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The Role of Environmental Exposures in the Etiology of Eosinophilic Esophagitis: A Systematic Review

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Abstract

Eosinophilic esophagitis (EoE) is an emerging clinicopathologic entity defined by abnormal esophageal eosinophilic infiltration. Management of this disease is hampered by limited understanding of etiologic and controllable risk factors. The aim of this systematic review was to determine the environmental risk factors for EoE. We searched PubMed, Web of Science, and EMBASE databases from 1950 through June 30, 2015. To identify additional relevant studies, we hand searched bibliographies of included articles. We limited the review to articles using human subjects, and consisting of case reports, case series, cross-sectional and cohort studies, or clinical trials. 19 articles discuss the risk of environmental exposures on EoE and indicate that environment plays a large role in the etiology of EoE. Seasonal, geographic, and climate-based differences in disease prevalence have been shown but the exact mediators of this process, possibly aeroallergens that vary over time and from place to place, remains elusive.

Introduction

Eosinophilic Esophagitis (EoE) is a newly recognized, immune-mediated, chronic disease defined by symptoms of esophageal dysfunction, eosinophilic infiltration of the esophagus that persists after a proton pump inhibitor (PPI) trial, and exclusion of secondary causes of eosinophilia.[1] While EoE was almost entirely unknown 20 years ago, it is now regularly encountered in endoscopy suites and is a leading cause of emergency department visits for food impactions in the US.[2-4] Accordingly, it now accounts for a substantial amount of health care-related spending in the United States.[5]

EoE affects infants, children, and adults, though the disease can manifest with different symptoms and endoscopic findings at different ages.[6,7] The etiology of EoE is still incompletely understood. Animal models show that allergen exposure can recapitulate the histopathologic phenotype of EoE through activation of Th2-immune cells, and similar

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mechanisms have been identified in humans.[8-11] Epidemiologic studies further support the role of allergens in disease pathogenesis, as patients frequently have a history of atopic disease or food allergies.[6] Moreover, allergen-free formulas are highly effective for treating this condition, and provide proof-of-principle of the importance of food allergens in EoE pathogenesis.[12,13] Dietary elimination therapies for EoE are supported by a broad base of literature, which suggests that dietary antigens can be crucial disease triggers.[14-27] Recent publications have also described variation in EoE prevalence by climate type, geography, and season, and a study of inheritance patterns in EoE suggest that environmental factors play a larger etiologic role than genetics.[28] However, with the exception of rare case reports,[29,30] it is difficult to identify an inciting allergic event that triggers EoE.

In contrast to the well-described role of limiting dietary triggers as a treatment for disease, the role of environmental exposures in the etiology of EoE is not well characterized. Therefore, the aim of this systematic review was to summarize the existing clinical literature on the etiology of EoE as it relates to environment exposures and the causation of disease.

Methods

Search Strategy

We conducted a systematic review by searching PubMed, Web of Science, and EMBASE databases. To identify relevant articles, two authors (DG, CC) independently performed the search, which was developed with the assistance of a reference librarian with expertise in systematic review methodology. We used the following search terms for eosinophilic esophagitis: *eosinophilic esophagitis OR allergic *esophagitis OR corrugated *esophagus OR ringed *esophagus. These terms are similar to those used in a previous systematic review on EoE diagnosis.[31] We limited the search to include only EoE papers on environmental, aeroallergen, or allergy related risk factors using the terms environment* OR pollen OR rural OR urban OR aeroallergen OR allergy OR allergic OR allergies OR allergen OR allergens OR diet OR dietary OR food. Articles relating to dietary therapy were excluded from abstraction. To limit the search to epidemiological topics, we further limited the search to papers including the terms risk factor OR risk factors OR exposure. The complete PubMed search string was (eosinophilic *esophagitis OR allergic *esophagitis OR corrugated *esophagus OR ringed *esophagus) AND (environment* OR pollen OR rural OR urban OR aeroallergen OR allergy OR allergic OR allergies OR allergen OR allergens OR diet OR dietary OR food) AND (risk factor OR risk factors OR exposure). This search string was reformatted as necessary for the syntax of EMBASE and Web of Science searches, and the “*” prior to terms ensured that European spelling would be detected as well. Both readers (DG, CC) subsequently hand searched the bibliographies of all identified articles and considered relevant articles for inclusion. We used the PRISMA checklist to ensure thorough methodology.[32]

Article Inclusion Criteria

All papers from 1950 through June 30, 2015 were eligible for inclusion. Due to the limited literature on this topic, we accepted case reports and case series as well as cross-sectional studies, cohort studies, and clinical trials focusing on EoE that were in any language.

