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Relation between eosinophilic esophagitis and oral immunotherapy for food allergy: a systematic review with meta-analysis

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ABSTRACT

Background: The onset of eosinophilic esophagitis (EoE) after oral immunotherapy (OIT) has been repeatedly described in patients with immunoglobulin E (IgE)-mediated food allergy in recent years, but the relation between the 2 conditions has not been fully assessed and quantified.
Objective: To provide a systematic review of the evidence for an association between OIT and EoE.
Methods: Electronic searches were performed with keywords relating to EoE and OIT in the MEDLINE, EMBASE, and SCOPUS databases. Summary estimates were calculated. A fixed-effects model was used depending on heterogeneity (I^2). Risk of publication bias was assessed by funnel plot analysis and the Egger test.
Results: The search yielded 118 documents, 15 of which were included in the quantitative summary. Most reported information came from children undergoing peanut, milk, and egg OIT. Significant publication bias in favor of studies reporting the development of EoE after OIT was documented. The overall prevalence of EoE after OIT was 2.7% (95% confidence interval 1.7%–4.0%, $I^2 = 0\%$). Differences between medium-to high-quality studies and those of low quality were documented (3.5% vs 2.5%, respectively). EoE often resolved after OIT discontinuation; histologic remission of EoE achieved after allergen immunotherapy also was documented in 2 patients whose topical fluticasone treatment failed.
Conclusion: New onset of EoE after OIT occurs in up to 2.7% of patients with IgE-mediated food allergy undergoing this treatment strategy. The limited data on the utility of allergen immunotherapy as a therapy for EoE prevent a recommendation for this treatment option.

Introduction

The prevalence of food allergy is increasing worldwide. Currently, it is estimated to affect up to 5% of the overall European and American populations,[1–3] causing considerable morbidity, negatively affecting patients' quality of life, and having proved costly in medical care.[4,5] Furthermore, food-induced anaphylaxis is increasing.[6] Currently, the only approved treatment for food allergy is strict dietary avoidance. Therefore, therapies for food allergy are urgently needed.

Eosinophilic esophagitis (EoE) has emerged in the past few years as a relevant, chronic esophageal disorder that represents the second most common cause of chronic esophageal symptoms, after gastroesophageal reflux disease, in developed countries and the main cause of esophageal dysfunction in children and young adults.[7,8] Indeed, an increasing prevalence of EoE has been observed, with the disorder currently affecting up to 43 to 56 of 100,000 inhabitants (children and adults) in Europe and the United States.[9–11] Firm evidence supports EoE as a particular form of food allergy[12–14] frequently associated in patients with concurrent T-helper cell type 2 immunoglobulin E (IgE)-mediated conditions.[15] Evidence has shown that dietary treatments based on food avoidance have proven efficacy in inducing the remission of EoE,[16] in addition to swallowed inhaled corticosteroids and exclusive feeding with elemental diets.[17]

Oral immunotherapy (OIT) has emerged as a new promising allergen-specific therapy for patients with IgE-mediated food allergy,[18] with specific focus on the foods most frequently inducing severe anaphylactic reactions and the most common food allergens, such as cow's milk, peanuts, and eggs.[19] With multiple exploratory trials published, there is a clear progression and interest in making this a treatment option for patients with food allergies. There are still many questions to be answered and parameters to fine tune before OIT becomes an accepted option outside the research setting.

An association between EoE and OIT has been suggested in recent years by several case reports and cohort studies. The onset of EoE in pediatric[20–22] and adult[23,24] patients undergoing OIT has been repeatedly described. At the same time, some investigators have tried to solve EoE by undertaking subcutaneous allergen immunotherapy against atopy-associated conditions. Although the

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2 conditions are caused by aberrant immune responses to ingested antigens and are potentially responsive to a food-elimination diet, a causal relation between food OIT and EoE remains controversial.

The aim of this review was to evaluate, assess, and quantify research supporting the association between allergen OIT and EoE and its causal relation in children and adults.

