

Pediatric Asthma and Food Allergy

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Abstract

Objective To quantitatively summarize the evidence from observational studies on the relation between pediatric asthma and food allergy.

Methods A literature search was conducted in Medline and EMBASE (August 2016). Two independent reviewers appraised the studies and extracted the estimates of interest. Methodological quality of the included studies was assessed using National Heart Lung and Blood Institute (NHLBI) Quality Assessment Tools. Data were pooled using random-effects meta-analysis.

Results A total of 32 relevant studies were identified but only 8 studies met the inclusion criteria. Using random-effect model, food allergy showed strong association with asthma in children (OR = 2.87 [95% CI: 2.05–4.00]; $P < 0.0001$).

Conclusions This study suggested that food allergy is associated with an increased risk of asthma in children.

Keywords Pediatric · Asthma · Food allergy · Sensitization · Risk

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Introduction

The prevalence of both asthma and food allergy appears to be on the rise in the pediatric population. About 14% of children across the world experience asthma symptoms, with highest morbidity and premature mortality reported in children aged 10–14 y [1]. Food allergy is more prevalent in children (4–8%) than in adults (5%) [2, 3], as most food allergies develop in early life and most of the children will eventually outgrow this allergic condition by early adolescence [4].

Asthma, a chronic inflammatory disorder of the airways, is characterized by recurrent breathing difficulties, chest tightness, coughing and wheezing [1]. It is classified into two major subtypes, allergic asthma and non-allergic asthma. Although both subtypes share similar clinical symptoms, they are triggered by different underlying causing factors. Allergic asthma is triggered by allergic reactions to allergens such as certain food, dusts, pollens, molds or mites through inhalation or ingestion; whereas non-allergic reaction is triggered by exercise, stress, certain medicines, cold air, airway infections, smoke or other irritants.

Food allergy is a well-known risk factor for the development of allergic asthma in children. Children with food allergy are at two times greater risk of developing asthma compared to the non-allergic children [3]. Food allergy is also reported to be a significant causative factor for severe or life-threatening asthma attacks in children [5]. A group of eight common food allergens that have been identified include bovine milk, peanut, fish, wheat, shellfish, egg, tree nuts and soy bean [6, 7]. Studies have shown that asthmatic children with multiple allergies are at the greater risk of developing asthma as well as increased severity of asthma [8, 9].

Over the past few decades, numerous studies have been conducted to investigate the relation between pediatric asthma and food allergy. However, up to date, reliable estimates of the

magnitude are lacking. This present study is the first meta-analysis performed to examine the magnitude of the relation between pediatric asthma and food allergy.

Material and Methods

A systematic review was carried out as guided by PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines [10]. The studies included in this analysis were obtained by performing a comprehensive electronic literature search in PubMed and EMBASE up to August 8, 2016 using the following keywords: “Childhood asthma” OR “pediatric asthma”, “food allergy” and “food hypersensitivity” in titles and abstracts. No date limits were applied to the search strategy. Studies identified from searching electronic databases were combined, duplicates removed and papers were screened for relevance to the review based on the information contained in the title and abstract. Additional references were located by searching the references cited in the identified studies.

Inclusion criteria were based on the PICOS method: (P) Children or subjects <18-y-old of any ethnicity or geographical area; (I) Exposure to food allergy through self-report of medical conditions, total and/or specific IgE measurement, and/or skin prick test; (C) The outcome group (asthmatic group) was compared with the control group (non-asthmatic); (O) Diagnosis of asthma through self-report of medical conditions or physician diagnosis; (S) The type of study design was either a meta-analysis, systematic review, randomized control trial, cohort study or case control study.

Data was extracted from all eligible publications independently by two of the authors, with particular regards to: the last name of the first author, publication year, study design, study size, population age, diagnosis of asthma, and effect size. For conflicting evaluations, an agreement was reached following a discussion.