Nonhuman studies, review articles, and letters to the editor that did not present new clinical information were excluded. Articles describing dietary elimination therapy of EoE were excluded. After the search was complete, one author (DG) reviewed the article titles and then abstracts to determine whether they were eligible for inclusion. This process was repeated independently by a second reviewer (CC). When there were discrepancies between our lists of papers to include, we read the full text and came to a consensus; adjudication, if needed, was performed by the senior author (ESD). Both reviewers agreed on the final list of included material before analysis began.

Data Abstraction

Extracted data included: study type, the number of patients in the study with EoE (which could be less than the total number of subjects in a study), number of patients in comparator group, study population demographics such as mean age, gender distribution, and allergy history, and main environmental risk related findings, reported as crude and adjusted risk estimates (RR, OR). Validity of articles was assessed examining study design, precision of estimates, and potential for bias and measurement error. Due to the wide range of study types and substantial heterogeneity between studies, a meta-analysis was not performed for this systematic review.

Results

Literature search results

The combined search yielded 240 articles; 19 met the inclusion criteria and were the focus of this review (Figure 1). These consisted of observational epidemiologic studies and case series. There were no randomized studies. One article was a case report,[33] two were case series,[30,34] one was a cross sectional study,[35] nine were case-control,[36-44] and six were cohort studies.[45-50] All articles were written in the last decade, with the earliest published in 2007. One study was conducted in Spain,[35] one in Canada,[40] and another in Australia,[42] with the remaining eleven completed in the US. Studies included adults and children.

The aim, year, and environmental exposure investigated are presented in Table 1. Only one study was population-based,[48] with the remaining drawing from clinical populations. All but three studies[40,44,45] reported positive findings (Table 2). Most studies, excluding four studies based in national pathology databases, were limited by a relatively small number of cases. Assessments of bias, precision, and measurement error are presented in Table 3. The following are the main categories of environmental risk factors determined from the literature search.

Pollen and Aeroallergens

An initial case report documented the correlation between the number of eosinophils seen on biopsy, clinical symptom severity, and pollen counts over the course of four years, demonstrating proof-of-principle that aeroallergens can impact disease activity in EoE.[51] While, another report did not confirm this relationship,[52] a retrospective cohort study of 127 adults found that the rate of EoE diagnosis throughout the year was correlated with fluctuations in daily average pollen counts in the Washington, DC, area.[47] Specifically, there

were approximately twice as many cases of EoE in the spring than the winter and that there was a strong statistical correlation between case volume and grass pollen. A cross-sectional study of 43 patients in Spain investigated the allergy sensitization profile of EoE patients [35] Patients had skin-prick test positive results for a variety of aeroallergens, including grasses and olive pollens, *Planatus,* and animal dander. Finally, a case series documented three patients who had new onset EoE after a large-volume allergen exposure.[30] This was a rare example of demonstrating an environmental trigger as causing EoE, with a mechanism that mirrors how some experimental animal models are induced.[8]

Insects

A prospective case-control study showed that sensitization to galactose-alpha-1,3-galactose, an allergic reaction to mammalian meat induced by a lone star tick bite, was not a risk factor for EoE.[44] One case report described a young child with EoE and food allergies who entered remission after high-dose immunotherapy to Dermatophagoides farinae and pteronyssinus.[33]

Climate

We identified one case-control study that examined the risk of esophageal eosinophilia by climate type.[38] Using a large national pathology database, the prevalence of EoE was compared between tropical, arid, cold, and temperate climate zones in the US using the Köppen – Geiger climate class system. For the 9,995 EoE cases and 71,948 controls included, there was a statistically significant increase in odds of EoE in arid, aOR 1.27 (95% CI 1.19, 1.36), and cold climates, aOR 1.39 (95% CI 1.34-1.47). No other publications to date have investigated a similar question.