Methods

This systematic review has been registered in the PROSPERO International Prospective Register of Systematic Reviews (www.crd.york.ac.uk/PROSPERO, registry number CRD42014009623) and reported in accord with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statements.[25]

Selection of Studies

A systematic literature search was performed independently by 2 authors (A.A. and J.M.T.) in 3 major bibliographic databases (PubMed, EMBASE, and SCOPUS) for the period up to March 2014. The search was not restricted to date or language of publication. To this end, a predetermined protocol was used in accord with the quality of reporting Meta-analyses of Observational Studies in Epidemiology.[26]

Comprehensive search criteria were used to identify articles dealing with the relation between EoE and immunotherapy. The thesauri for MEDLINE (MeSH) and EMBASE (EMTREE) were consulted using the following search strategy: (*eosinophilic esophagitis*) and (*immunotherapy* or *sublingual immunotherapy* or *desensitization, immunologic* or *immune tolerance*). For the SCOPUS database, only free text searches with truncations were carried out. The search was not restricted to date or language of publication.

In addition, the reference lists from retrieved articles and abstracts of conference proceedings (abstract books of the American Academy of Allergy, Asthma & Immunology and the European Academy of Allergy and Clinical Immunology Annual Meetings for 2004 through 2013) were examined to identify additional relevant studies. Two authors (A.J.L. and A.A.) independently screened the database search for titles and abstracts. If either reviewer judged that a title or abstract met the study eligibility criteria, the full text of the study was retrieved.

Inclusion Criteria

1. Studies were included in the systematic review if they provided original data on the occurrence of EoE in individual patients or a series of patients undergoing OIT or sublingual immunotherapy for an IgE-mediated food allergy, irrespective of study design (ie, randomized controlled trials, observational prospective and retrospective studies, and case series reports).
2. Studies evaluating the effectiveness of any kind of allergen immunotherapy in patients with previously demonstrated EoE also were considered if objective quantitative data on efficacy, in terms of histologic response, were provided (EoE remission was considered a peak eosinophil count <15 per high-power field in esophageal biopsies[15] after allergen immunotherapy).

Exclusion Criteria

1. Review articles on the treatment of EoE that did not provide original data on the causal relation between OIT and EoE.
2. Studies not carried out in humans.
3. Studies providing duplicate information (ie, repeated abstracts presented at different congresses or abstracts published later as a full-length article).
4. Subsets of cases or controls from a previously published article by the same researchers.
5. Studies using an allergen immunotherapy-based intervention simultaneously with another therapeutic alternative capable of decreasing esophageal inflammation (topical and systemic steroids and/or immunomodulatory drugs or dietary treatment) were not considered.

Quality Assessment

Cohort studies, case series, and case reports were evaluated for quality only if the article described all patients' demographic data, the diagnostic criteria for EoE, the proportion of patients undergoing sublingual immunotherapy or OIT subsequently developing EoE, treatment outcome, and study design. The type of food allergy being treated with immunotherapy also was assessed. Quality assessment was checked with a specific evaluation form for observational studies developed by the review group and based on the Strengthening the Reporting of Observational Studies in Epidemiology statements.[27] The study was considered to have a low risk of bias if each of the bias items could be categorized as low risk. Conversely, studies were judged to have a high risk of bias if just 1 of the items was deemed as high risk. Two authors (A.J.L. and A.A.) independently assigned each eligible study an overall rating of having a high, low, or unclear risk of bias. If there was any discrepancy, the third author (J.M.T.) was consulted.

Data Extraction

Two authors (A.J.L. and A.A.) independently extracted relevant information from each eligible study using a standardized data extraction sheet and proceeded to crosscheck the results. The data thus extracted included the trial study areas, the last name of the first author, publication year, age; sex and food allergy characteristics of the study participant, sample size, methodologic design, and study period. The effectiveness of allergen immunotherapy to induce EoE remission was assessed whenever possible. At the same time, data on key outcomes, including prevalence of EoE in patients undergoing sublingual immunotherapy or OIT, were extracted from all included studies. Disagreements between authors regarding data extraction were resolved through discussion.