The internal validity and risk of bias of each study was assessed using the National Heart Lung and Blood Institute (NHLBI) Quality Assessment Tools for (i) case-control studies [11], and (ii) observational cohort and cross-sectional studies [12]. An overall quality rating of “Good”, “Fair”, and “Poor” is determined for each study based on 14 different criteria. Two authors independently evaluated the components of the scale as “Yes”, “No” “Not Applicable” or “Not Recorded”. This was used to guide the overall rating for the quality of each study as “Good”, “Fair” or “Poor”. In case of disagreement a consensus opinion was reached.

The odd ratios (ORs) were used as the common measure of association between food allergy and asthma in children across the studies. A random effects meta-analysis was performed in accordance with the method of DerSimonian and Laird [13]. Potential publication bias was assessed by visual

inspection of the funnel plot in which the log ORs were plotted against their standard errors. Begg’s test and Egger’s test were used to estimate the severity of publication bias, with a *P* value <0.05 considered statistically significant [14, 15]. Statistical analysis was performed using StatsDirect Statistical Software (StatsDirect Ltd., United Kingdom).

Results

The systematic search yielded a total of 416 references from two electronic databases (Fig. 1). Removal of duplicates and screening of titles and abstracts utilizing the aforementioned criteria yielded 32 articles for full-text review. Of these, 25 were further excluded, leaving 8 eligible articles.

Table 1 shows the characteristics of eight studies examining the association between pediatric asthma and food allergy. The studies were published between 1997 and 2013. Of these, four were cross-sectional studies, three were cohort studies and one was case control study. Four were conducted in Europe, two in Middle-East, and one each in America and Asia. Asthma was diagnosed by self-report (6/8) or physician diagnosis (2/8). Food allergy was defined based on self-report (4/8) or specific Ig-E measurement and/or skin prick test (4/8). Quality assessment of the studies using the National Heart Lung and Blood Institute (NHLBI) Quality Assessment Tools rated four “Good” studies and four “Fair” studies (Table 1).