Urban vs rural populations

There were three studies that examined urban versus rural environments as a risk factor for EoE. The first study used a case control design to compare 335 pediatric EoE patients to clinic-based controls and to 2000 US census data.[36] After adjusting for race and other confounders, the aOR for EoE in suburban vs urban census blocks was 2.08 (95% CI 1.22–3.54) when compared to allergy clinic controls, but there was not a significant difference in risk of EoE when comparing cases to GI clinic controls. The second was a retrospective cohort that compared clinical features of EoE in urban and rural regions, based on 2010 US census data, using a population density cut off of 1000 people / square mile.[46] There was no statistically significant difference in prevalence between urban and rural areas, but some differences in clinical features. Urban patients, for example, were more likely to present with dysphagia, while rural patients were more likely to complain of heartburn and reflux. The third study used a large pathology database to assess population density as a risk factor for EoE.[37] 14,381 EoE cases were compared to almost 90,000 controls from throughout the U.S., and the odds of EoE increased with decreasing population density. For example, comparing the least to most dense quintile of population density, the aOR was 1.59 (95% CI 1.45-1.76).

Season

Multiple studies have observed that there can be seasonal variation of EoE diagnosis.[41,45,47-50] The first used a retrospective cohort design to compare rates of EoE diagnosis across seasons and adjusted for seasonal esophagogastroduodenoscopy (EGD) case volume.[45] They found that EoE diagnosis was more common in spring and summer, or outdoor months, than winter and fall, or indoor months. A similar study found that 33% of patients were diagnosed in the spring while only 16% were diagnosed in the winter, and temporal correlation with grass pollen counts was compelling.[47] A study in Olmstead County, Minnesota, examined all patients with EoE from 1976-2005 and found that significantly more patients were diagnosed in late summer and early fall.[48] A study of 234 children with EoE assessed both rate of diagnosis between months and inflammation severity based on histopathologic characteristics of biopsy tissue.[49] This study not only found that winter had significantly fewer newly diagnosed cases of EoE than did other seasons, but that winter cases had less severe inflammation than did summer and fall cases. A further study set in a large, national pathology database replicated these findings.[41] This study found the highest odds of diagnosis in July at an adjusted 1.13 (95% CI 1.03–1.24), and the relationship persisted through several sensitivity analyses. However, an adequately-powered, single-center registry study failed to identify a seasonal trend and found a pattern contrary to that reported in other studies.[50] A predominance of cases during the winter was significant in another study that examined the proportion of recurrent food bolus obstruction events attributed to EoE and found winter predominance.[42] These studies of seasonality of diagnosis of EoE are generally limited in that they assess the timing of diagnosis rather than actual onset of disease.

Early Life exposures

We identified three studies that examined the risk of EoE due to selected early life exposures in pediatric patients.[39,40,43] The first used a case-control design to assess exposures of interest including cesarean delivery, preterm birth, antibiotic use in infancy, group B streptococcal (GBS) infection, non-exclusive breast-feeding, and others.[39] While antibiotic use during infancy was the only exposure that resulted in a statistically significant increase in odds, with an OR of 6.0 (95% CI 1.7-20.8), there were trends towards increased risk with other exposures, particular cesarean delivery. A subsequent and larger case-control study replicated these findings with respect to antibiotic exposure, and found a statistically significant effect of cesarean delivery.[43] A further case-control failed to replicated effects of childhood antibiotics and cesarean delivery, found no effect of smoking or breastfeeding duration.[40]

Discussion

EoE is defined as an allergen/immune-mediated condition.[1,6] While the current model of EoE pathogenesis holds that an allergic exposure triggers a Th2-mediated response that results in eosinophils infiltrating the esophageal mucosa,[11] identifying the exact inciting event in a given patient is typically not possible.[30] For many patients, elimination of dietary allergens can induce remission,[27] and this observation has supported a central role for food allergy in the etiology of EoE.[7,11] However, emerging data suggest that the role of

environmental factors may also be important.[53] This systematic review, which assessed the impact of environmental exposures on disease development, has a number of interesting results. First, there are relatively limited data addressing the question of environmental risk factors in EoE. We found only 19 pertinent articles after a comprehensive search. Second, there were a number of potential risk factors for EoE, and evidence was strongest for an effect of climate or season, low population density, and early life exposures, but the evidence for an effect of pollen or aeroallergens was lower. Finally, there were no studies that conclusively demonstrated an etiologic environmental risk factor in a large population that was prospectively assessed.

