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FOOD ALLERGIES IN PEDIATRIC GROUP: A SYSTEMATIC REVIEW

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ABSTRACT

Allergy symptoms, ranging from mild urticaria to life-threatening anaphylaxis, are the result of an immunoglobulin E (IgE)-mediated hypersensitive response to food. Rising food allergy rates are a serious public health concern in developed nations during the last two decades. The current review aimed to systematically search in PubMed, Cochrane library, Embase, Scopus, Web of Science, CINAHL, OVID and google scholar databases. The search was conducted selecting articles published in all languages. Moreover, selected articles were chosen from peer-reviewed journals. The reference list of the selected articles was also screened to find additional articles. The selected period during the search was (2000– present). The absence of immunologic and clinical tolerance to food allergens is the underlying mechanism that causes food allergies. IgE-mediated food allergies are diagnosed using a combination of a thorough medical history, in-vivo and in-vitro studies of particular IgE, the elimination diet, and a double-blind, placebo-controlled food challenge. As of right now, the only way to treat allergies is via a very restrictive diet. Such a stance, which we would call "passive," does not exclude the possibility of adverse responses owing to inadvertent consumption of the offending food. An "active" strategy, such as specialized allergen immunotherapy, which is presently in development and utilized exclusively for research, is desperately required for the treatment of food allergies. The purpose of this article is to provide an up-to-date overview of the epidemiology, etiology, prevention, diagnosis, and treatment of IgE-mediated food allergies in juvenile populations.

INTRODUCTION

Food reactions, including allergies, have been recognized for millennia. Lucretius was cited as saying, "What is nourishment for one man may be poisonous to another" (99-55 BC). In the 1920s and 1930s, food intolerance was blamed for several diseases; by the 1980s, it had become a

widespread parental worry. Unsurprisingly, it was linked with a continuous rise in food allergy diagnoses [1]. This was the outcome of a rise in the incidence of atopic disorders due to various environmental and genetic causes, as well as an increase in public awareness. Immunoglobulin E (IgE)-mediated food allergy is a worldwide health problem affecting millions of people and interfering with several areas of their life [2,3].

The disorder may create tension, worry, and anxiety in both afflicted children and their parents. In addition, it has a detrimental influence on the nutritional health of children with a confirmed or suspected food allergy, since it results in the limitation, elimination, or full avoidance of some essential foods. Stigma, school bullying, and restrictions on usual social activities, such as attending parties and eating out, all have a substantial effect on the kid and the family. As for parents, holiday preparation becomes a nightmare, comparable to when a kid starts school or moves to a college campus and becomes independent [2-5].

The global incidence of food allergy is believed to be around 4% of children and 1% of adults, and its prevalence has grown over the previous two decades [2,4,5]. Food allergy is not entirely understood, and some unpleasant responses to food are not allergic, which contributes to differences in reported prevalence. When appropriately identified by testing and oral food challenge (OFC), the real incidence of food allergies is shown to be substantially lower, closer to 8% in young children and less than 4% in adults.

The main aims of our systematic review are:

- To investigate the prevalence of food allergies among children.
- To provide an overview of the burden of pediatric food allergy.

METHODS

Eligibility Criteria

- Studies including children aged 0-18 years
- Studies investigating food allergy with regard to prevalence, diagnosis and burden with regard to health-related quality of life

Study types

Randomised control trials (RCT), non-RCT, observational studies, case control studies. Case reports and case series were excluded.

Outcomes

Primary:

- Investigation of food allergies among pediatric age group

Secondary:

- Assessment of prevalence, diagnosis and health-related burden of food allergy among pediatric age group.

Data collection and analysis

Two reviewers extracted the following information from selected articles using the reference software Endnote 20. In order to remove duplicate articles and track the numbers required for the PRISMA flow diagram, reviewers then transferred articles into Covidence, a systematic review management tool.

Data analysis

The data that was recovered were entered into the Statistical Package for the Social Sciences, known as SPSS, and coded before a frequency analysis that was carried out in order to determine patterns of similarity. The content that is duplicated throughout the selected articles was organized into its own individual tabs so that it could be seen more clearly. The data was collected from the study that is considered to be eligible using descriptive statistics. After that, a narrative synthesis was constructed using the summaries of the selected articles. Forest plots were generated using extracted data entered to SPSS.