Statistical Analysis

Response percentages for dietary intervention were summarized with a fixed- or random-effects meta-analysis weighted for the inverse variance, according to the DerSimonian-Laird method. Summary estimates, including 95% confidence intervals, were calculated for the incidence of EoE after OIT and for the efficacy of allergen immunotherapy on EoE remission.

Heterogeneity between studies was assessed by χ^2 test (Cochran Q statistic) and quantified with the I^2 statistic. In general, I^2 was used to evaluate the level of heterogeneity, assigning the categories low, moderate, and high to I^2 values of 25%, 50%, and 75%, respectively.[28] Publication bias was evaluated with a funnel plot, the asymmetry of which was assessed through the Egger test.[29]

For the primary outcome, planned subgroup analyses were performed based on the primary population studied (patients with IgE-mediated food allergy or patients with EoE) and age (adults vs children).

A sensitivity analysis was performed for quality (risk of bias) and type of document (full-length article vs abstract presented at conference proceedings). All calculations were made with StatsDirect 2.7.9 statistical software (StatsDirect Ltd, Cheshire, United Kingdom).

Results

The search strategy yielded 118 reports. Ninety-one documents were excluded after examining the title and abstract because they

did not fulfill the inclusion criteria. For the remaining 27 reports that were considered potentially relevant, the full text was retrieved for detailed evaluation. Of these, 14 were excluded because they were subsequently published as full-length articles or had been presented multiple times at different conferences (5), they lacked confirmatory esophageal biopsies (4), no data for calculations were provided (3), there was additional treatment to allergen immunotherapy (1), or there was no relation to OIT (1). Two reports recovered after tracking the reference list of the examined studies were added. Hence, 15 studies were included in the systematic review (Fig 1), and all were published after 2009. Of these, 12 referred to OIT and were considered for meta-analytical calculations. One additional study reported on sublingual pollen immunotherapy[23] and 2 others on subcutaneous aeroallergen immunotherapy,[30,31] which were considered but not included in the summary estimations.

The major characteristics of each study on OIT are presented in Table 1.[20–22,24,32–39]

Of the 12 documents on OIT, 4 were full-length articles and 8 were abstracts. Overall, data from 711 patients (567 children and 144 not determined) were retrieved, with the size of the various study populations ranging from 1 case to 247 cases in the largest series.

Development of EoE After Food Immunotherapy

Twelve studies reported on the appearance of EoE after food OIT; 8 were retrospective case series carried out in pediatric populations, 3 were individual case reports, and 1 was a randomized controlled trial of 40 children with IgE-mediated egg allergy undergoing OIT (Table 1). The most common foods investigated to induce tolerance were milk (193 patients, 38 of whom received baked milk), peanuts (172 patients), and eggs (100 patients). Twelve patients also received wheat OIT. Interestingly, 1 additional patient developed EoE after sublingual pollen immunotherapy.[23] In general, EoE was clinically and histologically resolved after food OIT discontinuation.[20,23,37]

In general, approximately 2.7% of patients newly developed EoE after OIT (95% confidence interval 1.7%–4.0%, $I^2 = 0\%$; Fig 2). Differences were observed when (separately) analyzing reports published as full-length articles vs abstracts (3.5% vs 2.5%; Fig 3). In these cases, results provided homogeneity in accordance with I^2 statistics (0% and 25.2%, respectively).

A significant publication bias was documented in the funnel plot analysis ($P < .009$ by Egger test; Fig 4). The funnel plot showed some studies on the negative effect side of the central line, indicating that these studies reported a lower incidence of EoE after OIT and even a lack of association between these conditions. As a result, it is worth considering that the actual occurrence of EoE after OIT might occur at a low prevalence.