Data on climate and seasonality, while mixed, suggest that trends related to climate zone, seasonality, or aeroallergens may impact EoE diagnosis.[8,37,38,41,42,45,47-49,51,52] However, these studies are still at a general level, and it remains to be seen whether trends in seasonality or climate will be able to be linked to a discrete environmental factor that could impact an individual patient. A similar statement could be made for EoE being more common in areas with low population density.[36,37,46] This broad finding currently lacks a definitive explanation, and while multiple hypotheses are possible, further research is needed to explicate the underlying reasons for this trend. The studies on early life exposures, while intriguing and more granular, are still preliminary.[39,40,43] Recall bias is a particular concern with these studies, and prospective cohort studies are needed to confirm these findings. The impact of aeroallergens in individual patients has been demonstrated,[51] but why these might be important in some EoE patients and not in others remains to be determined. Interestingly, emerging data with component-resolved diagnostics shows that there can be cross reaction between certain environmental and food allergens,[54] and this could provide a link between an environmental and a dietary etiology of EoE. Finally, it is important to note that the quality of the studies included in this systematic review varied, ranging from case reports to retrospective cohorts, to prospective case-control designs. Overall, the findings summarized here do not yet prove causality of any particular exposure.

When interpreting the results from this study, there are several limitations to acknowledge. Because we were concerned with non-dietary environmental risk factors, articles relating to dietary therapy were excluded from this systematic review. We also excluded studies that evaluated the efficacy of treatments for EoE, limiting our search to articles that aimed to provide clinical evidence to the pathogenesis or etiology of EoE. Therefore, our findings should be taken in the context of the broader EoE literature that supports the efficacy of dietary elimination treatments for some patients with EoE.[27] In reality, the causal pathway from environmental exposure to clinical presentation with EoE is likely complex and the temporal association of particular exposure can be inherently limited if the subclinical phase of pathogenesis is long or if it varies greatly in duration. While it is possible that we may have missed some studies, our study design assessing multiple literature sources with two independent data abstractors was comprehensive.

In conclusion, we identified 19 papers assessing environmental risk factors for EoE, and several trends were identified. Studies that directly support the specific role of pollen and aeroallergens in EoE were not as strong in their findings as studies that indirectly supported a different environmental cause. Indirect evidence for an environmental exposure causing

EoE depends on reports highlighting increased diagnosis of EoE in spring or summer seasons, increased risk of EoE in arid or cold climate zones, higher rates of disease in rural areas with low population density, and selected early life exposures such as antibiotic use. These findings all suggest, but do not prove, that an environmental exposure contributes to EoE etiology. Whether this increased risk relates to differing environmental allergens, exposures from agricultural activity, or ecologic differences in social or economic factors should be an area of future investigation. Finally, possible early life factors that could increase the risk of EoE are intriguing, and if confirmed, could raise the possibility of disease prevention or modification.

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Abbreviations

aOR	adjusted odds ratio
EGD	esophagogastroduodenoscopy
EoE	eosinophilic esophagitis
OR	odds ratio
PPI	proton pump inhibitor

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Article highlights

- This systematic review identified 19 articles pertaining to environmental risk factors for EoE.
- Study designs included case reports, case series, case-control, and cohort studies. There were no experimental studies or clinical trials assessing environmental risk factors.
- Data were strongest for climate, seasonality, low population density, and early life exposures.
- Data were less strong for pollen and aeroallergens.
- The results suggest, but do not prove, that environmental exposures may contribute to EoE etiology, but additional prospective studies study at more granular levels are needed.