Study selection

Out of the whole list returned by the database search, one reviewer chose the most relevant titles. The abstracts of the remaining studies were reviewed first, following the aforementioned inclusion and exclusion criteria, after duplicates have been culled from the list using reference works. The other reviewer then categorized the research as “include,” “unsure,” or “reject”. An impartial third party was contacted in the event of a dispute.

Data synthesis

We expect that, owing to the nature of the topic, there was scarce of published randomized and non-randomized control studies accessible. In order to do this, we had two reviewers utilize a data extraction table to compile information on the study's design, population, inclusion/exclusion criteria, sample characteristics, methodology, and findings. This data was utilized to conduct in-depth analyses of the papers, from which appropriate conclusions were drawn to provide answers to the research questions. After assessing the title, abstract, and full text of the studies according to the eligibility criteria, the data of interest was collected using a standard form. The following information was collected:

- Authors,
- Date,
- Setting,
- Diagnosis of food allergy,

- Prevalence of food allergy,
- Health-related quality of life burden of food allergy,

Search strategy

The studies were identified through search in PubMed, Cochrane library, Embase, Scopus, Web of Science, CINAHL, OVID and google scholar databases. Grey literature was also searched. The search was conducted selecting articles published in all languages. Moreover, selected articles were chosen from peer-reviewed journals. The reference list of the selected articles was also screened to find additional articles. The selected period during the search was (2000– present).

Keywords
Allergy OR Food Allergy OR Child OR Pediatric OR Burden OR Health-related quality of life OR Allergen OR Anaphylaxis Immunoglobulin E OR Histamine OR Mast Cell OR Food Hypersensitivity OR Systematic Review

RESULTS

A total of 12,598 studies were identified in the search, all of them were assessed for eligibility, and 18 articles were included in this review (Figure 1).

