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Association between atopic manifestations and eosinophilic esophagitis

A systematic review and meta-analysis

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ABSTRACT

Background: Eosinophilic esophagitis (EoE) has repeatedly been associated with atopic manifestations, which are reported more frequently in these patients than in the general population.
Objective: To systematically assess the evidence and strength of the associations between EoE and atopy.
Methods: We performed a systematic search of the MEDLINE, EMBASE, and SCOPUS databases for case-control studies comparing the frequency of atopic diatheses among patients with EoE and control subjects representing the general population without EoE. Using random-effects meta-analyses, we calculated summary estimates, including 95% confidence intervals (CIs), for bronchial asthma, atopic rhinitis, and eczema. Publication bias risks were assessed by means of funnel plot analysis and specific statistical tests.
Results: Of the 2,954 references identified, data were collected from 21 studies, including a total of 53,542 patients with EoE and 54,759 controls. The criteria for defining a diagnosis of atopy in patients with EoE or controls was not structurally considered in most of the studies. Overall, allergic rhinitis was significantly more common among patients with EoE compared with control subjects (odds ratio [OR], 5.09; 95% CI, 2.91–8.90; $I^2 = 86.7\%$) as were bronchial asthma (OR, 3.01; 95% CI, 1.96–4.62; $I^2 = 84.5\%$) and eczema (OR, 2.85; 95% CI, 1.87–4.34; $I^2 = 57.1\%$). Food allergies and other atopic conditions were also assessed. No significant publication bias was found for studies dealing with allergic rhinitis and eczema in EoE.
Conclusion: Despite pointing to a significant association between atopy and EoE, most of the studies provided no normalized diagnostic criteria for atopy. Further research should provide clear and standardized definitions of such conditions.
Trial Registration: www.crd.york.ac.uk/PROSPERO Trial Identifier: CRD42016036161.

Introduction

Eosinophilic esophagitis (EoE) is a chronic, immune-mediated, inflammatory disorder defined symptomatically by esophageal dysfunction and histologically by eosinophil-predominant inflammation of the esophagus.[1,2] Currently, EoE constitutes the most prevalent cause of chronic dysphagia among children and young adults in the developed world.[3]

Since the initial descriptions of the disease more than 2 decades ago, EoE has been defined as a particular form of food allergy characterized by a T_H2-type immune reaction,[4] which could be reversed by avoiding exposure to certain food protein antigens in the diet.[5] In addition, EoE has repeatedly been recognized as an atopy-associated disorder, with most pediatric and adult patients presenting with a personal medical and/or family history of atopic conditions, such as asthma, rhinitis, conjunctivitis, eczema, and IgE-mediated food allergies,[1] along with food sensitizations identified through positive results in skin allergy tests.[6,7] Such is this association that the presence of atopic manifestations in a patient with esophageal symptoms (especially in the form of dysphagia or food impaction) constitutes a characteristic marker of EoE.[8]

Several studies have provided information on the prevalence of different atopic conditions in pediatric[9,10] and adult[11,12] patients with EoE and compared them with several groups of control subjects. The findings indicate that, overall, patients with EoE have

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a higher frequency of asthma, rhinoconjunctivitis, eczema, and food allergies than control groups; however, definitions for the associated atopic conditions have not always been provided,[13,14] and the selection process for the controls has not been such that they can be considered universally representative of the general population without EoE.[10,15] These 2 limitations have hampered researchers in their efforts to clearly assess the magnitude of the association between atopy and EoE.

The aim of this study was to conduct a systematic review of the literature and to perform a meta-analysis of the retrieved data to evaluate the presence of atopic diatheses in patients with EoE and to summarize the prevalence of atopic conditions in pediatric and adult patients with EoE compared with the non-EoE control population.

Methods

Protocol Registration

The protocol of this review has been registered with the international Prospective Register of Systematic Reviews (PROSPERO; www.crd.york.ac.uk/PROSPERO Trial Identifier: CRD42016036161) and has been reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.[16]

Search Strategy

A highly sensitive search strategy was designed to identify and retrieve all documents on the association between atopy and EoE in children and adults. This systematic literature search was performed independently by 2 researchers (A.A. and A.J.L.) on April 6, 2016, in 3 major bibliographic databases (PubMed, EMBASE, and Scopus) for the period up to March 2016. The search was not restricted with regard to the language of publication. A predetermined protocol was used in accordance with the quality standards for reporting meta-analyses of observational studies in epidemiology.[17]

We consulted the thesauri for MEDLINE (MeSH) and EMBASE (EMTREE) using the following search strategy: ("eosinophilic esophagitis" OR "eosinophilic oesophagitis") AND ("asthma" OR "rhinitis, allergic [MeSH Terms]" OR "rhinitis" OR "conjunctivitis, allergic [MeSH Terms]" OR "conjunctivitis" OR "dermatitis, atopic [MeSH Terms]" OR "dermatitis" OR "eczema" OR "food hypersensitivity [MeSH Terms]" OR "food allergy" OR "anaphylaxis" OR "atopy").

As for the SCOPUS database, only free-text searches with truncations were performed. To identify additional relevant studies, we also examined the reference lists from all retrieved articles and the abstracts of conference proceedings published in annual abstract books between 2006 and 2015 for the following organizations: American Association of Allergy, Asthma, and Immunology, European Academy of Allergy, Asthma, and Immunology, American Gastroenterological Association (*Digestive Disease Week*), American College of Gastroenterology, and the United European Gastroenterology.

Inclusion Criteria

Observational prospective and retrospective case-control studies and case series reports were all included if data on the frequency or prevalence of the various atopic manifestations in patients and controls were provided. A diagnosis of EoE was based on esophageal symptoms plus an esophageal eosinophilic infiltration of 15 eosinophils per high-power field or more at baseline endoscopy, as reported in source documents. For control subjects, EoE had to have been ruled out by means of esophageal biopsies. The diagnostic criteria used by the original authors to define each atopic comorbidity were also taken into consideration.

