1	-	2
Lu (2020)	1	1	-	1	1	4
Tong (2020)	1	1	-	1	-	3
Hu (2021)	1	1	-	1	-	3
Huang (2021)	1	1	-	1	1	4

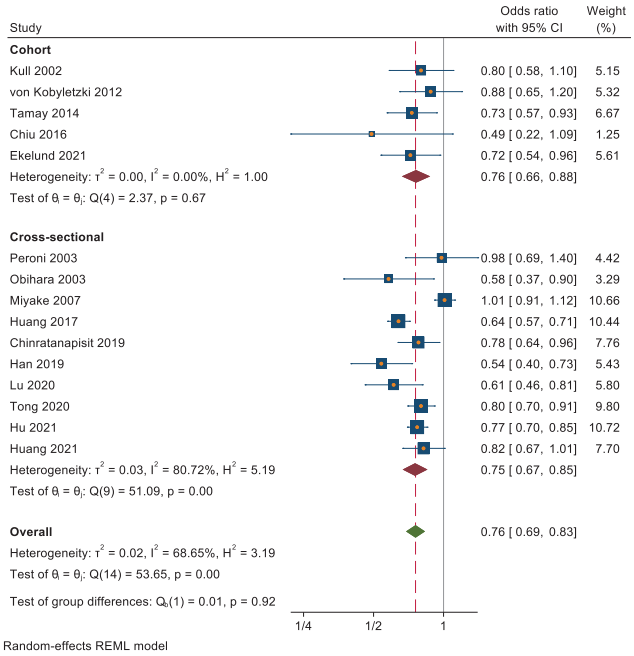

Figure S1. The risk of allergic rhinitis and subgroup analysis by study design: nonexclusive breastfeeding ≥6 months vs <6 months.

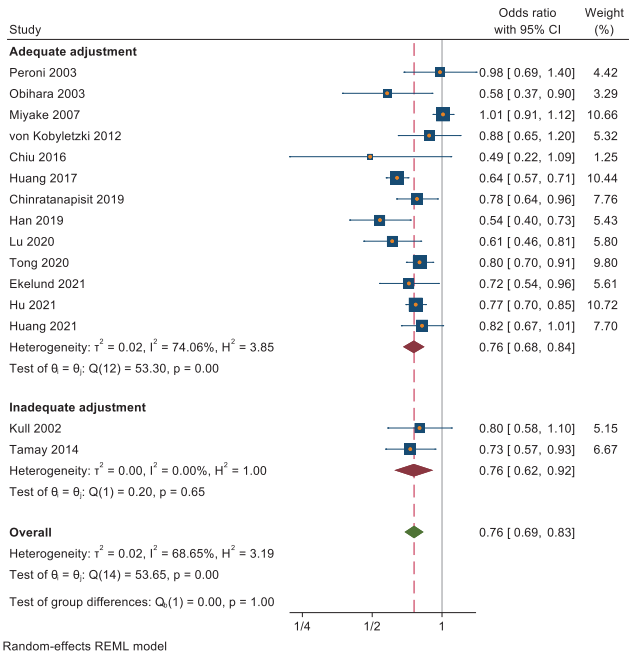

Figure S2. The risk of allergic rhinitis and subgroup analysis by adjustment for confounders: nonexclusive breastfeeding ≥6 months vs <6 months.

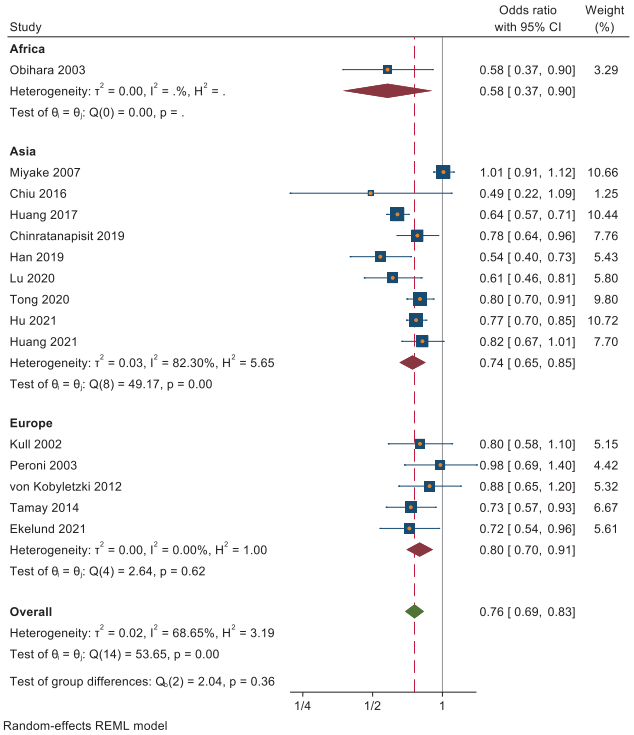

Figure S3. The risk of allergic rhinitis and subgroup analysis by region: nonexclusive breastfeeding ≥6 months vs <6 months.