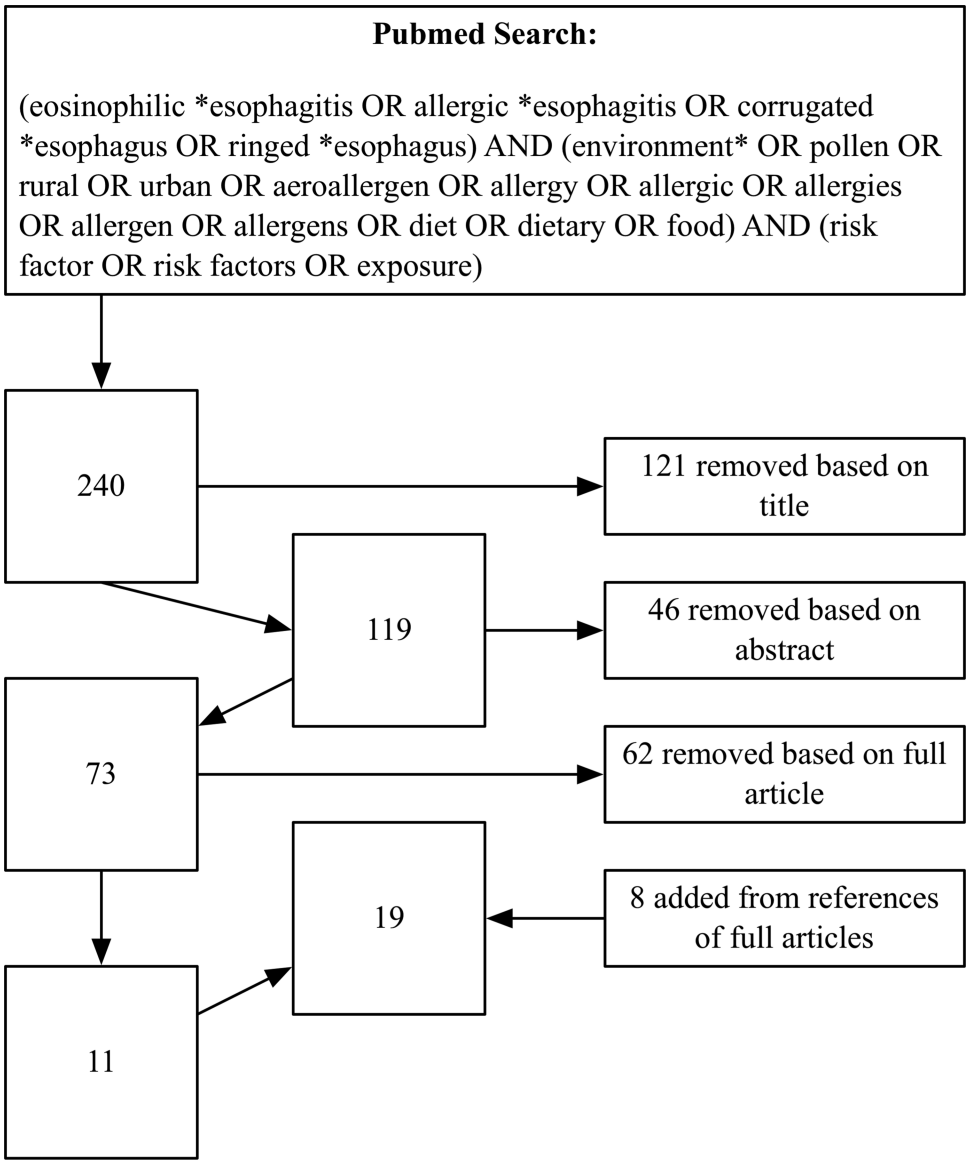

Figure 1.

The combined search yielded 240 articles; 19 met the inclusion criteria and were the focus of this review. Of the initial 240 publications, we excluded 121 based on the title. These were typically review articles, based on animal models, or focused on treatment or diagnostic criteria. Of the remaining 119 articles, an additional 46 were excluded after reading the abstract. After reading the full text of the remaining articles, more were excluded as they did not address the topic of interest. Hand searching the bibliography of the 11 included articles as well as germane review articles resulted in inclusion of an additional 8 articles not found in the initial search strategy

Table 1

Aim, design, year, and exposure of interest for studies included for analysis.