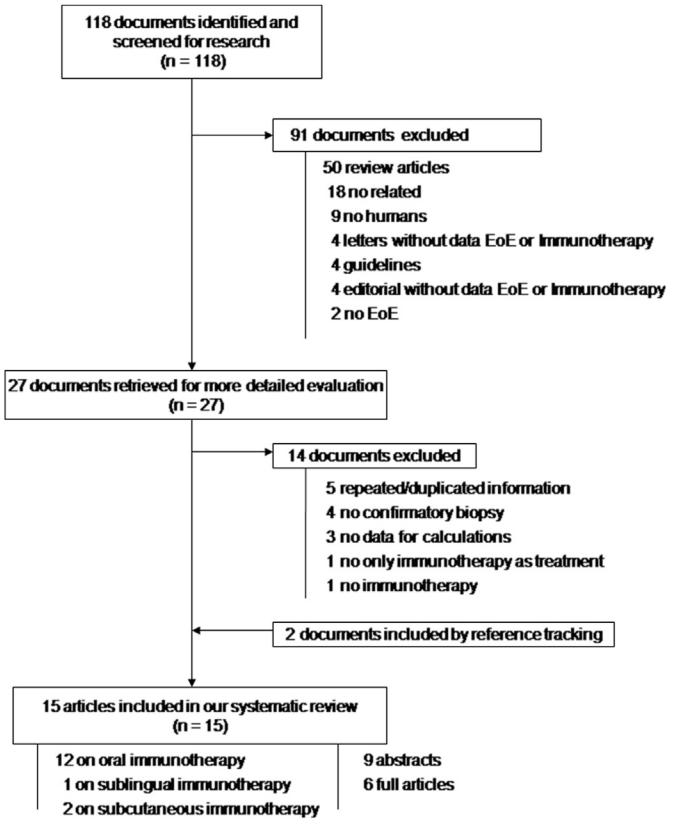

Figure 1. Flowchart for identifying studies that were included in and excluded from the systematic review with meta-analysis. EoE, eosinophilic esophagitis.

Allergen Immunotherapy as an Effective Treatment for EoE

The effectiveness of allergen immunotherapy in resolving EoE was documented in only 2 single case reports, but neither reported on OIT. The first described a 30-year-old man with topical steroid-refractory EoE and positive skin prick test reactions against dust mites, cockroaches, common weeds, and trees who received immunotherapy to these allergens over a course of 3 years without a relapse of symptoms and with complete resolution of eosinophilic infiltration.[31] In the second, a 4-year-old boy with dust mite–induced chronic rhinitis showed improvement within 2years after high-dose immunotherapy.[30]

Table 1
Demographics and characteristics of studies included in this systematic review on the relation between EoE and OIT

Study	Population	Type of OIT	N	Design	Outcome indicator
Full-length articles					
Hofmann et al,[22] 2009	children	peanut OIT	28	retrospective	1 of 28 developed EoE after OIT
Ridolo et al,[32] 2011	child	egg OIT	1	case report	1 developed EoE after OIT
Sánchez-García et al,[20] 2012	children	milk OIT	110	retrospective	3 of 110 developed EoE after OIT
Fuentes-Aparicio et al,[21] 2013	children	egg OIT	40	randomized clinical trial	1 of 40 developed EoE after OIT
Abstracts					
Mansfield et al,[24] 2009	children and adults	peanut OIT	25	retrospective	1 of 25 developed EoE after OIT
Wasserman et al,[33] 2011	not reported	peanut OIT	75	retrospective	4 of 75 developed EoE after OIT
Antunes et al,[34] 2011	child	milk OIT	1	case report	1 developed EoE after OIT
Vickery et al,[35] 2011	not reported	peanut OIT	44	retrospective	1 of 44 developed EoE after OIT
Stein et al,[36] 2012	children	milk OIT	247	retrospective	3 of 247 developed EoE after OIT
Ibrahim et al,[37] 2013	child	milk OIT	1	case report	1 developed EoE after OIT
Sugimoto et al,[38] 2013	children	OIT (egg, milk, wheat)	101	retrospective	1 of 101 developed EoE after milk OIT
Nowak-Wegrzyn et al,[39] 2013	children	baked milk	38	retrospective	2 of 38 developed EoE after immunotherapy

Abbreviations: EoE, eosinophilic esophagitis; OIT, oral immunotherapy.