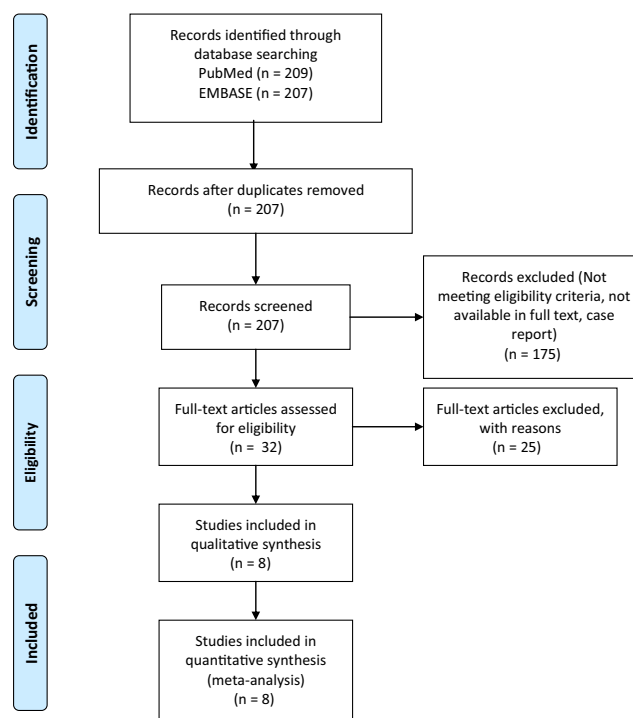
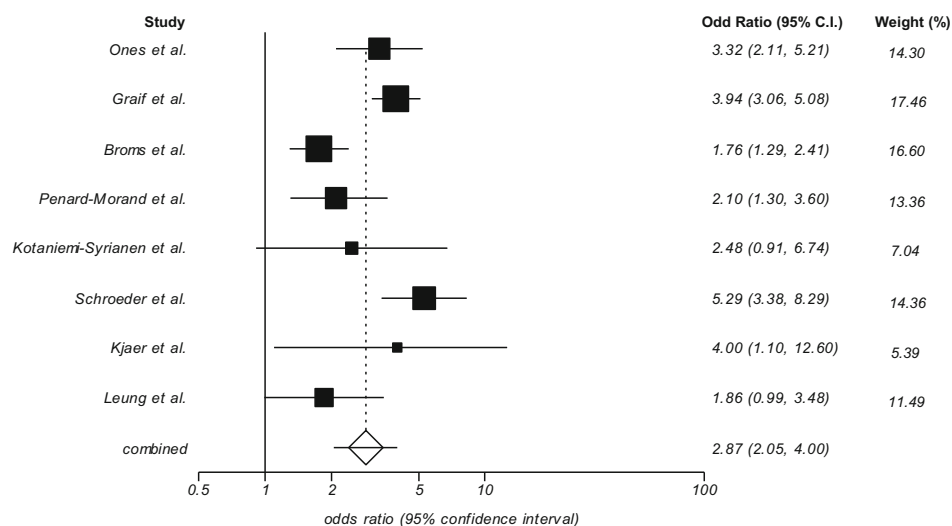
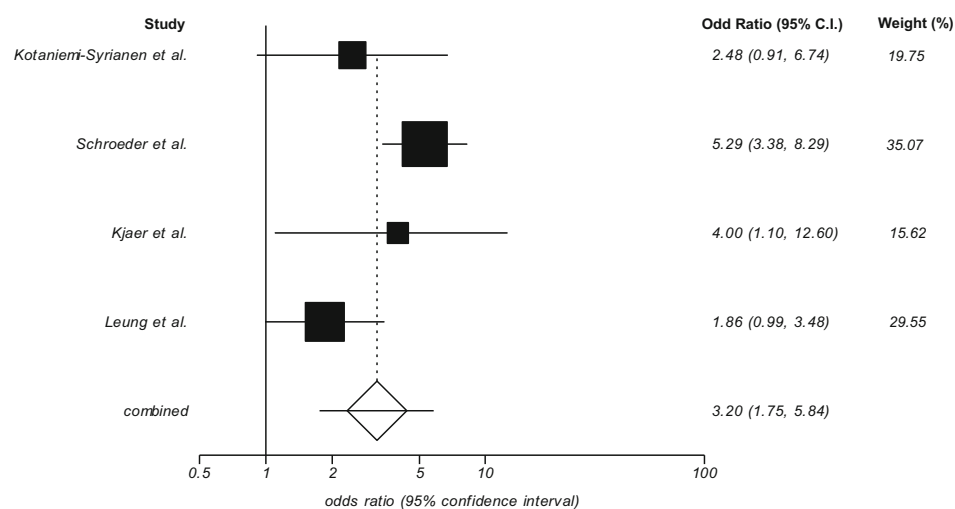
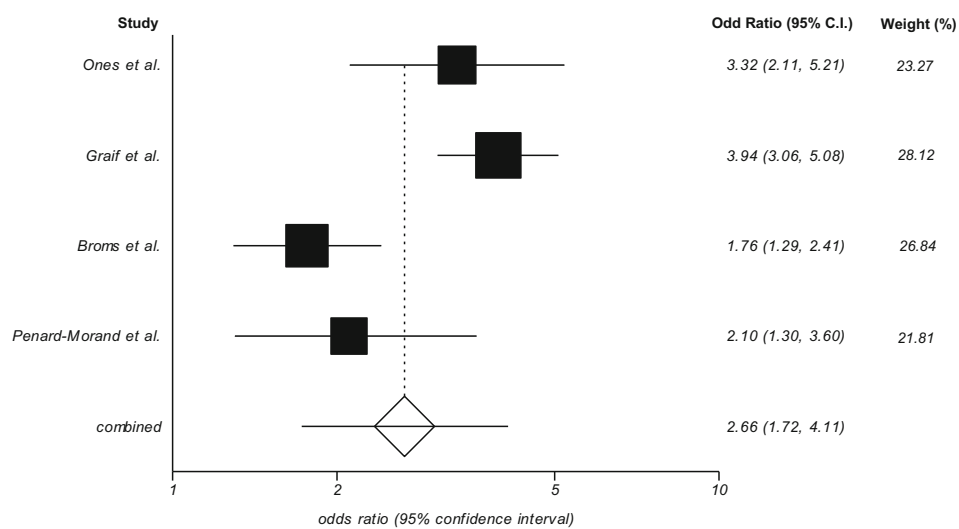