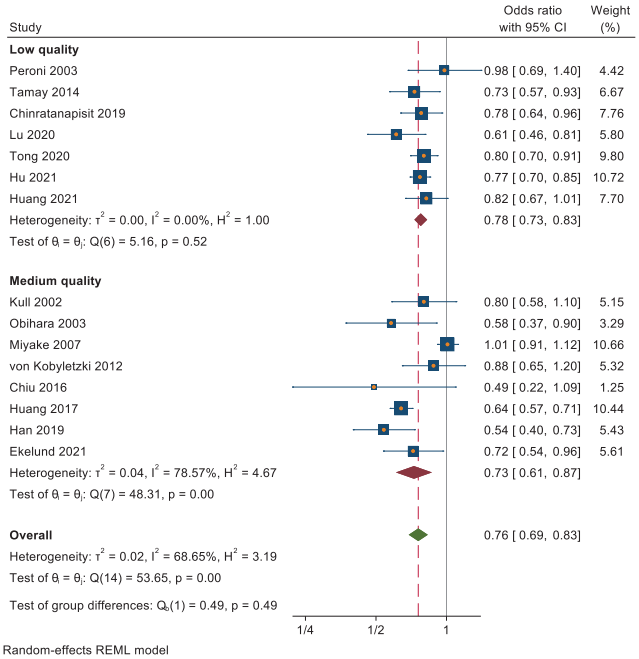

Figure S4. The risk of allergic rhinitis and subgroup analysis by study quality: nonexclusive breastfeeding ≥6 months vs <6 months.

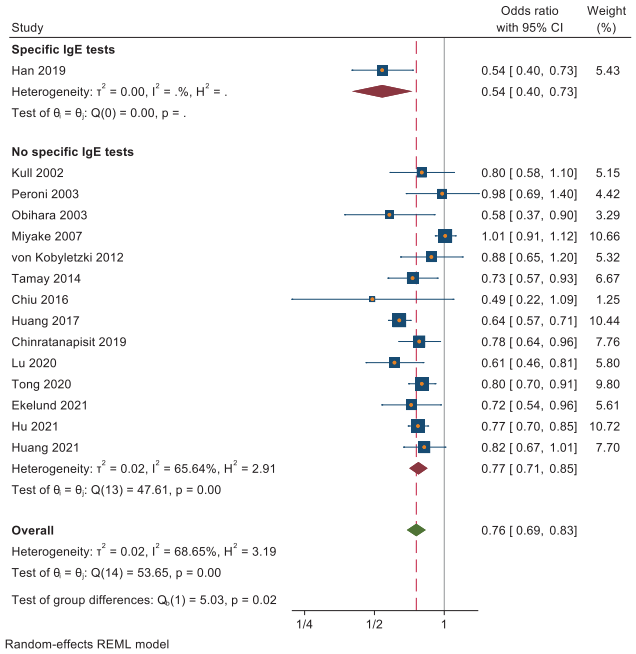

Figure S5. The risk of allergic rhinitis and subgroup analysis by AR diagnostic tools: nonexclusive breastfeeding ≥6 months vs <6 months.

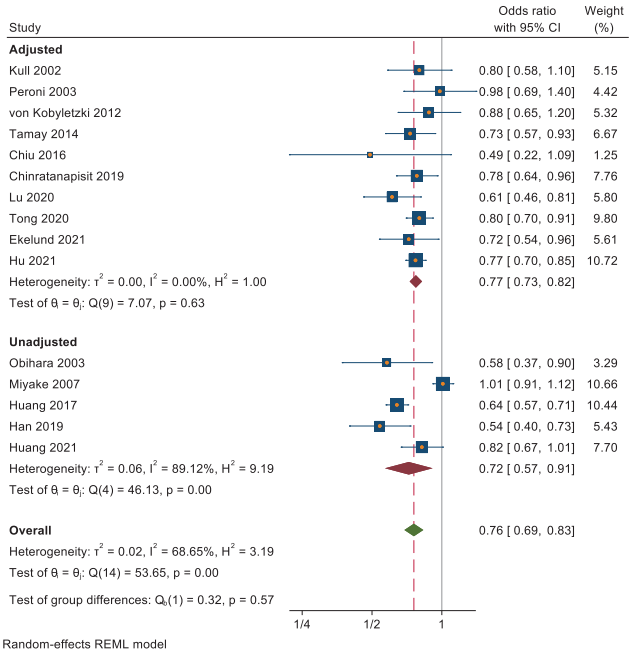

Figure S6. The risk of allergic rhinitis and subgroup analysis by available odds ratio: nonexclusive breastfeeding ≥6 months vs <6 months.