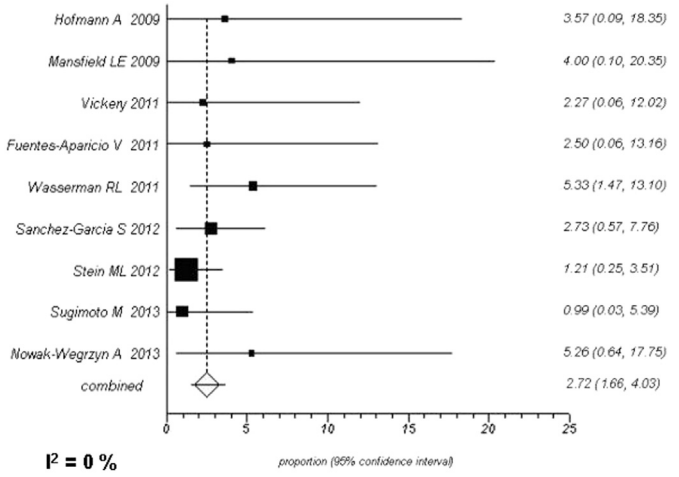

Figure 2. Overall combined prevalence figures for the onset of eosinophilic esophagitis after sublingual or oral food immunotherapy in patients with IgE-mediated food allergy. The percentage of eosinophilic esophagitis occurrence after food immunotherapy was extracted from each article and abstract and 95% confidence intervals were calculated using the exact binomial method. A random-effects model was used to calculate the overall effect size. An I^2 of 0% indicates that intra-study differences (heterogeneity) account for only 0% of the variability in the overall effect size.

Subgroup Analysis

An analysis of subgroups categorized according to quality and type of document was carried out (Table 2). Only 3 studies, which also were published as full-length articles, were considered to be of acceptable quality. The occurrence of EoE as a consequence of sublingual immunotherapy or OIT was higher in studies of high to medium quality compared with that found in low-quality studies (3.51% vs 2.5%, respectively).

Discussion

This systematic review of 12 recently published documents on the relation between OIT and the subsequent development of EoE showed that up to 2.7% of patients with IgE-mediated food allergy undergoing this treatment option could develop this complication. Available results, which predominantly come from research including pediatric patients, were shown to be highly homogeneous and did not significantly vary according to the type of document or the quality of the research.

The progressive expansion of food allergy, especially in industrialized countries, has motivated the introduction of new treatment modalities that try to achieve permanent tolerance in patients with IgE-mediated food allergy and prevent severe events in patients with anaphylaxis through promoting food desensitization. The desensitized state, which is defined as the ingestion of a substantial amount of food in the home diet without severe reaction to accidental exposures, has been shown to be achieved by approximately 50% to 75% of children treated with OIT.[19] The rate of permanent tolerance achieved after OIT is unknown. However, researchers agree that a longer period of OIT treatment can result in permanent tolerance, which may be considered the most ambitious objective to pursue.

Allergen immunotherapy modifies allergic disease expression, although the exact mechanism beyond desensitization by OIT is not clear. This therapy results in an increase in suppressor T-cell activity mediated by T-helper cell type 17, the decrease of specific IgE serum levels and activity, and an increase in serum levels of allergen-specific IgG4. In fact, immunologic changes have been associated with the ability to tolerate larger amounts of milk, including the detection of increased levels of IgG4, according to a recent double-blinded, placebo-controlled study carried out in children with milk allergy.[40] Interestingly, the possibility of IgG4 being involved in the pathophysiology of EoE has been raised. Clayton et al[41] demonstrated that homogenates of esophageal tissues from patients with EoE was characterized by a 45-fold increase in IgG4 compared with controls, but no significant increases in other IgG subclasses, IgM, or IgA. A dense perivascular IgG4 plasma cell infiltration also was documented in patients with EoE, which was absent in control samples. This association of EoE with IgG4 deposits needs further investigation to elucidate a possible causative mechanism. In fact, the involvement of the same food to which OIT was carried out owing to an IgE-mediated allergy in subsequently triggering EoE has been repeatedly documented.[20,23,37]