Exclusion Criteria

Review articles on EoE that did not provide original data on the frequency of atopic manifestations along with clinical guidelines and consensus documents were excluded. Studies not performed on humans or providing duplicated information (ie, repeated abstracts presented at different congresses or abstracts published later as a full article) were also excluded. Likewise, subsets of cases or controls from previously published articles by the same authors were also excluded.

Study Selection

The titles and abstracts of the retrieved documents were independently checked by 2 reviewers (A.A. and J.G.-C.) according to our selection criteria. Full-text copies of potentially relevant studies were obtained, and the same reviewers independently assessed each article's eligibility for inclusion. Any discrepancies were resolved by consensus or arbitration by a third reviewer (A.J.L.).

Risk of Bias Assessment

Case-control studies and case-control series were evaluated for risk of bias if the article described the criteria used to diagnose EoE and each atopic manifestation assessed and also included the following information: demographic data for patients and controls, study period, and study design. Risk of bias was evaluated with the aid of the Joanna Briggs Institute critical appraisal checklist for case-control studies,[18] accessible on http://joannabriggs.org/research/critical-appraisal-tools.html. Studies were considered to be at low risk for bias if each of the bias items could be categorized as low risk. On the contrary, studies were judged to have a high risk of bias if even one of the items was deemed high risk. Using these criteria, 2 researchers (A.A. and A.J.L.) independently gave each eligible study an overall rating of high, low, or unclear risk of bias; disagreements were resolved by consensus.

Data Extraction

Four reviewers (J.G.-C., A.A., M.M.C.-M., and A.J.L.) independently extracted relevant information from each eligible study using a standardized data extraction sheet and then proceeded to cross-check the results. The data extracted included the last name of the first author, publication year, country, study design, age and sex of study participants, sample size, study period, and, whenever possible, selection criteria for control groups as well as definition criteria for atopic manifestations. At the same time, data on the prevalence of each atopic manifestation assessed in patients with EoE and in controls were extracted from all studies included. Disagreements between reviewers regarding data extraction were resolved through discussion. If necessary, the original authors of the various studies were contacted by e-mail for additional information.

Statistical Analysis

Estimates for the prevalence of each atopic manifestation in patients with EoE and controls were summarized with the aid of a fixed- or random-effects meta-analysis, depending on intrastudy heterogeneity, weighted for inverse variance following the method elaborated by DerSimonian and Laird. Summary estimates, including 95% confidence intervals (CIs), were calculated for each season and month, whenever possible.

Heterogeneity among studies was assessed by means of a χ^2 test (Cochran Q statistic) and quantified with the I^2 statistic. Generally, 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.[19] Publication bias was evaluated with the aid of a funnel plot, the asymmetry of which was assessed with the Begg and Mazumdar correlation rank test[20] and with the Egger[21] and Harbord tests.[22]

For the primary outcomes, planned subgroup analyses were performed based on patient age (children vs adults), document

type (full-length article vs abstract presented at a conference), and risk of bias (low vs high). All calculations were made with StatsDirect statistical software, version 2.7.9 (StatsDirect Ltd, Cheshire, England). Differences in estimates among subgroups were calculated with the aid of random-effects meta-regression using aggregate-level data. The SEs in each atopic manifestation for all studies had previously been estimated for all the dependent variables. These last analyses were performed with STATA 12.0 software (StataCorp, College Station, Texas).

Results

Literature Search

The search strategy yielded 2,954 references; 2,868 were excluded after examining the title and abstract because they did not fulfil the inclusion criteria. Of the remaining 86 documents retrieved for complete evaluation, 65 were excluded for the following reasons: lack of data on atopy frequency for calculations (n = 41), no control group (n = 14), repeated or duplicated