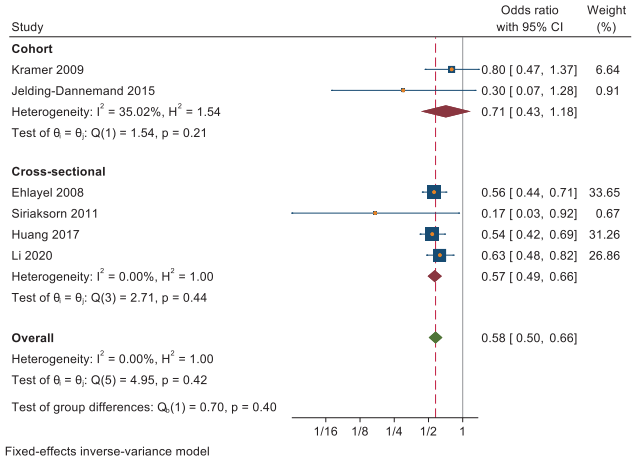

Figure S7. The risk of allergic rhinitis and subgroup analysis by study design: exclusive breastfeeding ≥6 months vs <6 months.

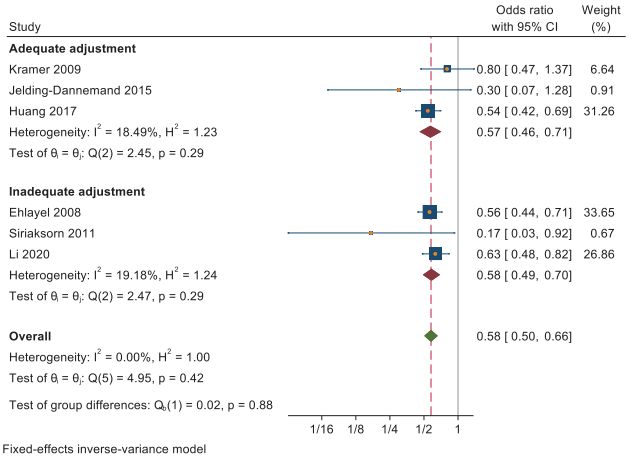

Figure S8. The risk of allergic rhinitis and subgroup analysis by quality of adjustment for confounders: exclusive breastfeeding ≥6 months vs <6 months.

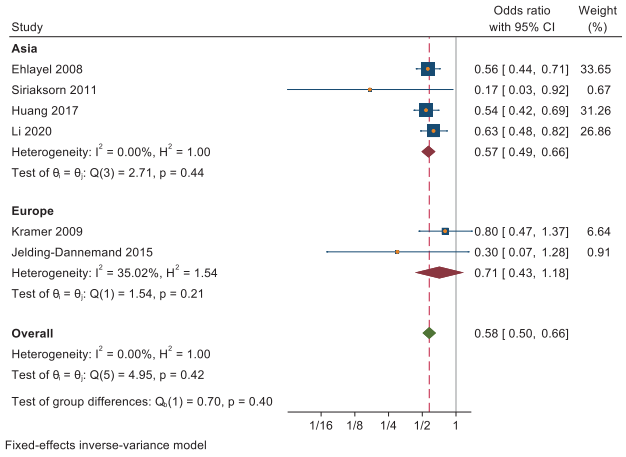

Figure S9. The risk of allergic rhinitis and subgroup analysis by region: exclusive breastfeeding ≥6 months vs <6 months.