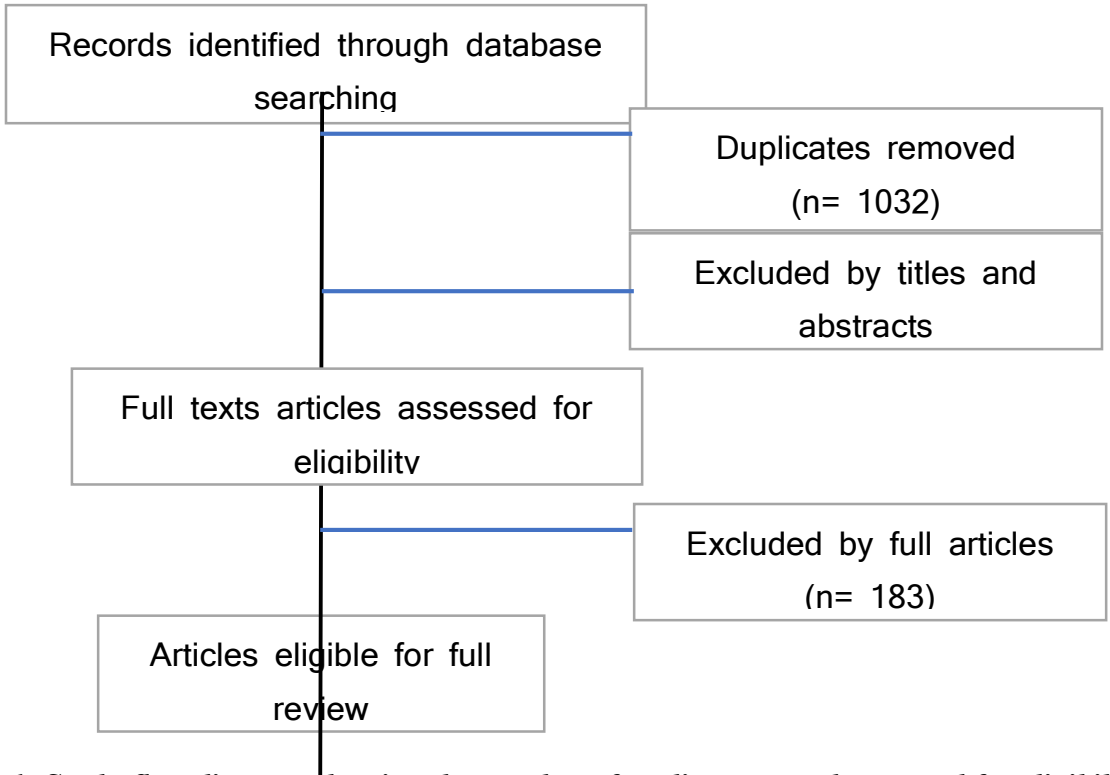


Figure 1: Study-flow diagram showing the number of studies screened, assessed for eligibility and included in the review

Epidemiology

In the last two to three decades, the prevalence of food allergies has increased, posing a public health problem, particularly in industrialized nations [6]. Between 6% and 8% of children in Europe [7] and the United States [8] suffer from food allergies, respectively.

It is difficult to determine the exact prevalence of food allergies in a population; in fact, the gold standard for diagnosis is the double-blind placebo-controlled food challenge (DBPCFC), which is not risk-free and can only be performed in specialized centers [6].

Due to this, the majority of studies rely on self-reported evidence or parent reports. This has led to an obvious and well-known overestimation of food allergy prevalence. In fact, surveys are frequently based on questionnaires that do not distinguish between IgE-mediated and non-IgE-mediated food allergies, but rather on reported symptoms that have not been confirmed by a DBPCFC [9,10].

Every food has the potential to cause an allergic reaction. Milk, egg, peanuts, tree nuts, shellfish, and fish are the foods most commonly associated with food allergies. In light of this, the review will concentrate on the prevalence of food allergies to the aforementioned foods [11].

There are few DBPCFC studies in the literature that demonstrate the occurrence of a food allergy. These include the EuroPrevall and HealthNuts studies [12-13]. The EuroPrevall research involved 12,049 children from nine European nations, of whom 9,336 were observed for two years. The incidence of cow's milk allergy was 0.54% (95% confidence interval [CI]: 0.41–0.70). In the Netherlands and the United Kingdom, the incidence was 1%, but it was less than 0.3% in Lithuania, Germany, and Greece [14]. The frequency of hen's egg allergy was 1.23 percent on average in children under the age of two, ranging from 2 percent in the United Kingdom to less than 0.1 percent in Greece [15].

The HealthNuts trial enrolled 5276 Australian children aged one year. It found a prevalence of 11% of food allergies proven with the oral food challenge assessing three foods: peanuts (3%; 95% confidence interval [CI], 2.4% to 3.8%), raw eggs (8.9%; 95% CI, 7.8% to 10%), and sesame (0.8%; 95% CI, 0.5% to 1.1%) [9]. The prevalence of peanut, egg, and sesame allergies was 1.9% (95% confidence interval [CI], 1.6% to 2.3%), 1.2% (95% CI, 0.9% to 1.6%), and 0.4% (95% CI, 0.3% to 0.6%), respectively [16]. Hazelnut was the most prevalent tree-nut allergy in Europe, whereas walnut and cashew were the most common tree-nut allergens in the United States [17].

A comprehensive evaluation of 61 research on the prevalence of fish and shellfish allergies revealed that fish allergy prevalence ranged from 0% to 7% and shellfish allergy prevalence ranged from 0% to 10.3% [18]. Understanding how many children are affected by food allergies and which ones are at the highest risk for developing them could provide insight into the genetic and environmental factors that cause food allergies and, consequently, which preventative measures could be used to reduce their prevalence.

Diagnosis

Numerous research [19-23] have attempted to determine the true diagnostic value of the SPT, and it has become evident that a negative test eliminates a food allergy by 90%, but a positive test does

not confirm the diagnosis but rather indicates a state of sensitization. Diagnostic decision levels have been determined in several investigations for the common allergens, often with a cutoff of 95%–100% positive predictive value (PPV), and they may boost the specificity of the SPT (Table 1).