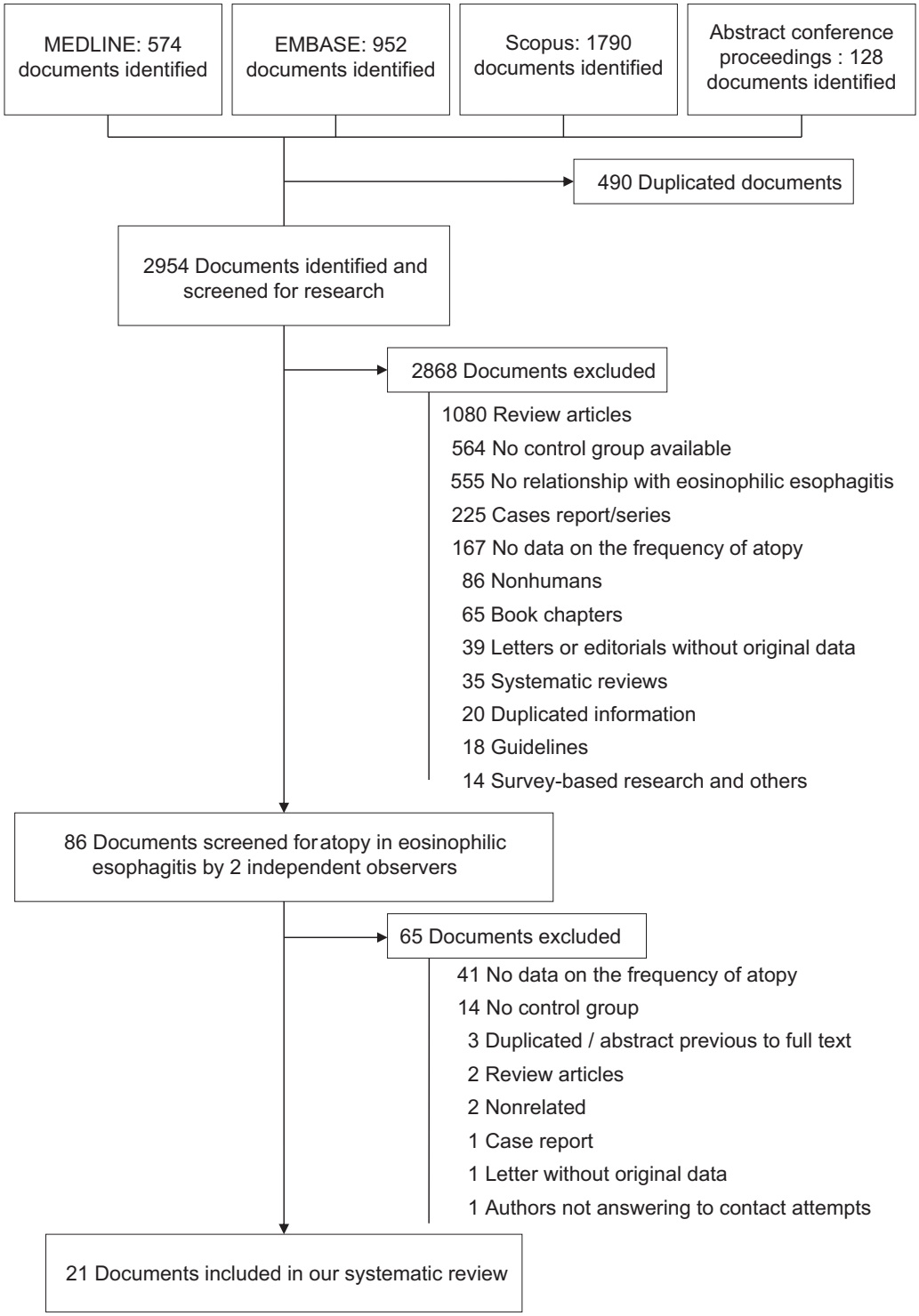

Figure 1. Flowchart for the process of identifying studies that were included in and excluded from the systematic review.

Table 1
Demographics and Characteristics of Concurrent Atopic Manifestations of EoE and Control Subjects in Studies Included in Our Systematic Review and Meta-analysis

Study	No. of patients		Population	Asthma, no. (%)		Rhinitis, no. (%)		Eczema, no. (%)	
	EoE	Non-EoE		EoE	Non EoE	EoE	Non EoE	EoE	Non EoE
Aceves et al,[25] 2009	35	27	Children	9 (25.7%)	4 (14.8%)	24 (68.6%)	12 (44.4%)	-	-
Cassell et al,[35] 2009	35	7	Children	15 (42.9%)	2 (28.6%)	-	-	15 (42.9%)	1 (14.3%)
Dellon et al,[11] 2009	BA:130 FA:85 R+E:130	BA: 208 FA: 167 R+E: 193	Both	39 (30)	25 (12)	-	-	-	-
Dellon et al,[34] 2015	81	144	Adults	22 (27.2)	33 (22.9)	50 (61.7)	69 (47.9)	5 (6.2)	10 (6.9)
DeBrosse et al,[27] 2011	42	167	Adults	-	-	19 (45.2)	45 (26.9)	-	-
Duffeyet al,[37] 2016	4,009	>100,000	Both	OR: 3.95	-	-	-	-	-
Foroutan et al,[14] 2010	6	62	Adults	1 (16.7)	1 (1.6)	3 (50)	3 (4.8)	0 (0)	1 (1.6)
Garcia-Compean et al,[12] 2011	6	144	Adults	-	-	-	-	-	-
Ravi et al,[28] 2011	BA:130 R:207	59	Adults	62 (47.7)	8 (13.6)	142 (68.6)	9 (15.2)	-	-
Joo et al,[29] 2012	8	114	Adults	1 (12.5)	5 (4.4)	3 (37.5)	9 (7.9)	2 (25)	5 (4.4)
Jensen et al,[9] 2013	31	26	Children	18 (58.1)	10 (38.5)	-	-	-	-
Leung et al,[10] 2015	23	14	Children	13 (56.5)	5 (35.7)	13 (56.5)	7 (50)	7 (30.4)	2 (14.3)
Mackenzie et al,[24] 2008	31	230	Adults	13 (41.9)	41 (17.8)	-	-	-	-
Mansoor et al,[38] 2010	12,770	45,516,840	Both	3,258 (25.5)	2,503,426 (5.5)	3,333 (26.1)	2,230,325 (4.9)	2,605 (20.4)	2,503,426 (5.5)
Mulder et al,[30] 2013	44	44	Both	14 (31.8)	14 (31.8)	10 (22.7)	2 (4.5)	6 (13.6)	1 (2.3)
Peterson et al,[36] 2015	4,423	22,627	Both	OR: 4.0		-		OR: 3.0	
Sealock et al,[31] 2013	31	966	Adults	4 (12.9)	67 (6.9)	-	-	-	-
Slae et al,[32] 2013	102	167	Children	48 (47.1)	55 (32.9)	63 (61.8)	59 (35.3)	58 (56.9)	64 (38.3)
Sugnaman et al,[23] 2007	45	BA & R: 25,906 E: 2,968 A:142	Children	30 (66.7)	2927 (11.3)	42 (93.3)	2759 (10.6)	25 (55.5)	959 (32.3)
Veerappan et al,[26] 2009	25	360	Adults	8 (32)	39 (10.8)	-	-	4 (16)	24 (6.7)
Zafra et al,[33] 2013	25	17	Both	-	-	20 (80)	5 (29.4)	-	-

Abbreviations:
A, anaphylaxis; BA, bronchial asthma; E, eczema; EoE, eosinophilic esophagitis; FA, food allergy; OR, odds ratio; R, rhinitis.
[a]Type of control subjects: (1) gastroesophageal reflux patients; (2) patients undergoing endoscopy (EoE ruled out); (3) database-registered individuals; (4) healthy volunteers (endoscopically assessed).
[b]Atopy-defining method: (5) patient- or parent-reported atopic background; (6) allergist/immunologist-diagnosed atopic disease; (7) codified database; (8) nondefined.

information (n = 3), no relation to the research topic (n = 2), review articles (n = 2) or letters (n = 1) with no original data, or single case reports (n = 1). In addition, the authors of one of the articles did not answer our request for further clarification. In the end, 21 studies (comprising 17 full articles[9–12,14,23–34] and 4 abstracts[35,36]) were included in the quantitative summaries of our systematic review (Fig 1). The references retrieved consisted of 11 prospective and 9 retrospective observational studies along with a case-control design and a population database study. They were conducted in the United States (n = 13), Canada (n = 3), Mexico (n = 1), Spain (n = 1), Iran (n = 1), Korea (n = 1), and Australia (n = 1). Characteristics of the studies included are summarized in Table 1. Quality assessment revealed 9 of the 21 retrieved studies having a low risk of bias (eTable 1).