First Author	Aim	Design	Year	Environmental exposure of Interest
Lee[46]	Compare demographic and clinical characteristics of urban vs. rural EoE patients with PPI trial,	Cohort, retrospective	2015	Population Density (urban vs. rural)
Castro Jiménez[35]	To describe the demographic, clinical characteristics, and allergy sensitization of EoE patients in Spanish region.	Cross-sectional	2013	Aeroallergens
Wolf[30]	To offer initial human evidence of EoE etiology mechanism proven in mice models	Case series	2013	Aeroallergens
Ramirez[33]	To describe a case of dust mite hypersensitivity and EoE with clinical and pathologic improvement after desensitization	Single case	2013	Aeroallergens
Hurrell[38]	To examine the relationship between EE (not EoE) and climate.	Case control	2012	Climate
Jensen[39]	To explore early life exposures as risk factors for EoE	Case control	2013	Childhood antibiotics, cesarean section
Radano[43]	To investigate associations between EoE and dietary, environmental, and medical exposures during infancy	Case control	2014	Childhood antibiotics, cesarean section
Slae[40]	To determine whether smoking and other exposures linked with the development of atopic disease are also associated with EoE	Case control	2015	Childhood antibiotics, cesarean section, breast-feeding, smoking
Franciosi[36]	To determine demographic, socioeconomic, and geographic characteristics of CHOP's EoE cohort for pediatric patients.	Case control	2009	Population Density (urban vs. rural)
Roy-Ghanta[34]	To identify the specific environmental and food allergy profile of adults with EoE.	Case series	2008	Multiple
Jensen[37]	To assess the relationship between EoE prevalence and population density.	Case control	2014	Population Density (urban vs. rural)
Philpott[42]	To determine if a seasonal and geographical pattern exists in EoE patients with recurrent FBOE	Case control	2015	Season
Moawad[47]	To determine if there is seasonal variation and if it correlates with seasonal pollen count.	Cohort, retrospective	2010	Aeroallergens, Season
Almansa[45]	To determine whether there is a seasonal pattern in the diagnosis of EoE in adults	Cohort, retrospective	2009	Season
Elias[50]	To confirm in a larger group of patients a seasonal pattern of EoE diagnosis.	Cohort, retrospective	2015	Season
Jensen[41]	To determine if there is seasonal variation in the detection and diagnosis of EE and EoE	Case control	2015	Season
Prasad[48]	To assess the epidemiology and outcomes of EE in Olmsted County, Minnesota, over the last 3 decades	Cohort, retrospective	2009	Season
Wang[49]	To examine the seasonal distribution of newly diagnosed EoE children	Cohort, retrospective	2007	Season
Burk[44]	To test whether sensitization to alpha-gal is a risk factor for EoE.	Case control	2015	Insect

EoE, eosinophilic esophagitis; PPI, proton pump inhibitor; FBOE, food bolus obstruction events; EE, esophageal eosinophilia.

Table 2

Study and comparator populations, demographics, and main findings.

First Author	Study Population	Cases	Comparator Population	M:F ratio	Mean age in years (range)	Cauc. race (%)	PMH atopic disease	Main Findings
Lee[46]	University of Iowa GI clinic patients with EGD and biopsy for esophageal indications	57	n/a	2:1 M	26.7 (NR)	91	1.8% seasonal allergy, 12.3% asthma	EoE was equally common, dysphagia significantly more common in urban than rural setting.
Castro Jiménez[35]	2006 - 2011 EoE patients at GI clinic of Ciudad Real University General Hospital	43	n/a	3:1 M	33.6 (6-63)	NR	83.7	Patients with EoE have diverse sensitizations to specific IgE, skin prick testing, and patch testing.
Wolf[30]	3 patients with EoE after specific large-volume aeroallergen exposures	3	n/a	All male	23.7 (20-29)	NR	NR	Description of history of exposure prior to diagnosis
Ramirez[33]	1 case of EoE in a young child	1	n/a	Male	4	NR	Food allergies	EoE remission after dust mite desensitization
Hurrell[38]	United States national pathology database of 233,649 patients	9,995	71,948 non-case from 2008-2010	2:1M cases; 1:2M controls	Cases: 44.4 (NR); controls: 53.7 (NR)	NR	NR	Tropical aOR 0.87 (0.71-1.08), arid aOR 1.27 (1.19-1.36), temperate (ref.), cold aOR 1.39 (1.34-1.47)
Jensen (2013)[39]	Pediatric EoE patients, 2004-2010, and population of 26 cleft lip/palate patients from UNC	31	26 from plastic surgery clinic; 26 from GERD patients	NR	Cases - 11 (NR); GERD control - 12 (NR); plastics control - 8 (NR)	73-85	Cases 74%; GERD 54%; plastics 35% allergy	OR 6.0 for antibiotics
Radano[43]	EoE cases from clinic visits between March 2011 and May 2012 and endoscopies between January 2008 and May 2012	25	74 recruited from well-child, follow-up clinics	4:1M cases; 2:1M controls	Cases median 3.4; controls 4.3	68% cases, 68% controls	Cases 75% eczema, 67% food allergy	EoE more often cesarean section (60% vs 34%, p=0.03) and antibiotic use in first year of life (67% vs 33%, p=0.004)
Slae[40]	EoE cases, controls from pediatric clinic and endoscopy visits, recruitment period not specified	102	167	4:1M cases; 1:1M controls	Cases: 10.8 (NR); controls: 10.0 (NR)	NR	Cases 57% eczema, 47% asthma, 62% allergic rhinitis (AR), 10% food	Smoking, breast-feeding, cesarean section, childhood antibiotics not found associated with EoE.
Franciosi[36]	CHOP EoE patients, using a 20 eosinophil per high-power field cut off	335	Pediatric GI and pediatric allergy clinics	3:1 M	NR	83.6	NR	aOR 2.08 (1.22-3.54) for Suburban living (vs urban) in EoE group, compared to allergy patients
Roy-Ghanta[34]	Adult patients with EoE by consensus guidelines seen in University allergy clinic	23	N/A	1.6:1 M	35.2 (18-57)	NR	78	Patients sensitized to danders, grass pollen,