IgE-mediated food allergies may also be studied using in vitro studies detecting s-IgE. Similar to the SPT, there is a link between the specific s-IgE concentration and the likelihood of a clinical response to a particular diet. Several research have tried to establish diagnostic predictive values. In general, undetectable levels of s-IgE are linked with a modest risk (10–25%) of an allergic response to the meal, but the risk rises as s-IgE levels rise. The values vary according on the allergen type, as shown in Table 1 [19].

When implementing these findings in clinical practice, it is important to remember that the published predictive values pertain to the particular groups examined, which may vary from the populations to whom these predictive tests must be applied. Consequently, a degree of prudence is always required with anticipated clinical risks [24].

Component-Resolved-Diagnosis (CRD), also known as the determination of specific IgE to a single allergen, is a new advancement in the diagnosis of food allergy. Various allergen components have been discovered and given a distinctive name consisting of the first three letters of the genus, the first letter of the species, and a number that typically indicates the chronological order of discovery [25]. For instance, 'Cor a 1' is the first allergen described in hazelnut (Corylus avellana), which is the scientific name. Cor a 1-2-8-9-10-11-12-13-14, TLP (thaumatin-like protein) have been identified as 10 components of hazelnut [26]. As documented for other allergenic molecules of other drugs [27], knowledge of some of these components, such as Cor a 14, has been linked with an increased risk of severe responses.

Table 1: Predictive value of cut-offs for skin prick test (SPT) weal diameter and specific immunoglobulin E (s-IgE) level for a positive oral food challenge (OFC) [19]

Food	**>95% PPV**	
	SPT (mm)	**s-IgE (KU/L)**
Egg white	≥7	≥7
Cow's milk	≥8	≥15
Peanut	≥8	≥14
Fish		≥20

However, the therapeutic implications of this knowledge have yet to be determined, and it should be noted that not all allergen molecules are presently accessible for laboratory testing, since more yet to be found.

The Basophil Activation Test (BAT) is an additional food allergy test that is transitioning from the laboratory to clinical practice [28]. When basophil cells of the patient are exposed to the offending food extract in a test tube, BAT may be viewed as an in-vitro OFC [29]. The BAT is based on flow cytometry, which measures the surface expression of activation markers on allergen-stimulated basophils. BAT has been tested in the detection of several food allergies, and its stated sensitivity varies from 77% to 98%, with specificity ranging from 75% to 100%. [30-35].

The DBPCFC is the gold standard for food allergy diagnosis. It involves the progressive administration of the suspicious meal under medical supervision in order to determine the clinical response or level of tolerance to the food. Due to the potentially hazardous nature of the test, it must be administered by competent professionals in a setting conducive to handling adverse responses. In the face of a substantial objective or persistent subjective response, it is typically stopped. In situations of uncertainty, it is repeated a few days later [25].

The OFC is often conducted in open or single-blind mode in regular clinical practice. The DBPCFC (in which both the patient and the physicians are unaware of whether they are consuming the "actual" test meal or a placebo) is conducted in questionable circumstances or for research reasons. If the provocation test is negative, it is best practice to confirm it with an open test in which the patient consumes the food in its original form, since this helps rule out false negatives (which occur between 1 and 3 percent of the time) [36].

Dietary elimination is a highly valuable diagnostic strategy for food allergy, particularly when persistent skin or gastrointestinal responses manifest. This is often utilized in the first stages of diagnosis to confirm the decrease of symptoms after a few weeks of exclusion. Elimination diets must always be short-term and performed for a specified reason [37]. Figure 2 shows the most frequent types of food causing allergy to children according to included studies.

