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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 the PubMed, Web of Science, and EMBASE databases from January 1, 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, and clinical trials. Nineteen 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 reported, but the exact mediators of this process, possibly aeroallergens that vary over time and from place to place, remain elusive.

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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 trial, and exclusion of secondary causes of eosinophilia.[1] Although 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 United States.[2-4] Accordingly, it now accounts for a substantial amount of health care–related spending in the United States.[5]

Eosinophilic esophagitis affects infants, children, and adults, although 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 have found that allergen exposure can recapitulate the histopathologic phenotype of EoE through the activation of T_H2 immune cells, and similar mechanisms have been identified in humans.[8-11] Epidemiologic studies further support the role of allergens in disease pathogenesis because 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 variations in EoE prevalence by climate type, geography, and season, and a study of inheritance patterns in EoE suggests that environmental factors play a larger etiologic role than genetics.[28] However, except for 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 environmental exposures and causation of the disease.

METHODS

Search Strategy

We conducted a systematic review by searching the PubMed, Web of Science, and EMBASE

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databases. To identify relevant articles, 2 authors (D.J.G. and C.C.C.) independently performed the search, which was developed with the assistance of a reference librarian with expertise in systematic review methods. We used the following search terms for EoE (the "*" before terms ensured that European spellings were detected): **eosinophilic esophagitis* OR *allergic *esophagitis* OR *corrugated *esophagus* OR *ringed *esophagus*. These terms are similar to those used in a previous systematic review of EoE diagnosis.[31] We limited the search to include only EoE articles on environmental, aeroallergen, or allergy-related risk factors by 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 epidemiologic topics, we further limited the search to articles 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. Both readers (D.J.G. and C.C.C.) subsequently hand searched the bibliographies of all identified articles and considered relevant articles for inclusion. We used the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist to ensure thorough methods.[32]

Article Inclusion Criteria

All articles published from January 1, 1950, through June 30, 2015, were eligible for inclusion. Owing 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 written 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, 1 of us (D.J.G.) reviewed the article titles and then abstracts to determine whether they were eligible for inclusion. This process was repeated independently by a second reviewer (C.C.C.). When there were discrepancies between the lists of articles to include, we read the full text and came to a consensus; adjudication, if needed, was performed by the senior author (E.S.D.). Both reviewers agreed on the final list of included material before analysis began.

ARTICLE HIGHLIGHTS

- This systematic review identified 19 articles pertaining to environmental risk factors for eosinophilic esophagitis (EoE).
- Study designs included case reports, case series, case-control studies, 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 at more granular levels are needed.

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 participants in a study); the number of patients in the comparator group; study population demographic characteristics, such as mean age, sex distribution, and allergy history; and main environmental risk—related findings, reported as crude and adjusted risk estimates (risk ratio and odds ratio [OR]). The validity of the articles was assessed by examining study design, precision of estimates, and potential for bias and measurement error. Owing 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). Of the initial 240 publications, we excluded 121 based on the title. These were