Overall, data from 53,423 individual patients with EoE and 54,759 individual control subjects were retrieved and compared. Two of the selected studies also included control groups, but from population databases.[36,37]

Control Populations

The frequency or prevalence of the different atopic manifestations among patients with EoE was compared with that observed in several types of control populations, including series of patients with gastroesophageal reflux disease (GERD),[9,11,12,25,30,33,35] other patients,[14,24,26,27,29,31,32,34] and healthy volunteers,[10,27] all of whom were endoscopically assessed with a diagnosis of EoE specifically ruled out. In all cases, EoE was considered as independent from GERD and other upper gastrointestinal tract diseases. Some studies included database-registered subjects as control groups.[23,28,36–38]

Table 1 (Continued).

Food allergy, no. (%)		Other atopy, no. (%)		Period	Design	Country	Type of control subjects[a]	Atopy-definition method[b]
EoE	Non EoE	EoE	Non EoE					
11 (31.4%)	2 (7.4%)	-	-	-	Prospective Case - control	United States	(1)	(6)
-	-	**Any Allergy Disease**		-	Retrospective chart review	United States	(1)	(7)
		33 (94.3)	4 (57.1)					
22 (35.9)	5 (3)	**Allergic rhinitis/dermatitis**		2000–2007	Retrospective Case - control	United States	(1)	(6)
		48 (36.9)	27 (14)					
35 (43.2)	21 (14.6)	**Any Atopic disease**		2011–2013	Prospective Case - control	United States	(2)	(5)
		56 (69.1)	83 (57.6)					
15 (35.7)	22 (13.2)	-		1982–1999	Retrospective nested case – control	United States	(2+4)	(5)
-	-	-		-	Retrospective Population-databased	United States	(3)	(7)
0 (0)	1 (1.6)	**Atopy**		2006	Cross-sectional study	Iran	(2)	(5)
		6 (100)	10 (16.2)					
-	-	**Atopy**		2007–2009	Prospective	Mexico	(1)	(8)
		4 (66.7)	32 (22.2)					
-	-	-	-	2002–2007	Retrospective	United States	(3)	(7)
1 (12.5)	7 (6.1)	-	-	2009	Prospective	Korea	(2)	(5)
20 (64.5)	8 (30.8)	**Environmental allergy**		2004–2010	Case-control	United States	(1)	(5)
		23 (74.2)	14 (53.8)					
7 (30.4)	2 (14.3)	**Environmental allergy**		2010–2013	Prospective	Canada	(4)	(5)
		6 (26.1)	5 (35.7)					
13 (41.9)	24 (10.4)	-		2005–2007	Prospective	United States	(2)	
2,260 (17.7)	637,236 (1.4)	**Drug Allergy**		6,099,257 (13.4)	Population database	United States	(3)	(7)
		4,227 (33.1)	6,099,257 (13.4)					
15 (34.1)	3 (6.8)	**Drug Allergy**		1997–2009	Retrospective Case-control	Canada	(1)	(6)
		1 (2.3)	5 (11.4)					
		Environmental allergy						
		19 (43.2)	6 (13.6)					
		Atopy						
		30 (68.2)	19 (43.2)					
-		**Anaphylaxis**		-	Retrospective Case-control	United States	(3)	(7)
		OR: 13.3						
-	-	**Seasonal allergy**		-	Prospective Case-control	United States	(2)	(5)
		10 (32.3)	161 (16.7)					
10 (9.8)	4 (2.4)	-	-	-	Cross-sectional Case-control	Canada	(2)	(5)
-	-	**Anaphylaxis**		-	Prospective	Australia	(3)	(6)
		11 (24.4)	3 (2.1)					
4 (16)	30 (8.3)	**Seasonal Allergy**		2007	Prospective Cohort	United States	(2)	(5)
		11 (44)	142 (39.4)					
11 (44)	3 (17.6)	-	-	2009–2011	Prospective Case-Control	Spain	(1)	(6)

Diagnostic Criteria for Atopy in Patients With EoE

The criteria for defining a diagnosis of atopy among patients with EoE and control subjects varied widely across the different studies, from self-reported or parent-reported atopic background[9,10,14,24,26,27,29,31,32,34] to strict allergist/immunologist-provided diagnoses.[11,23,25,30,33] In addition, atopic background was sometimes defined according to information registered in a database,[28,35–38] and in a few studies,[12] it was reported with no details on the diagnostic method.

Frequency of Atopic Manifestations in Patients With EoE

Bronchial asthma

Sixteen studies examined the frequency of asthma in patients with EoE compared with controls. Overall, bronchial asthma was significantly more common among patients with EoE than in control subjects, with an odds ratio (OR) of 3.01 (95% CI, 1.96–4.62; $I^2 = 84.5\%$) (Fig 2). Similar ratios were found when children and adults were analyzed separately, with ORs of 3.04 (95% CI, 2.26, 4.4) and 2.92 (95% CI, 1.71, 4.98), respectively (Table 2).

Subgroup analyses according to type of document (full-text article vs abstract) and risk of bias (low vs high) revealed higher OR values for the latter in both cases, although these differences did not reach statistical significance (Table 3).