Side effects during the initial dosage increase and during home dosing are commonly described in patients undergoing OIT.[42] Although most reactions are mild and decrease in frequency with the longer duration of OIT,[19] severe anaphylactic reactions requiring epinephrine administration have been reported. Some controlled risks can be taken in the attempt to avoid any other severe anaphylactic reaction. The putative development of EoE after OIT, triggered by the same offending food that caused an IgE-mediated

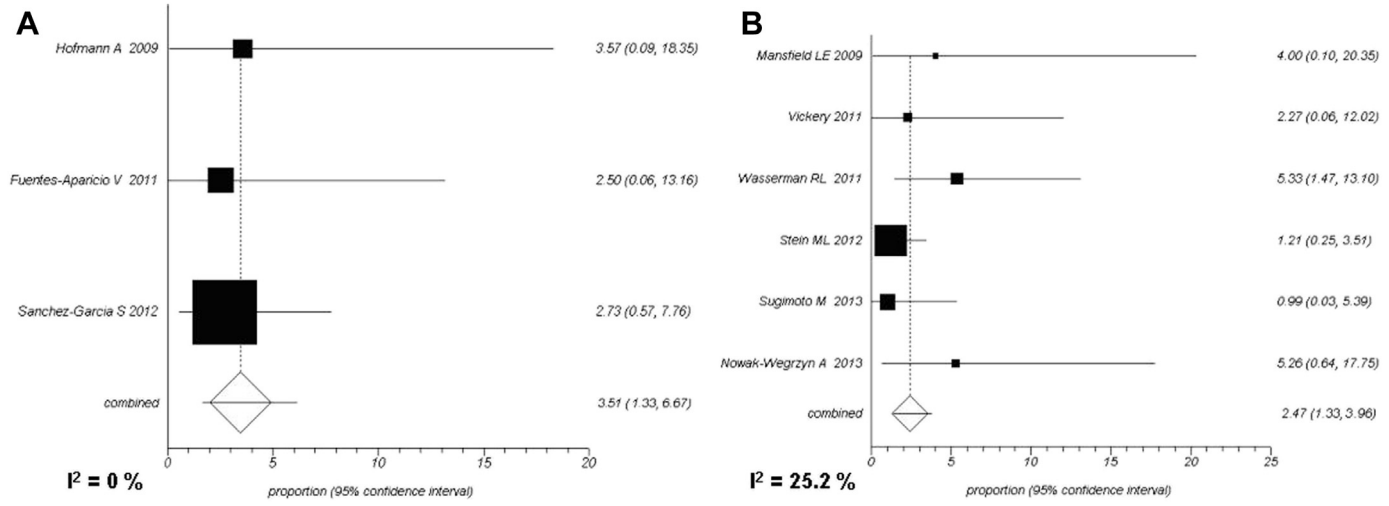

Figure 3. Subgroup analysis of studies evaluating the prevalence of eosinophilic esophagitis after oral food immunotherapy in patients with IgE-mediated food allergy in research published as *(A)* full-length articles and *(B)* abstracts. I^2 denotes intra-study differences of statistical heterogeneity.