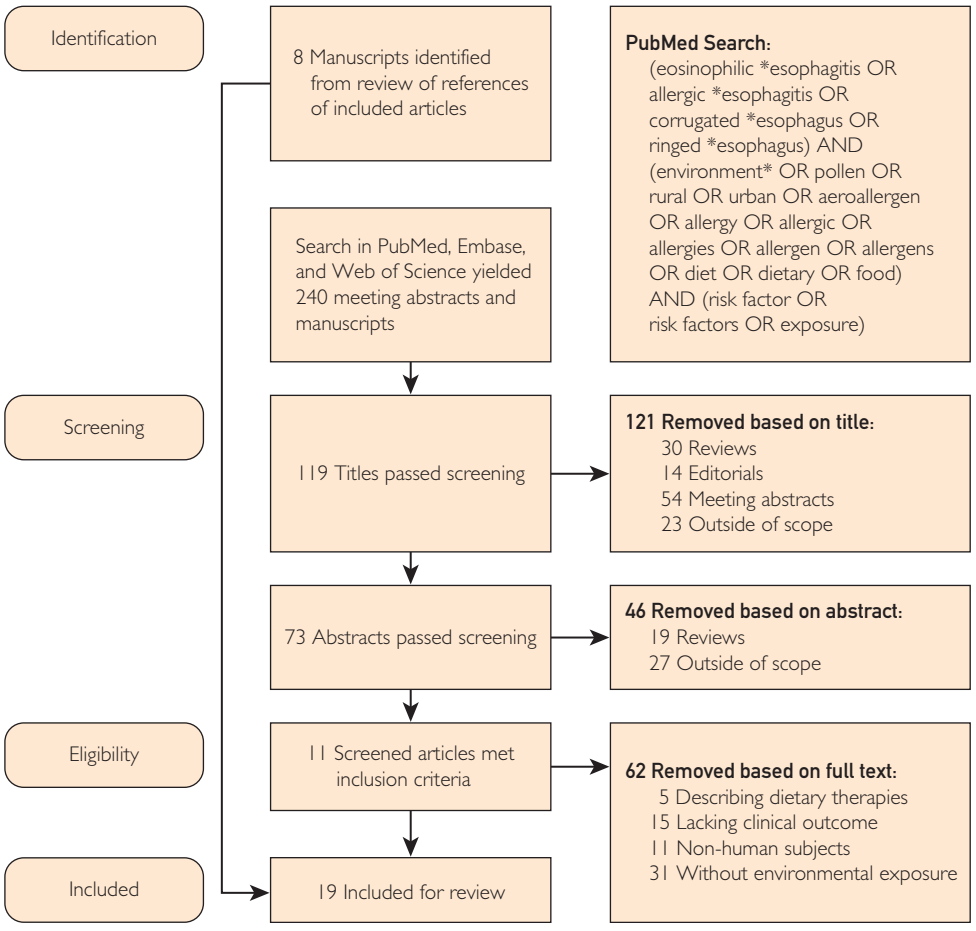

FIGURE. The combined search yielded 240 articles; 19 met the inclusion criteria and were the focus of this review. Of the initial 240 publications, we excluded 121 based on the title. These were typically review articles, based on animal models, or focused on treatment or diagnostic criteria. Of the 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.

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 73 articles, 62 were excluded because they did not address the topic of interest. Hand searching the bibliographies of the 11 included articles and germane review articles resulted in inclusion of an additional 8 articles not found in the initial search strategy. The 19 included articles consisted of observational epidemiologic studies and case series. There were no randomized studies. One article was a case report,[33] 2 were case series,[30,34] 1 was a cross-sectional study,[35] 9 were case-control studies,[36-44] and 6 were cohort studies.[45-50] All the articles were published in the past decade, with the earliest published in 2007. One study was conducted in Spain,[35] 1 in Canada,[40] and another in Australia,[42] with the remaining 11 completed in the United States. Studies included adults and children.

The aim, year, and environmental exposure investigated are presented in Table 1. Only 1 study was population based,[48] with the remaining drawing from clinical populations. All but 3 studies[40,44,45] reported positive findings (Table 2). Most studies, excluding 4

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TABLE 1. Aim, Design, and Exposure of Interest for Studies Included for Analysis