According to the Egger test results, there was a significant publication bias regarding the frequency of asthma in EoE ($P = .01$), suggesting the absence of studies with small sample sizes reporting a lack of association between EoE and atopy (eFig 1).

Allergic rhinitis

The comparative frequency of allergic rhinitis in patients with EoE compared with control subjects was evaluated in 12 studies (Fig 3), which together had a pooled OR of 5.09 (95% CI, 2.91–8.90;

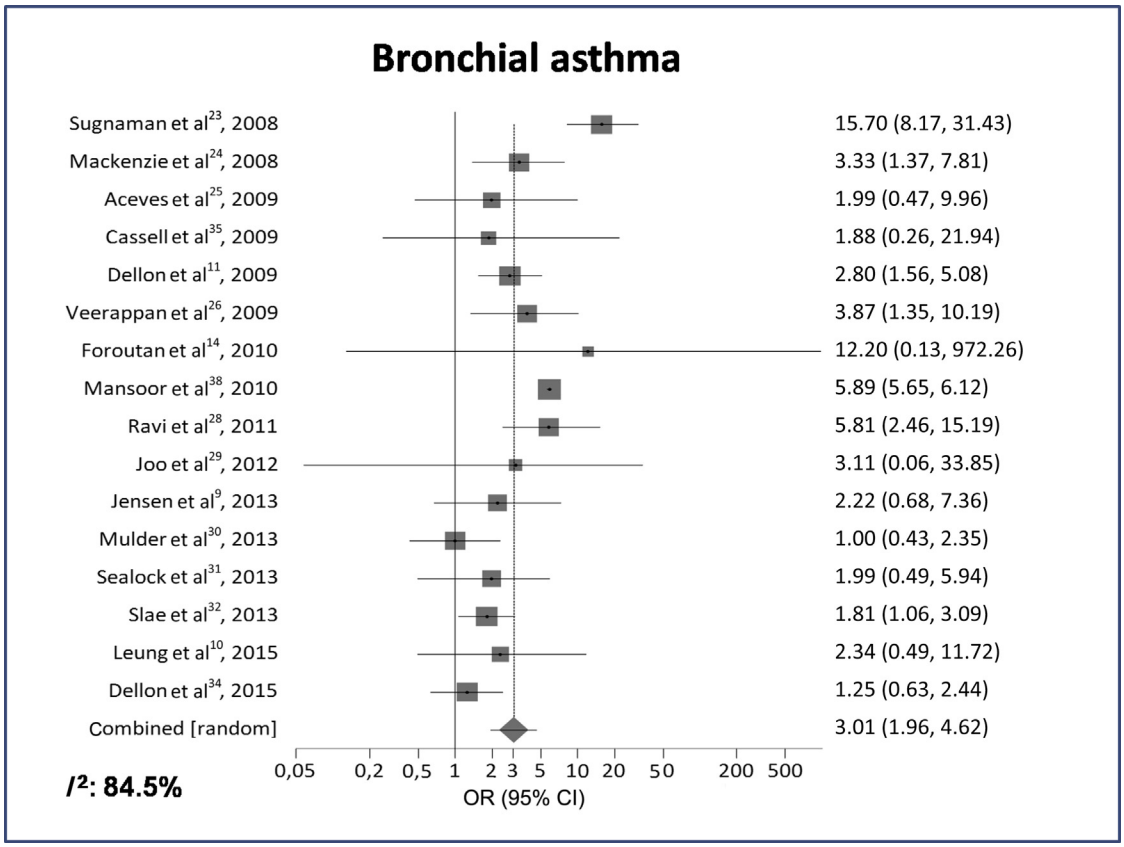

Figure 2. Pooled analysis for the odds ratios (ORs) and 95% confidence intervals (CIs) of the association of bronchial asthma with eosinophilic esophagitis (EoE) compared with non-EoE controls. A random-effects model was used to calculate the overall effect size. The I^2 statistic indicates intrastudy heterogeneity.

$I^2 = 86.7\%$); no significant differences were observed when children and adults were considered separately (Table 2). However, studies with a high risk of bias had a significantly higher OR of 10.6 (95% CI, 5.1–22.2) compared with that of studies with a low risk of bias (OR, 2.5; 95% CI, 1.6–4.1) ($P = .04$).

For studies reporting the frequency of rhinitis in patients with EoE compared with controls, the funnel plot revealed no obvious asymmetry (eFig 1), with both the Begg test ($P = .54$) and the Egger test ($P = .33$) indicating no evidence of publication bias.

Atopic eczema

The 10 studies comparing the frequency of eczema in patients with EoE and control subjects had a pooled OR of 2.85 (95% CI, 1.87–4.34; $I^2 = 57.1\%$) (Fig 3), with no obvious publication bias according to the funnel plot analysis (eFig 1) and the Begg test ($P = .38$).

Subgroup analysis revealed no significant differences when children and adults were considered separately (Table 2); however, significant differences in ORs were observed, depending on whether the studies were published as full articles (OR, 2.3; 95% CI, 1.6–3.2) or only as abstracts (OR, 4.4; 95% CI, 4.2–4.6) ($P = .02$). The OR for studies with a high risk of bias (OR, 2.2; 95% CI, 0.9–5.1) was also slightly higher than that of studies with a low risk of bias (OR, 3.2; 95% CI, 2.3–5.0) (Table 3).

Other forms of atopy assessed

The frequency of food allergy in patients with EoE and non-EoE control subjects was assessed in 15 individual studies, with results ranging from 0% to 44% for the former. However, the criteria used to define *food allergy* were extremely varied, ranging from food sensitization exclusively to food-induced anaphylaxis and even celiac disease. Thus, summary estimates were not considered appropriate because of clinical heterogeneity. Other studies included results for seasonal allergy[26,31] and environmental allergy,[9,10,30] neither of which could be subjected to meta-analysis because they did not refer to specific atopic diatheses.