Fig. 1 Flow diagram demonstrating search strategy used

Table 1 Characteristics of included studies

Study Basics			Food Allergy Assessment			Asthma Ascertainment	Study Quality
Study	Year of Publication	Design	Sample Size (n)	Age group	Country	OR (95% C.I.)	
Ones et al.	1997	Cross-sectional	2216	6–12 y	Turkey	3.32 (2.11–5.21)	Self-report (Physician diagnosis) Fair
Graif et al.	2012	Cross-sectional	14,187	13–14 y	Israel	3.94 (3.06–5.08)	Self-report (Questionnaire) Fair
Broms et al.	2013	Cross-sectional	4886	1–6 y	Sweden	1.76 (1.20–2.41)	Self-report (ISAAC Questionnaire) Fair
Penard-Morand et al.	2005	Cross-sectional	6672	9–11 y	France	2.10 (1.30–3.60)	Self-report (Physician diagnosis) Fair
Kotaniemi-Syrjänen et al.	2003	Cohort	80	<2 y	Finland	2.48 (0.01–6.74)	Self-report (SPT positive, symptoms) Good
Schroeder et al.	2009	Cohort	567	Children >6 y Children <6 y	USA	5.29 (3.38–8.29)	Total and specific IgE measurement Self-report (Questionnaire) Good
Kjaer et al.	2009	Cohort	404	0–6 y	Denmark	4.00 (1.10–12.60)	• Questionnaire (Clinical criteria) • Total and specific IgE measurement • Skin prick test Physician diagnosis Good
Leung et al.	2002	Case Control	310	<15 y	Hong Kong	1.86 (0.99–3.48)	Specific IgE measurement Physician diagnosis Good

(a) ALL INCLUDED STUDIES**(b) COHORT AND CASE CONTROL****(c) CROSS-SECTIONAL**

◀ **Fig. 2** Meta-analysis results of the included studies presented in the forest plot of **a** all included studies, **b** cohort and case control studies, and **c** cross-sectional studies

Both the results of cross-sectional studies (OR = 2.66 [95% CI: 1.72–4.11]; $P < 0.0001$) and cohort/case control (OR = 3.20 [95% CI: 1.75–5.84]; $P < 0.001$) showed a significant association of asthma and food allergy in children. The overall meta-analysis results of the 8 studies was OR = 2.87 [95% CI: 2.05–4.00] with $P < 0.0001$. The results are illustrated in Fig. 2.

Visual inspection of the funnel plot of the eight included studies (Fig. 3) indicated asymmetry that would be suggestive of publication bias. However, Begg's test ($P = 0.40$) and Egger's test ($P = 0.78$) did not show significant evidence of publication bias.

Discussion

To the best of authors' knowledge, the present study is the first meta-analysis performed to describe the strength of the association between food allergy and asthma in the pediatric population. The meta-analysis results of the four cross-sectional prevalence studies indicated strong and robust association between food allergy and incidence of asthma in children, with reported overall OR = 2.66 [95% C.I.: 1.72–4.11]. The meta-analysis results of the four cohort/case-control studies also reported comparable results, *i.e.*, OR = 2.87 [95% CI: 2.05–4.00], indicating that food allergy is associated with increased risk of developing asthma in children. An early life food sensitization precedes the development of allergic asthma and other atopic disorders such as atopic dermatitis and/or allergic