Reference, year	Aim	Design	Environmental exposure of Interest
Lee et al,[46] 2015	To compare demographic and clinical characteristics of urban vs rural patients with EoE with a PPI trial.	Cohort, retrospective	Population density (urban vs rural)
Castro Jiménez et al,[35] 2013	To describe the demographic and clinical characteristics and allergy sensitization of patients with EoE in a Spanish region.	Cross sectional	Aeroallergens
Wolf et al,[30] 2013	To offer initial human evidence of the EoE etiology mechanism proved in mouse models.	Case series	Aeroallergens
Ramirez and Jacobs,[33] 2013	To describe a case of dust mite hypersensitivity and EoE with clinical and pathologic improvement after desensitization.	Single case	Aeroallergens
Hurrell et al,[38] 2012	To examine the relationship between EE (not EoE) and climate.	Case-control	Climate
Jensen et al,[39] 2013	To explore early-life exposures as risk factors for EoE.	Case-control	Childhood antibiotics, cesarean delivery
Radano et al,[43] 2014	To investigate associations between EoE and dietary, environmental, and medical exposures during infancy.	Case-control	Childhood antibiotics, cesarean delivery
Slae et al,[40] 2015	To determine whether smoking and other exposures linked with the development of atopic disease are also associated with EoE.	Case-control	Childhood antibiotics, cesarean delivery, breast-feeding, smoking
Franciosi et al,[36] 2009	To determine demographic, socioeconomic, and geographic characteristics of CHOP's EoE cohort for pediatric patients.	Case-control	Population density (urban vs rural)
Roy-Ghanta et al,[34] 2008	To identify the specific environmental and food allergy profile of adults with EoE.	Case series	Multiple
Jensen et al,[37] 2014	To assess the relationship between EoE prevalence and population density.	Case-control	Population density (urban vs rural)
Philpott et al,[42] 2015	To determine whether a seasonal and geographic pattern exists in patients with EoE with recurrent FBOEs.	Case-control	Season
Moawad et al,[47] 2010	To determine whether there is seasonal variation and whether it correlates with seasonal pollen count.	Cohort, retrospective	Aeroallergens, season
Almansa et al,[45] 2009	To determine whether there is a seasonal pattern in the diagnosis of EoE in adults.	Cohort, retrospective	Season
Elias et al,[50] 2015	To confirm in a larger group of patients a seasonal pattern of EoE diagnosis.	Cohort, retrospective	Season
Jensen et al,[41] 2015	To determine whether there is seasonal variation in the detection and diagnosis of EE and EoE.	Case-control	Season
Prasad et al,[48] 2009	To assess the epidemiology and outcomes of EE in Olmsted County, MN, over the past 3 decades.	Cohort, retrospective	Season
Wang et al,[49] 2007	To examine the seasonal distribution of newly diagnosed EoE in children.	Cohort, retrospective	Season
Burk et al,[44] 2015	To test whether sensitization to galactose-α-1,3-galactose is a risk factor for EoE.	Case-control	Insect

CHOP = Children's Hospital of Philadelphia; EoE = eosinophilic esophagitis; FBOE = food bolus obstruction event; PPI = proton pump inhibitor.

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 4 years, demonstrating proof-of-principle that aeroallergens can affect disease activity in EoE.[51] Although 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 in the winter,

TABLE 2. Study and Comparator Populations, Demographics, and Main Findings

Reference, year	Study population	Cases (No.)	Comparator population	Sex (M:F ratio)	Mean age (y [range])	White race (%)	History of atopic disease (%)	Main findings
Lee et al,[46] 2015	University of Iowa GE clinic patients with EGD and biopsy for esophageal indications	57	NA	2:1	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 et al,[35] 2013	2006-2011 EoE patients at GE clinic of Ciudad Real University General Hospital	43	NA	3:1	33.6 (6-63)	NR	83.7	Patients with EoE have diverse sensitizations to specific IgE, skin prick testing, and patch testing
Wolf et al,[30] 2013	3 Patients with EoE after specific large-volume aeroallergen exposures	3	NA	All male	23.7 (20-29)	NR	NR	Description of history of exposure before diagnosis
Ramirez and Jacobs,[33] 2013	1 Case of EoE in a young child	1	NA	Male	4	NR	Food allergies	EoE remission after dust mite desensitization
Hurrell et al,[38] 2012	US national pathology database of 233,649 patients	9995	71,948 noncases from 2008-2010	2:1 cases; 1:2 controls	Cases: 44.4 (NR); controls: 53.7 (NR)	NR	NR	Tropical aOR, 0.87 (95% CI, 0.71-1.08), arid aOR, 1.27 (95% CI, 1.19-1.36), temperate (ref.), cold aOR, 1.39 (95% CI, 1.34-1.47)
Jensen et al,[39] 2013	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 controls: 12 (NR); plastics controls: 8 (NR)	73-85	Cases: 74 GERD, 54 plastics, 35 allergy	OR, 6.0 for antibiotics
Radano et al,[43] 2014	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	4:1 cases; 2:1 controls	Cases: median, 3.4; controls: 4.3	Cases: 68; controls: 68	Cases: 75 eczema, 67 food allergy	EoE more often cesarean delivery (60% vs 34%; P=.03) and antibiotic use in first year of life (67% vs 33%; P=.004)
Slae et al,[40] 2015	EoE cases and controls from pediatric clinic and endoscopy visits, recruitment period not specified	102	167	4:1 cases; 1:1 controls	Cases: 10.8 (NR); controls: 10.0 (NR)	NR	Cases: 57 eczema, 47 asthma, 62 AR, 10 Food	Smoking, breast-feeding, cesarean delivery, childhood antibiotics not found to be associated with EoE
Franciosi et al,[36] 2009	CHOP EoE patients, using 20 eosinophils per HPF as a cutoff value	335	Pediatric GE and pediatric allergy clinics	3:1	NR	83.6	NR	aOR, 2.08 (95% CI, 1.22-3.54) for suburban living (vs urban) in EoE group vs allergy patients
Roy-Ghanta et al,[34] 2008	Adult patients with EoE by consensus guidelines seen in University allergy clinic	23	NA	1.6:1	35.2 (18-57)	NR	78	Patients sensitized to danders, grass pollen, mite allergen, ragweed, and tree pollen