First Author	Study Population	Cases	Comparator Population	M:F ratio	Mean age in years (range)	Cauc. race (%)	PMH atopic disease	Main Findings
								mite allergen, ragweed, and tree pollen mite allergen, ragweed, and tree pollen
Jensen (2014)[37]	Patients with >15 eosinophils per HPF and dysphagia from national pathology database	14,381	292,621 non-cases	2:1 M cases; 1:2 M controls	Cases: 45 (NR); controls 54 (NR)	86	NR	aOR 1.59 (1.45-1.76) odds of EoE bottom to top quintile of pop density.
Philpott[42]	Patients with recurrent food bolus obstruction event (FBOE) at 5 tertiary hospitals	6	19 non-case recurrent FBOE	4:1 M cases; 3:1 M controls	Cases: 39.1 (NR); controls: 62.0 (NR)	NR	NR	67% to 5% EoE vs. non-case October 1 to January 1, p=0.005
Moawad[47]	Adult EGD population 2006-2008, symptoms and histology of EoE at Army Medical Center	127	n/a	6:1M	NR (19-92)	82	33% AR	EoE diagnosis was significantly more common in Spring and less in winter, not seen with trees or weeds
Almansa[45]	37 EoE cases, 41 validation at Mayo Clinics, consensus diagnosis between August 2006 and July 2007	79	EGD case volume during that time period	3:2M	51.5 (16.1)	94.9	51% clinical history of allergies	More diagnoses in spring and summer months than fall and winter, p<0.019, despite constant EGD rate
Elias[50]	Adult patients from center's disease registry	372	N/A	3:1M	41.9 (14.7)	NR	72% AR, 46% asthma	No significant seasonal trend, more cases in opposite seasons reported elsewhere
Jensen (2015)[41]	Patients with >15 eosinophils per high powered field from national pathology database	14,524	90,459 normal controls	2:1M	45.0 (16.2)	NR	NR	Small but consistent seasonal variation in diagnosis with cases more frequent during summer months
Prasad[48]	Residents of Olmstead County, Minnesota, from 1976-2005 with EoE, consensus diagnosis	78	N/A	1:1M adults; 2:1M children	Adults: 37 (NR); Children: 10 (NR)	NR	Adults: 50% allergy; children: 53.8%	More EoE diagnosis in late summer and early fall
Wang[49]	234 EoE patients, Pediatric Hospital, 1998-2004	234	N/A	2:1M	7.0 (0.2-19.5)	NR	32% any atopy	Winter had fewer EoE diagnoses than the other seasons, and less severe inflammation than Summer and Fall
Burk[44]	Prospective collection of 50 cases and 50 controls among UNC EGD patients	50	EGD non-cases	3:2M	38.1 (10.6)		Asthma 35%; eczema 9%; AR 65%; food 32%	Alpha-gal sensitization not significantly greater in cases than controls.

M:F, male to female; PMH, past medical history; Cauc., Caucasian; GI, gastroenterology; EGD, esophagogastroduodenoscopy; NR, not reported; GERD, gastroesophageal reflux disease; EoE, eosinophilic esophagitis; EE, esophageal eosinophilia; OR, odds ratio, aOR, adjusted odds ratio; ref., referent group.

Table 3

Potential for bias, imprecision, and measurement error in each study.