Finally, our search uncovered 2 articles that reported on the frequency of drug allergy in patients with EoE compared with

Table 2
Summary of ORs and 95% CIs for the Association of Several Atopic Manifestations in Patients With Eosinophilic Esophagitis Compared With Control Subjects Representative of the General Population in Published Studies on Children, Adults, or Individuals in Whom Patient Age Was Not Specified

Condition	Overall		I^2	Children		I^2	Adults		I^2	Age Not Specified		I^2
	OR (95% CI)	n		OR (95% CI)	n		OR (95% CI)	n		OR (95% CI)	n	
Asthma	3.01 (1.96–4.62)	16	84.5	3.04 (2.26–4.4)	6	84.2	2.92 (1.71–4.98)	7	47.2	2.91 (1.2–7.07)	3	89.9
Rhinitis	5.09 (2.91–8.90)	12	86.7	5.86 (1.07–32.28)	4	92.1	4.87 (1.9–12.51)	5	81.2	6.86 (6.59–7.13)	3	0
Eczema	2.85 (1.87–4.34)	10	57.1	2.37 (1.64–3.43)	4	0	2.07 (0.76–5.59)	4	34.2	4.4 (4.22–4.6)	2	0
Drug allergy	0.95 (0.06–15.27)	2	84.8	-	-	-	-	-	-	-	-	-

Abbreviations: CI, confidence interval; OR, odds ratio.

Table 3
Subgroup Analyses of ORs and 95% CIs for the Association of Several Atopic Manifestations in Patients With Eosinophilic Esophagitis Compared With Control Subjects Representative of the General Population in Studies Published as Full Articles Compared With Abstracts, With an Assessment of Bias Risk

	Overall OR (95% CI)	n	I^2
Text format			
Asthma			
Full text	2.9 (1.8–4.6)	14	73.8
Abstract	4.7 (2–11.4)	2	37.6
Rhinitis			
Full text	5.7 (2.8–11.5)	11	83.8
Abstract	-	1	-
Dermatitis			
Full text	2.3 (1.6–3.2)	8	0
Abstract	4.4 (4.2–4.6)	2	0
Risk of bias subgroups			
Asthma			
Low risk	2.4 (1.8–3.3)	8	0
High risk	3.7 (2–6.9)	8	86.4
Rhinitis			
Low risk	2.5 (1.6–4.1)	6	33
High risk	10.6 (5.1–22.2)	6	86.2
Dermatitis			
Low risk	2.2 (0.9–5.1)	4	32.3
High risk	3.2 (2.3–5)	6	57

Abbreviations: CI, confidence interval; OR, odds ratio.

controls,[30,36] showing no significant differences between these 2 populations (OR, 0.95; 95% CI, 0.06–15.27).

Discussion

The present systematic review and meta-analysis of 21 observational case-control studies attempts to quantify for the first time the association between EoE and several atopic manifestations. To this end, data were retrieved from 53,542 individual patients with EoE and 54,759 control subjects, apart from data from population databases. Our first findings underscored the varied criteria used by the authors of the different studies to define each form of atopy. Thus, only 5 of the 21 retrieved studies clearly defined the diagnostic criteria used for asthma, rhinitis, or eczema as being a diagnosis established by an allergist or immunologist.[11,23,25,30,33] The rest of the studies used patient- or parent-reported diagnoses or offered no definition of the data source whatsoever. Even taking this limitation into account, our research found that patients with EoE have a significantly higher chance of presenting with bronchial asthma, allergic rhinitis, and eczema compared with the control population, with ORs ranging from 2.8 to 5.1 times greater. Documents published exclusively as abstracts and those with a higher risk of bias tended to reveal higher ORs for all the assessed atopic manifestations compared with full articles and studies with a low risk of bias. In any case, significant associations between atopic manifestations and EoE were demonstrated in all cases with regard to control subjects representative of the general population.

The increased frequency of several allergic diatheses in patients with EoE has been recognized since the very early descriptions of the disease more than 2 decades ago.[39,40] Subsequent studies have repeatedly linked EoE with bronchial asthma, allergic rhinitis, and conjunctivitis to the point that the presence of atopic manifestations in a patient referred for esophageal symptoms (especially dysphagia or food impaction) was proposed as a characteristic marker of EoE.[8] Most patients with EoE possess a family and/or personal allergic background, with food and aeroallergen sensitization commonly described in patients of all ages.[7,41] All these data have been used to support the allergic nature of EoE, which was definitively established after demonstrating disease remission brought on by exclusive feeding of patients with an amino acid–based elemental diet lacking all antigenic capacity.[5] However, despite the well-known association between atopy and EoE, to date no studies had tried to systematically analyse the magnitude of this association.

Our results bolster the strength of repeated reports on the close association between EoE and atopy. Nevertheless, despite accurately quantifying the frequency of various atopic manifestations in patients with EoE compared with the general population, a causal relationship between the 2 conditions cannot be established. In fact, some evidence points to the independent evolution of EoE and the atopic manifestations that commonly present in the same patients. For example, the elimination of foods that give positive results on skin prick tests usually fails to achieve disease remission,[42,43] even though positive skin prick test results are observed in more than 80% of adult patients.[44] Indeed, atopic features and allergy sensitization patterns in patients with EoE appear to be no different from those in atopic individuals without EoE living in the same geographic area and exposed to common allergens,[45] with no significant differences regarding history of allergic rhinitis, atopic dermatitis, IgE-mediated food allergy, sensitization to aeroallergens, and family history of atopy.[46]