Continued on next page

TABLE 2. Continued

Reference, year	Study population	Cases (No.)	Comparator population	Sex (M:F ratio)	Mean age (y [range])	White race (%)	History of atopic disease (%)	Main findings
Jensen et al,[37] 2014	Patients with >15 eosinophils per HPF and dysphagia from national pathology database	14,381	292,621 noncases	2:1 cases; 1:2 controls	Cases: 45 (NR); controls: 54 (NR)	86	NR	aOR, 1.59 (95% CI, 1.45-1.76) odds of EoE bottom to top quintile of population density
Philpott et al,[42] 2015	Patients with recurrent FBOEs at 5 tertiary hospitals	6	19 noncase recurrent FBOEs	4:1 cases; 3:1 controls	Cases: 39.1 (NR); controls: 62.0 (NR)	NR	NR	67% to 5% EoE vs noncase, October 1 to January 1, P=.005
Moawad et al,[47] 2010	Adult EGD population 2006-2008, symptoms and histology of EoE at Army Medical Center	127	NA	6:1	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 et al,[45] 2009	37 EoE cases, 41 validations at Mayo Clinics, consensus diagnosis between August 2006 and July 2007	79	EGD case volume during that period	3:2	51.5 (16.1)	94.9	51 Clinical history of allergies	More diagnoses in spring and summer months than in fall and winter, P<.019, despite constant EGD rate
Elias et al,[50] 2015	Adult patients from center's disease registry	372	NA	3:1	41.9 (14.7)	NR	72 AR, 46 asthma	No significant seasonal trend, more cases in opposite seasons reported elsewhere
Jensen et al,[41] 2015	Patients with >15 eosinophils per HPF from national pathology database	14,524	90,459 controls	2:1	45.0 (16.2)	NR	NR	Small but consistent seasonal variation in diagnosis, with cases more frequent during summer months
Prasad et al,[48] 2009	Residents of Olmstead County, MN, from 1976-2005 with EoE, consensus diagnosis	78	NA	1:1 adults; 2:1 children	Adults: 37 (NR); children: 10 (NR)	NR	Adults: 50 allergy; children: 53.8	More EoE diagnosis in late summer and early fall
Wang et al,[49] 2007	234 EoE patients, Pediatric Hospital, 1998-2004	234	NA	2:1	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 et al,[44] 2015	Prospective collection of 50 cases and 50 controls among UNC EGD patients	50	EGD noncases	3:2	38.1 (10.6)	86	35 Asthma, 9 eczema, 65 AR, 32 food	Galactose-α-1,3-galactose sensitization not significantly greater in cases than in controls

aOR = adjusted odds ratio; AR = allergic rhinitis; CHOP = Children's Hospital of Philadelphia; EE = esophageal eosinophilia; EGD = esophagogastroduodenoscopy; EoE = eosinophilic esophagitis; FBOE = food bolus obstruction event; GE = gastroenterology; GERD = gastroesophageal reflux disease; HPF = high-power field; NA = not applicable; NR = not reported; OR = odds ratio; ref. = referent group; UNC = University of North Carolina.