Reference	Bias	Direction of Bias	Precision	Measurement error
Lee et al., 2015[46]	Not population-based, non-randomized	Indefinite, possibly dependent on local referral patterns	Sufficient to detect large, consistent effects	Consensus diagnostic criteria, valid geocoding
Castro Jiménez et al., 2013[35]	Not population-based, non-randomized, doesn't temporally place sensitization ahead of EoE diagnosis	Likely toward larger effect due to selective referral of patients with suspected atopy	Appropriate for inference	Use of valid diagnostic criteria and tests hypersensitivity in multiple pathways
Wolf et al., 2013[30]	Study describes cases but does not report numeric estimates.	Not applicable	Not applicable	Consensus definition of cases, exposure history soon after event minimizes recall bias
Ramirez et al., 2013[33]	Study describes cases but does not report numeric estimates.	Not applicable	Not applicable	Consensus definition of case, prick and patch testing
Hurrell et al., 2012[38]	Large national pathology registry, not population-based, general to endoscopy population	Toward exaggerated effect, socioeconomic or ethnic patterns	Appropriate for inference	Non-consensus diagnostic criteria, indefinite PPI trial
Jensen et al., 2013[39]	Multiple control groups, not population-based, potential for recall bias	Likely toward larger effect due to recall bias	Appropriate for inference	Use of valid diagnostic criteria and standardized collection instruments
Radano et al., 2014[43]	Not population-based, non-randomized, single center, appropriate adjustment procedures	Indefinite, possibly dependent on local referral patterns	Appropriate for inference	Consensus diagnostic criteria, standardized data collection instruments
Slae et al., 2015[40]	Not population-based, non-randomized, single center, controls represent EGD population	Indefinite, possibly dependent on local referral patterns	Appropriate for inference	Consensus diagnostic criteria, standardized data collection instruments
Franciosi et al., 2009[36]	Not population-based, non-randomized, single center	Indefinite, possibly dependent on local referral patterns	Appropriate for inference	Consensus diagnostic criteria, valid geocoding
Roy-Ghanta et al., 2008[34]	Not population-based, non-randomized, doesn't temporally place sensitization ahead of EoE diagnosis	Likely toward larger prevalence of sensitivity due to selective referral of patients with suspected atopy	Appropriate for inference	Use of valid diagnostic criteria but specific IgE testing only
Jensen et al., 2014[37]	Large national pathology registry, not population-based, general to endoscopy population	Toward exaggerated effect, socioeconomic or ethnic patterns	Appropriate for inference	Non-consensus diagnostic criteria, indefinite PPI trial, sensitivity analyses
Philpott et al., 2015[42]	Not population-based, but likely adequate approximation of catchment area given acuity of event	Indefinite, socioeconomic or ethnic differences from controls, case definition	Sufficient to detect large, consistent effects	Non-consensus diagnostic criteria, indefinite PPI trial
Moawad et al., 2010[47]	Findings internally valid but limited to a single center, influence of scheduling practices is difficult to quantify.	Possibly toward null due to case definition	Sufficient to detect large, consistent effects	Non-consensus diagnostic criteria, indefinite PPI trial
Almansa et al., 2009[45]	Findings internally valid but limited to a single center, influence of scheduling practices is difficult to quantify.	Likely towards overestimating seasonal trend	Sufficient to detect large, consistent effects	Season of incidence from timing of diagnosis limited by long subclinical phase
Elias et al., 2015[50]	Findings internally valid but limited to a single center, influence of scheduling practices is difficult to quantify.	Likely towards overestimating seasonal trend	Appropriate for inference	Limits of retrospective collection, long subclinical phase

Reference	Bias	Direction of Bias	Precision	Measurement error
Jensen el al., 2015[41]	Large national pathology registry, not population-based, general to endoscopy population	Possibly toward null due to case definition, strongest control of confounding	Appropriate for inference	Non-consensus diagnostic criteria, indefinite PPI trial, sensitivity analyses
Prasad et al., 2009[48]	Population-based study of incident diagnoses, case definition lacks PPI trial	Possibly toward null due to case definition	Appropriate for inference	Non-consensus diagnostic criteria, indefinite PPI trial
Wang et al., 2007[49]	Findings internally valid but limited to a single center, influence of scheduling practices is difficult to quantify.	Indefinite, possibly dependent on local referral patterns	Appropriate for inference	63% with negative 24-hour pH-impedance, no PPI trial
Burk et al., 2015[44]	Not population-based, non-randomized	Cohort, prospective	Appropriate for inference	Sensitization to Galactose-alpha-1,3-galactose proxy for exposure to lone star tick