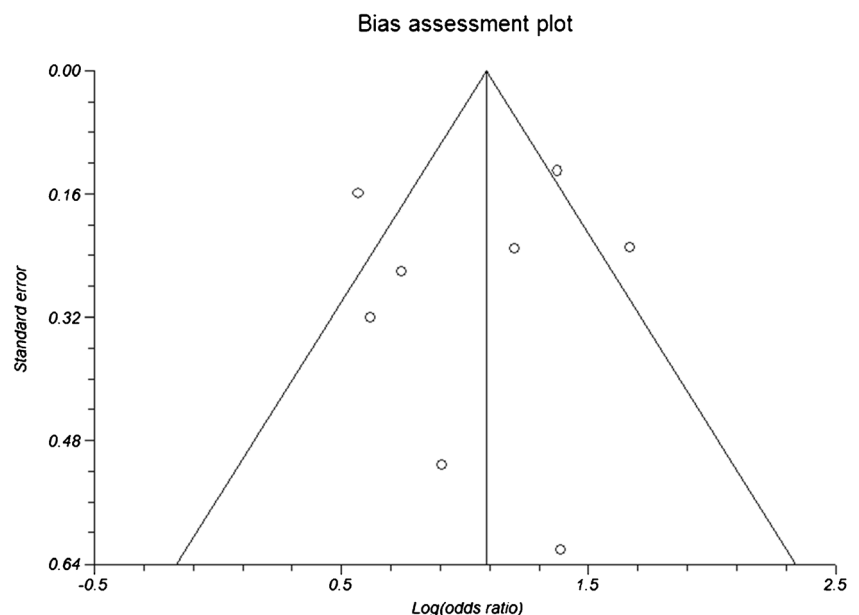
rhinitis [16, 17]. In addition, food allergy may be a risk factor for asthma morbidity in asthmatic children. In a prospective cohort study, asthmatic children with food sensitization had higher rates of hospitalization and asthma-controller medication use [18].

The underlying mechanism of food allergy in the development of asthma is not clearly known. It is postulated that asthma is mediated primarily by immunoglobulin E (IgE) [19]. In the presence of allergens (dietary allergenic proteins), IgE activates mast cells to release inflammatory mediators (such as histamines and leukotrienes). These inflammatory mediators induce inflammation in the airways, resulting in breathing difficulties and wheezing, which are the characteristic symptoms of allergic asthma [19].

A limitation of this study would be the diagnostic methods of food allergy employed in the included studies may not accurately represent a true food allergy. In some of the included studies, allergen-specific IgE blood test and skin prick test (SPT) were used in the diagnosis of food allergy. It should be noted that the results of the two diagnostic tests may not necessarily correlate with double-blinded placebo controlled food challenge (DBPCFC), which is considered as the gold standard for diagnosing food allergy [20]. A positive test result in IgE blood test or SPT does not necessarily equate to clinical allergy. However, SPT and/or Ig-E blood test are preferred instead of DBPCFC as the latter may not be practical in terms of efficiency, safety and cost effectiveness, particularly in the clinical setting or studies that involve a large sample size.

Out of the 8 included studies, 6 studies employed self-report method in the diagnosis of asthma. Compared to other diagnostic methods such as clinical diagnostic interviews and physician diagnosis, self-report is often preferred due to the fact that it is a more cost-effective and time-efficient way of

Fig. 3 Funnel plot for assessment of publication bias among studies included in the meta-analysis of the association between pediatric asthma and food allergy



obtaining data, particularly when the studies involve a large sample size. However, self-report is always susceptible to response biases such as social desirability bias, demand characteristics and acquiescence bias.

In conclusion, this study demonstrated a strong association between food allergy and pediatric asthma. In view of the fact that food allergy is often overlooked compared to other risk factors such as inherited traits, environmental factors (such as cigarette smoke or air pollution) and other factors, the findings of this study facilitates to call for greater awareness in food allergy management as a necessary step to prevent or reduce the risk of asthma development in the pediatric population.

Contributions All the authors involved in study design. HZ and CD performed the meta-analysis and wrote the manuscript. JP reviewed and finalized the manuscript, and will act as guarantor for the paper.

Compliance with Ethical Standards

Conflict of Interest None.

Source of Funding None.

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Appendix 1

Inclusion and exclusion criteria (PICO)

Research Question: Does food allergy increase the risk of asthma in children?

Participants

Children or subjects < 18-y-old of any ethnicity or geographical area.

Intervention

Exposure to food allergy through self-report of medical conditions, total and/or specific IgE measurement, and/or skin prick test.

Comparison

The outcome group (asthmatic group) was compared with the control group (non-asthmatic).

Outcomes

Diagnosis of asthma through self-report of medical conditions or physician diagnosis.

Design

Meta-analysis, systematic review, randomized control trial, cohort study or case control.