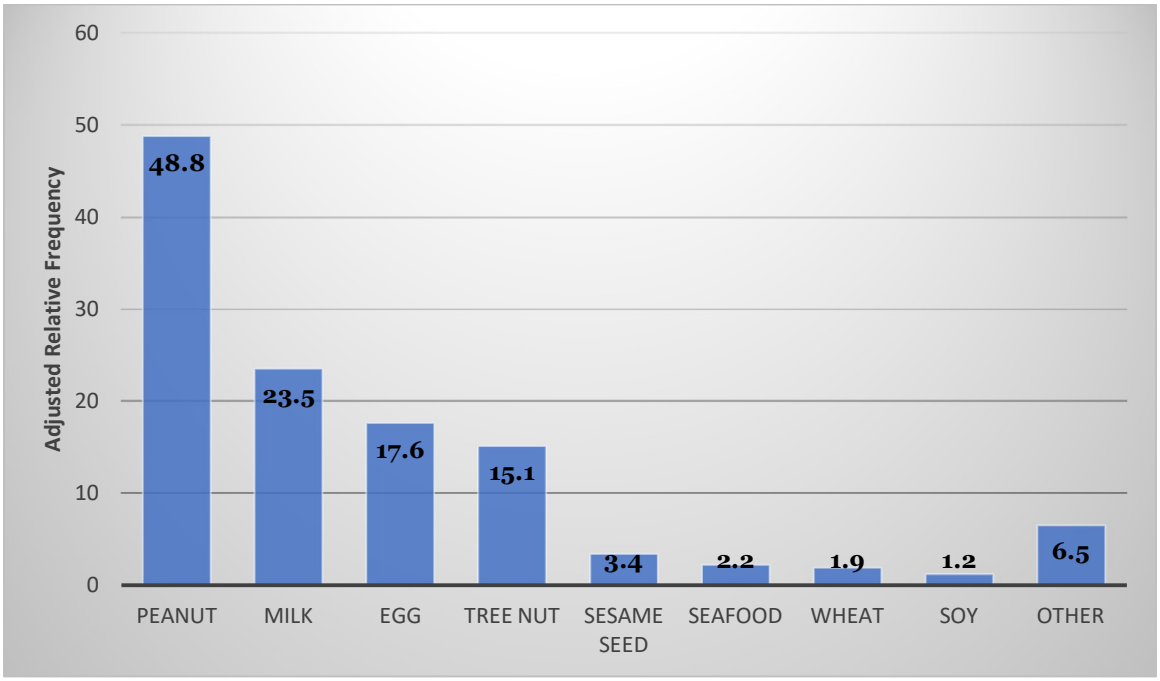


Figure 2: Most common food allergies among pediatric group

By the exception of IgE-mediated anaphylaxis, the diagnosis of food allergies should in reality always be verified with OFC. Given that tolerance to the allergenic food is often gained over time, it is recommended to regularly (once a year) do an in-vivo and in-vitro test of the individual's allergic condition, maybe also with an OFC [38].

The provocation–neutralization test, cytotoxic testing, kinesiology, and electrode dermal tests have little diagnostic value. Regarding the detection of specific IgG for food, their ineffectiveness undiagnosing a food allergy or programming an exclusion diet has been documented [38]. Consequently, there are a number of diagnostic tests for IgE-mediated food allergies; nonetheless, the clinical history remains the most significant diagnostic tool for achieving an accurate diagnosis. In vivo and in vitro assays, together with clinical history, may be utilized to lessen the requirement for OFC. The role of the physician is to analyze the findings of all available tests to determine whether an OFC is required for diagnosis.

Health Burden

The findings of this analysis indicate that children and adolescents with food allergy had a lower HRQL, especially older children and those with more severe indications of the illness. Compared to HRQL, the relationship between food allergy and psychosocial functioning is less evident; nonetheless, there is evidence relating food allergy to higher levels of psychological distress. Qualitative research shows that the majority of the hardship associated with childhood food allergy derives from concerns around exposures outside the house and the social repercussions of the disease. The current review also highlights several gaps in the literature, including a dearth of longitudinal research, research focusing on predictors of psychological distress among children and adolescents with food allergy, and studies comparing bullying rates in food-allergic and non-food-allergic samples. Not only should more focus be made on mitigating the social and psychological effects of food allergy, but also on identifying and supporting people who are most severely affected by the illness [39].