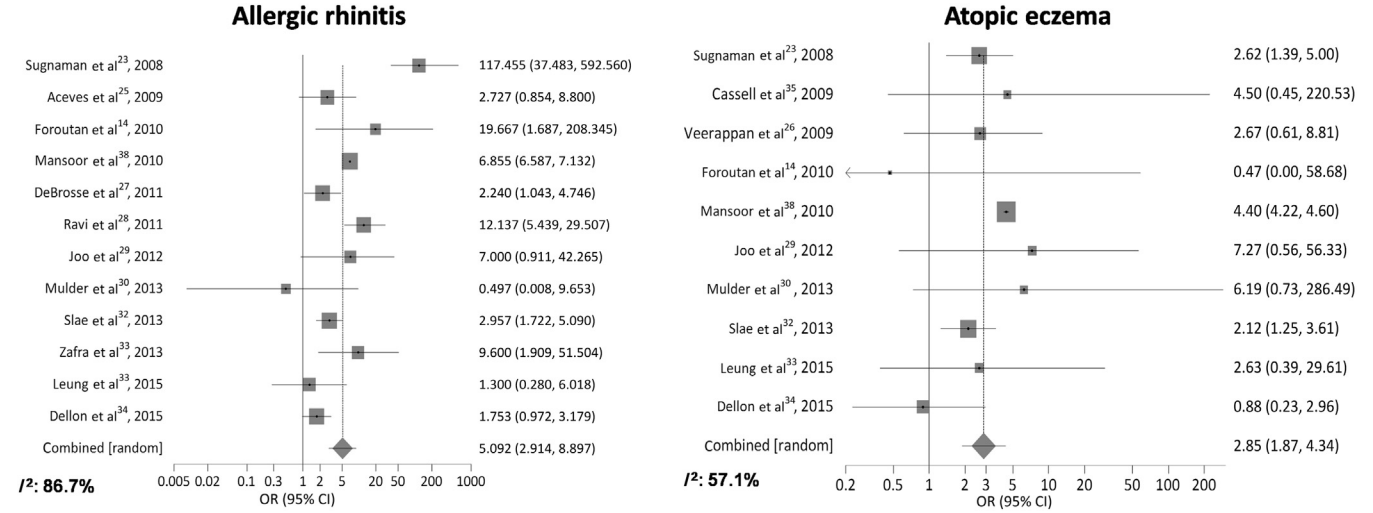

Figure 3. Pooled analysis for the odds ratios (ORs) and 95% confidence intervals (CIs) of the association of allergic rhinitis and eczema with eosinophilic esophagitis (EoE) compared with non-EoE controls. A random-effects model was used to calculate the overall effect size. The I^2 statistic indicates intrastudy heterogeneity.

The potential role of airborne allergens in triggering EoE was also suggested after some early studies in children[47,48] and adults[49] noted an increase in EoE diagnoses during pollen seasons. This observation supporting the hypothesis of a relevant role for aeroallergens in the development and/or recrudescence of EoE in parallel to what happens with other atopic disorders frequently observed in these same patients has been put into question by more recent research.[50] Thus, after compiling all the published data on this topic through a systematic search in multiple databases and subsequently analyzing the data with the aid of a random-effects meta-regression model of seasonal meta-analyses, no significant seasonal variations in the overall incidence of EoE and its flare-ups were observed. Further research revealed that demographic, clinical, and histopathologic esophageal features were identical in patients with EoE who did not present with other atopic manifestations, with the response to food elimination diets being equally effective in patients with EoE with negative allergy test results.[51] Another study found that IgE-bearing mast cells were increased in atopic patients with EoE but not in nonatopic patients with EoE,[52] with no differences observed with regard to mast cell counts or activation between atopic and nonatopic patients.[53] Thus, although various atopic manifestations are present in most patients with EoE, this association does not appear to have a causal relationship, but rather it seems that both diseases have independent courses. To date, no peripheral markers have proven useful for monitoring EoE,[54,55] which appears to be a disease restricted to the esophagus, with few or no systemic manifestations. Finally, in contrast with most atopic manifestations, which are IgE-mediated, consistent evidence has ruled out a relevant role for IgE in the pathophysiology of EoE.[56] Common genetic and environmental etiologic factors that contribute to the independent development of atopy and EoE are the best explanation for the association of both entities to date.[9,57]

Our research also aimed to evaluate the prevalence of other atopic conditions among patients with EoE, including food allergy. We found a wide variation in the criteria used by the authors of the different studies to define food allergy, ranging from food sensitivity (a positive result on an allergy test with no clinical significance) to food anaphylaxis, with some studies also including celiac disease. Likewise, other studies assessed environmental allergy or seasonal allergy without defining the exact atopic manifestations included, thus preventing us from being able to use their results. The updated consensus recommendations for EoE in children and adults published in 2011[1] already noted the inconsistencies in the reporting of associated atopic conditions in the available EoE literature and recommended the use of standard definitions for such conditions. Finally, even though our research found some data on the association of drug allergy with EoE, the association with atopy is doubtful because drug reactions are being discovered as associated with single-nucleotide polymorphisms in certain enzymes or varieties in T-cell epitopes.[58]

One of the major strengths of the present study is our search strategy, which entailed an exhaustive literature search of 3 major databases and in the abstract indexes of the principal allergy and gastroenterology congresses. Moreover, recovered studies were critically appraised according to their methodologic aspects, and different researchers independently extracted the data from the studies included. Because no significant publication bias was observed in most of the funnel plot analyses, we are confident that the 21 documents retrieved represent all the relevant information available on this topic.

Still, several limitations should be noted for a better interpretation of our results. First, the quality of the available evidence on the prevalence of different atopic manifestations in patients with EoE was only moderate, with all the retrieved studies being observational in nature and 8 of 21 studies having a retrospective design. Second, with regard to the assessment of diagnostic criteria to define atopic manifestations, we cannot fully trust that they have been defined with accurate criteria in all patients and controls included in our systematic review. Neither can we be sure that every case of rhinitis or asthma was allergic in nature rather than of intrinsic origin. Third, variations in the diagnostic criteria for EoE during the period covered by our systematic review (eg, eosinophil count threshold and exclusion of proton pump inhibitor–responsive esophageal eosinophilia) were not taken into account because they were considered homogeneous enough to the included in a single diagnostic category.