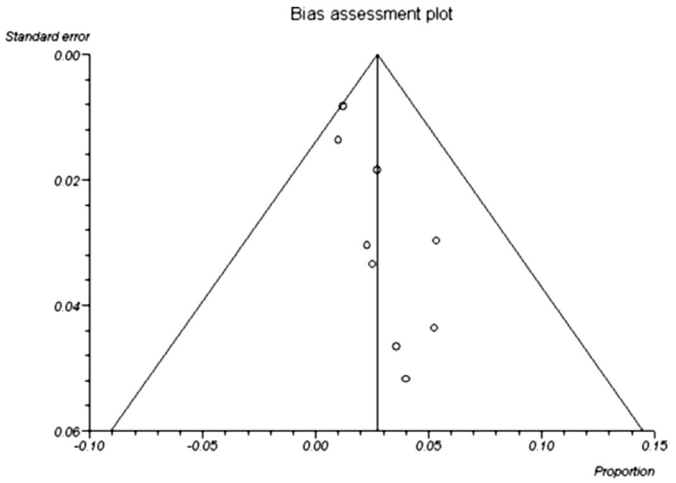

Figure 4. Begg funnel plot of studies evaluating the publication bias of studies on the onset of eosinophilic esophagitis after sublingual or oral food immunotherapy in patients with IgE-mediated food allergy. Statistically significant publication bias was found in favorable studies positively reporting the development of eosinophilic esophagitis after oral immunotherapy.

allergy, also should be taken into account as a potential side effect of OIT, but it should not preclude this treatment option in all patients. Indeed, this meta-analysis documented that EoE appeared in "only" up to 4% of patients undergoing OIT. Although EoE significantly affects quality of life in affected patients[43,44] and occasionally causes severe complications,[45,46] no fatalities have been related to this disease to date compared with anaphylactic reactions.

This systematic literature search also retrieved information on the potential utility of allergen immunotherapy to induce histologic and clinical remission of EoE. However, available data on this possibility are very limited and restricted to 2 individual cases, which prevent any definitive conclusions. In fact, despite EoE being widely considered a particular form of food allergy, the involvement of foods triggering EoE was not present in all patients, because the response to complete food allergen avoidance by exclusively feeding patients with an amino acid–based elemental diet is not 100%[16]; the disease could be triggered and maintained by airborne allergens in fewer than 10% of patients who do not respond to an elemental diet. Several investigators also have documented seasonal variations in the diagnosis of EoE, because significantly more cases were diagnosed during the spring and summer than during the autumn and winter months.[47,48] However, one cannot assume from this a direct etiologic relation, and the most common complaint of worsening environmental allergies also provides a better chance to achieve a diagnosis of an associated EoE merely through accumulating symptoms.

The strength of this research lies in the fact that it compiled the results of an exhaustive literature search of 3 major databases; recovered studies were critically appraised according to their methodologic aspects and different authors independently extracted the data from the studies included. Thus, the possibility of not recovering all the relevant information published on the causal association between OIT and EoE was minimized by this exhaustive search. A significant publication bias was demonstrated by funnel plot analyses; few studies on the negative effect side (at the left hand of the central line) indicated reporting biases, which arise when the dissemination of research findings is influenced by the nature and direction of results. In the present case, funnel plot analysis showed a trend toward reporting a positive association between OIT and EoE and a lack of studies in which EoE was not a consequence of OIT. The present search, which was specifically designed to retrieve documents describing these 2 conditions, definitively influenced this publication bias and may have contributed to the assumption that EoE after OIT appears more often that its real prevalence. In any case, the 2.7% can undoubtedly be considered the upper prevalence limit for this complication of OIT, with an extremely high concordance according to I^2 statistics. In addition, most retrieved documents were case reports and retrospective case series, with only a single randomized controlled trial included. Despite the high homogeneity of these results independent of study design, quality, and type of publication, a publication bias remains.

In conclusion, this research found the development of EoE in up to 2.7% of patients with IgE-mediated food allergy undergoing OIT. In contrast, there was a lack of sufficient support to consider allergen immunotherapy-based treatment for patients with EoE. Further well-designed original research is needed to confirm the results of this systematic review.

Table 2
Summary of prevalence of EoE onset in patients with IgE-mediated food allergy undergoing oral food immunotherapy[a]

Interventions	Incidence	n
EoE after immunotherapy (overall)	2.72% (1.7–4)	9
Subgroups according to quality (type of publication)		
Medium to high (full-length article)	3.51% (1.3–6.7)	3
Low (abstract)	2.5% (1.3–4)	6

Abbreviation: EoE, eosinophilic esophagitis.
[a]Remission rates (95% confidence intervals) for documents published as articles and as abstracts.

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