DISCUSSION

The prevalence of food allergy has been increasing over the past few decades in line with other allergic diseases [40], currently affecting approximately 5% of the population in Western countries [41]. This increase has occurred too rapidly to be explained by genetics alone. Although still today the knowledge of the pathogenesis of food allergy remains to be fully elucidated [40], it is known that host genetics, epigenetics and environmental exposures [42] play a role in determining food allergy risk. It has also been hypothesized that the increase in food allergy may relate to the simultaneous rise in vitamin D insufficiency and/or vitamin A sufficiency [43].

Once the allergen is identified, all guidelines recommend strict allergen avoidance [44-49]. In fact, this is the most effective form of preventing a reaction that can range from a non-serious skin reaction to a potential life-threatening anaphylactic reaction [50]. However, guaranteeing strict avoidance may be troublesome. There is the potential for nutritional deficiencies [50] accidental exposure, cross-contamination or even mislabelling of processed foods, despite existing labelling legislation [50-54]. Currently, precautionary allergen labelling (PAL; ‘may contain traces’) [51-

53] is an emerging issue due to excessive PAL by food processing companies, in order to avoid liability. This restricts patients to a diet very difficult to comply with, restricting the food-allergic patients to extremely limited food choices and leading to PAL disregard.

Food allergies impair quality of life (QoL) and are still the main cause of anaphylaxis in all age groups. Forty to 100% of fatal anaphylaxis occur due to foods consumed or prepared outside the home [50]. Patient education is crucial. In the case of infants and children, families, close relatives, friends and caregivers should be properly informed [53] of how to intervene when an anaphylactic reaction occurs, given these are potentially fatal [55]. Due to all the aforementioned, active therapy should be considered. Immunotherapy with allergens is the only treatment that can change the course of allergic disease. This is achieved by inducing allergen-specific immune tolerance in a subset of patients. Such induced tolerance [50-56] or sustained unresponsiveness [56-57], defined as the ability to ingest a previously allergenic food without symptoms regardless of long avoidance periods or irregular consumption, is the goal of immunotherapy with food allergens. However, and due to the risk of adverse reactions, including anaphylaxis [41], immunotherapy with food allergens is not recommended for routine clinical use. The procedure should be performed only in highly specialized centres with expert staff and adequate equipment [56-58]. Immunotherapy has several routes of administration and has been performed subcutaneously, sublingually, epicutaneously and orally. Oral immunotherapy (OIT) is more effective for food allergy than the other routes, in part because much larger doses can be administered. However, safety has been a major limitation [59].

Currently, and in order to improve the safety profile of OIT and maintain or increase its efficacy, adjuvant therapy with the IgE monoclonal antibody omalizumab has been extensively used in severe peanut allergy, milk allergy, egg allergy and multiple food allergy, with significant clinical improvement both in adults and children [59-65]. Moreover, omalizumab has the ability to prevent systemic reactions to OIT, thus enabling completion of treatment in patients who otherwise would have to stop it prematurely [65-70]. Taken together these results suggest that omalizumab may be particularly beneficial in the most severe patients, at high risk of fatal anaphylaxis. Omalizumab also allows a more rapid desensitization and has been shown to reduce the time to achieve maintenance dose [68-70]. An alternative approach to OIT is to use omalizumab as monotherapy, to prevent severe reactions upon allergen exposure. This approach seems effective, as reported in pilot experiences designed to establish proof of concept of the effectiveness of omalizumab monotherapy in food-allergic patients [70].

CONCLUSION

In conclusion, there has to be additional investigation into methods for optimizing treatment, such as mixing delivery routes to boost the efficiency and safety of immunotherapy. In addition, immunomodulatory drugs are under investigation and, if proven effective, might revolutionize the treatment of food allergies. Children's food allergies are on the rise and may have life-threatening consequences. The clinical history provides important background for interpreting the results of modern diagnostic testing. However, the diagnostic use of the oral meal challenge is limited.

Recently, new techniques for diagnosis have been developed. Treatments available now only try to reduce the frequency of anaphylactic attacks, and there is currently no cure or therapy that will create natural tolerance that will last a person's whole life. There is new data that suggests introducing the allergic food to babies at a younger age might help reduce the prevalence of food allergies.

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