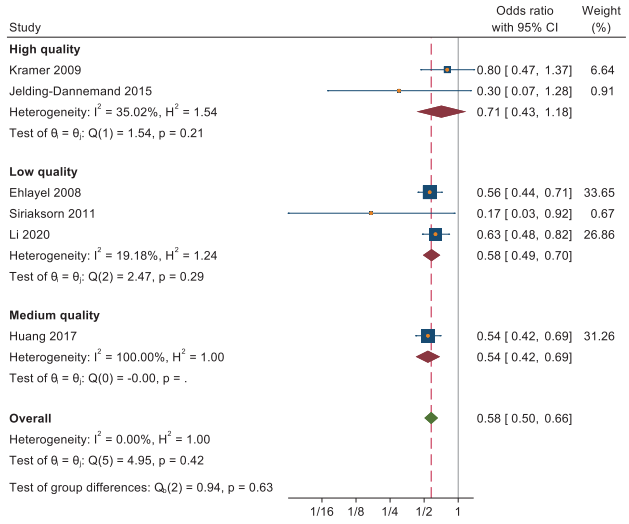

Figure S10. The risk of allergic rhinitis and subgroup analysis by study quality: exclusive breastfeeding ≥6 months vs <6 months.

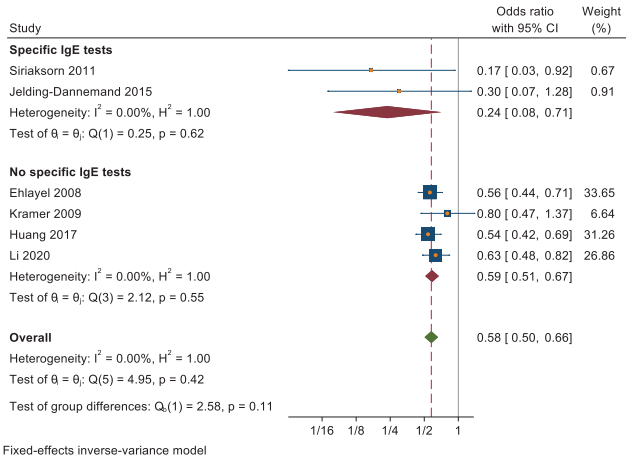

Figure S11. The risk of allergic rhinitis and subgroup analysis by AR diagnostic tools: exclusive breastfeeding ≥6 months vs <6 months.

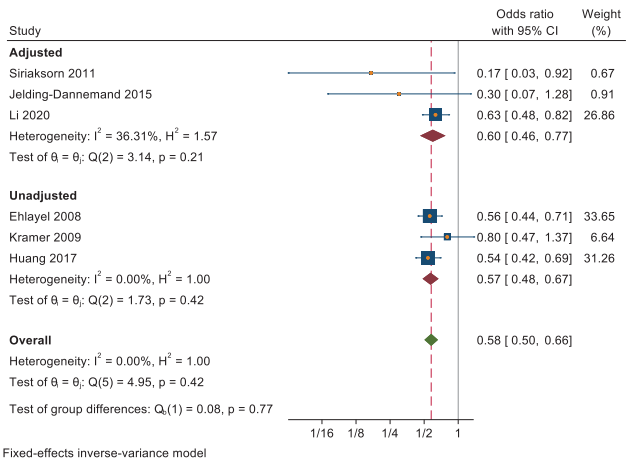

Figure S12. The risk of allergic rhinitis and subgroup analysis by available odds ratio: exclusive breastfeeding ≥6 months vs <6 months.

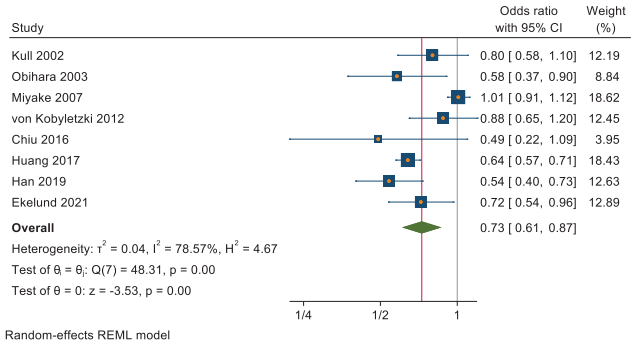

Figure S13. Sensitivity analysis of the risk of allergic rhinitis by removing low-quality studies: nonexclusive breastfeeding ≥6 months vs <6 months.

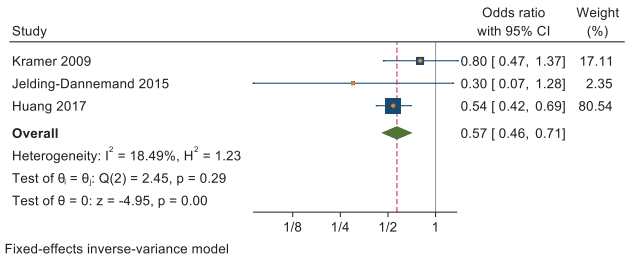

Figure S14. Sensitivity analysis of the risk of allergic rhinitis by removing low-quality studies: exclusive breastfeeding ≥6 months vs <6 months.