In conclusion, the present study found that an accurate diagnosis of atopy is lacking in most of the research evaluating the prevalence of asthma, rhinitis, and eczema among patients with EoE. Still, the prevalence of these 3 conditions seems to be significantly higher in children and adults with EoE compared with control subjects representative of the general population. Further research should clearly document and use standard definitions of allergic rhinitis, asthma (including its severity and level of control), skin allergy, and food allergy (rather than mere sensitization) when assessing and documenting concurrent allergic diseases in patients with EoE.

Supplementary Data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.anai.2017.02.006

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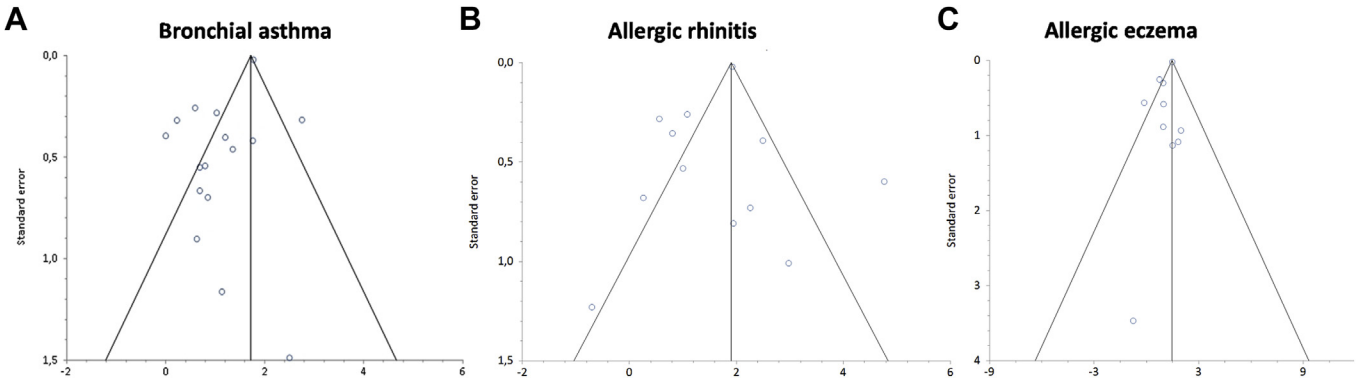
eTable 1
Quality Assessment (Risk of Bias) of the 21 Documents Included in Our Systematic Review, Evaluated With the Aid of the Joanna Briggs Institute Critical Appraisal Checklist for Case-Control Studies

Study	1. Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?	2. Were cases and controls matched appropriately?	3. Were the same criteria used for identification of cases and controls?	4. Was exposure measured in a standard, valid and reliable way?	5. Was exposure measured in the same way for cases and controls?	6. Were confounding factors identified?	7. Were strategies to deal with confounding factors stated?	8. Were outcomes assessed in a standard, valid and reliable way for cases?	9. Was the exposure period of interest long enough to be meaningful?	10. Was appropriate statistical analysis used?	Overall score
Aceves et al,[25] 2009	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	NA	Yes	Low risk o f bias
Cassell et al,[35] 2009	Unclear	Unclear	Yes	Yes	Yes	Unclear	Unclear	Unclear	NA	Yes	High risk of bias
Dellon et al,[11] 2009	Yes	Unclear	Yes	Yes	Yes	Unclear	Unclear	Yes	NA	Yes	Low risk of bias
Dellon et al,[34] 2015	Yes	Unclear	Yes	Yes	Yes	Unclear	Unclear	Unclear	NA	Yes	Low risk of bias
De Brosse et al,[27] 2011	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Unclear	NA	Yes	Low risk of bias
Duffey et al,[37] 2016	Unclear	Unclear	Yes	Yes	Yes	Unclear	Unclear	Unclear	NA	Yes	High risk of bias
Foroutan et al,[14] 2010	Yes	Unclear	Yes	Yes	Yes	Unclear	Unclear	Unclear	NA	Yes	High risk of bias
Garcia-Compean et al,[12] 2011	Yes	Yes	No	No	Yes	Unclear	Unclear	No	NA	Yes	High risk of bias
Ravi et al,[28] 2011	Yes	Yes	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	NA	Yes	High risk of bias
Joo et al,[29] 2012	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Unclear	NA	Yes	Low risk of bias
Jensen et al,[9] 2013	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Unclear	NA	Yes	Low risk of bias
Leung et al,[10] 2015	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Unclear	NA	Yes	Low risk of bias
Mackenzie et al,[24] 2008	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Unclear	NA	Yes	Low risk of bias
Mansoor et al,[38] 2010	Yes	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	NA	Yes	High risk of bias
Mulder et al,[30] 2013	Yes	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Unclear	NA	Yes	High risk of bias
Peterson et al,[36] 2015	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	NA	Yes	High risk of bias
Sealock et al,[31] 2013	Yes	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Unclear	NA	Yes	High risk of bias
Slae et al,[32] 2013	Yes	Yes	Yes	Unclear	Yes	Unclear	Unclear	Unclear	NA	Yes	High risk of bias
Sugnaman et al,[23] 2007	Unclear	Unclear	No	Yes	No	Unclear	Unclear	Yes	NA	Yes	High risk of bias
Veerappan et al,[26] 2009	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Unclear	NA	Yes	Low risk of bias
Zafra et al,[33] 2013	Yes	Yes	Unclear	Unclear	Yes	Unclear	Unclear	Yes	NA	Yes	Low risk of bias

Abbreviation: NA, not applicable.



eFigure 1. Begg funnel plot of studies on the association of atopic manifestations with eosinophilic esophagitis compared with controls, including bronchial asthma (A), allergic rhinitis (B), and allergic eczema (C). The solid line in the center is the natural logarithm of pooled remission rates, whereas the 2 oblique lines represent pseudo 95% confidence limits.