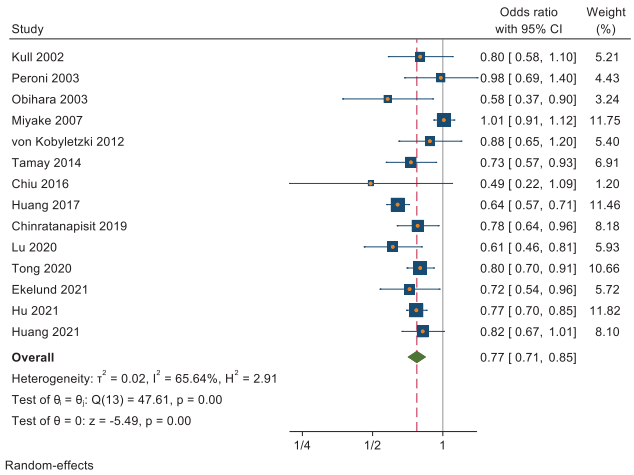

Figure S15. Sensitivity analysis of the risk of allergic rhinitis by removing studies with high-risk populations: nonexclusive breastfeeding ≥6 months vs <6 months.

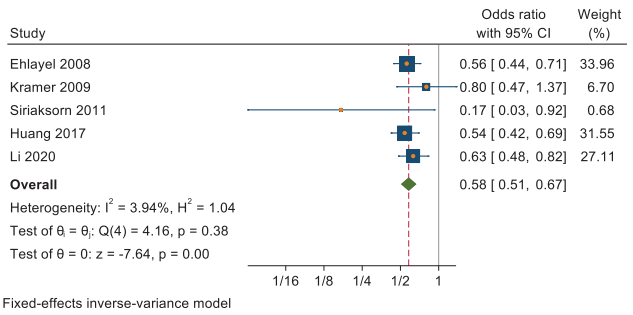

Figure S16. Sensitivity analysis of the risk of allergic rhinitis by removing studies with high-risk populations: exclusive breastfeeding ≥6 months vs <6 months.

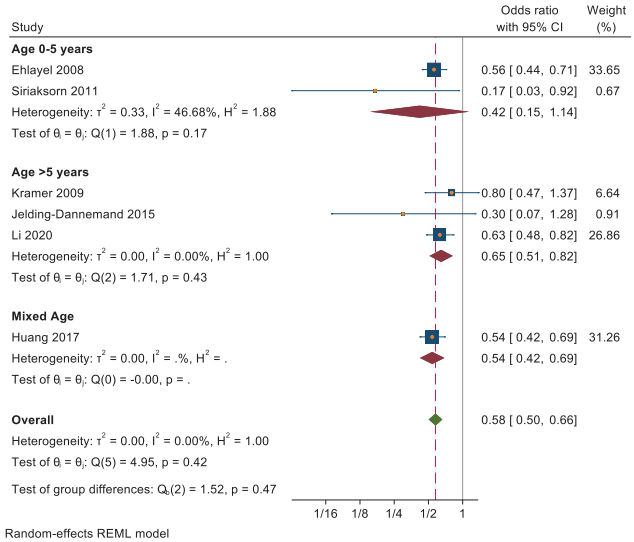

Figure S17. Sensitivity analysis of the risk of allergic rhinitis by using random-effects model: exclusive breastfeeding ≥6 months vs <6 months.

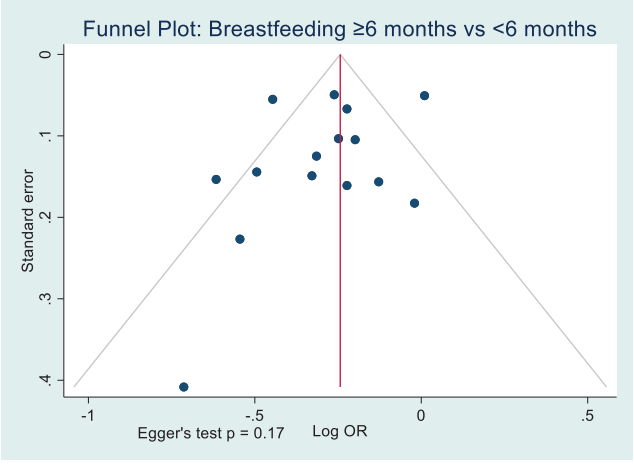

Figure S18. Funnel plot for the risk of allergic rhinitis: nonexclusive breastfeeding ≥6 months vs <6 months. Abbreviation: OR, odds ratio.