TABLE 3. Potential for Bias, Imprecision, and Measurement Error in Each Study

Reference, y	Bias	Direction of bias	Precision	Measurement error
Lee et al,[46] 2015	Not population based, nonrandomized	Indefinite, possibly dependent on local referral patterns	Sufficient to detect large, consistent effects	Consensus diagnostic criteria, valid geocoding
Castro Jiménez et al,[35] 2013	Not population based, nonrandomized, does not 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,[30] 2013	Study describes cases but does not report numeric estimates	NA	NA	Consensus definition of cases, exposure history soon after event minimizes recall bias
Ramirez and Jacobs,[33] 2013	Study describes cases but does not report numeric estimates	NA	NA	Consensus definition of case, prick and patch testing
Hurrell et al,[38] 2012	Large national pathology registry, not population based, general to endoscopy population	Toward exaggerated effect, socioeconomic or ethnic patterns	Appropriate for inference	Nonconsensus diagnostic criteria, indefinite PPI trial
Jensen et al,[39] 2013	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,[43] 2014	Not population based, nonrandomized, 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,[40] 2015	Not population based, nonrandomized, 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,[36] 2009	Not population based, nonrandomized, single center	Indefinite, possibly dependent on local referral patterns	Appropriate for inference	Consensus diagnostic criteria, valid geocoding
Roy-Ghanta et al,[34] 2008	Not population based, nonrandomized, does not temporally place sensitization ahead of EoE diagnosis	Likely toward a 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,[37] 2014	Large national pathology registry, not population based, general to endoscopy population	Toward exaggerated effect, socioeconomic or ethnic patterns	Appropriate for inference	Nonconsensus diagnostic criteria, indefinite PPI trial, sensitivity analyses
Philpott et al,[42] 2015	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	Nonconsensus diagnostic criteria, indefinite PPI trial
Moawad et al,[47] 2010	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	Nonconsensus diagnostic criteria, indefinite PPI trial
Almansa et al,[45] 2009	Findings internally valid but limited to a single center, influence of scheduling practices is difficult to quantify	Likely toward overestimating seasonal trend	Sufficient to detect large, consistent effects	Season of incidence from timing of diagnosis limited by long subclinical phase
Elias et al,[50] 2015	Findings internally valid but limited to a single center, influence of scheduling practices is difficult to quantify	Likely toward overestimating seasonal trend	Appropriate for inference	Limits of retrospective collection, long subclinical phase
Jensen et al,[41] 2015	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	Nonconsensus diagnostic criteria, indefinite PPI trial, sensitivity analyses
Prasad et al,[48] 2009	Population-based study of incident diagnoses, case definition lacks PPI trial	Possibly toward null due to case definition	Appropriate for inference	Nonconsensus diagnostic criteria, indefinite PPI trial
Wang et al,[49] 2007	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-h pH impedance, no PPI trial
Burk et al,[44] 2015	Not population based, nonrandomized	Cohort, prospective	Appropriate for inference	Sensitization to galactose-α-1,3-galactose proxy for exposure to lone star tick

EGD = esophagogastroduodenoscopy; EoE = eosinophilic esophagitis; NA = not applicable; PPI = proton pump inhibitor.

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and 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 patients with EoE.[35] Patients had positive skin prick test results for a variety of aeroallergens, including grasses and olive pollens, *Planatus*, and animal dander. Finally, a case series documented 3 patients who had new-onset EoE after a large-volume allergen exposure.[30] This was a rare example 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 found that sensitization to galactose-α-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 *Dermatophagoides pteronyssinus*.[33]

Climate

We identified 1 case-control study that examined the risk of EoE by climate type.[38] Using a large national pathology database, the prevalence of EoE was compared among tropical, arid, cold, and temperate climate zones in the United States using the Köppen-Geiger climate class system. For the 9995 EoE cases and 71,948 controls included, there was a statistically significant increase in the odds of EoE in arid (adjusted OR [aOR], 1.27; 95% CI, 1.19-1.36) and cold (aOR, 1.39; 95% CI, 1.34-1.47) climates. No other publications to date have investigated a similar question.

Urban vs Rural Populations

There were 3 studies that examined urban vs rural environments as a risk factor for EoE. The first study used a case-control design to compare 335 pediatric patients with EoE with clinic-based controls and with 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) compared with allergy clinic controls, but there was not a significant difference in risk of EoE comparing cases with gastroenterology clinic controls. The second study 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 cutoff point of 1000 people per square mile.[46] There was no statistically significant difference in prevalence between urban and rural areas, but there were some differences in clinical features. Urban patients, for example, were more likely to present with dysphagia, and rural patients were more likely to experience heartburn and reflux. The third study used a large pathology database to assess population density as a risk factor for EoE.[37] A total of 14,381 EoE cases were compared with almost 90,000 controls from throughout the United States, 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 study used a retrospective cohort design to compare rates of EoE diagnosis across seasons and adjusted for seasonal esophagogastroduodenoscopy case volume.[45] They found that EoE diagnosis was more common in spring and summer, or the outdoor months, than in winter and fall, or the indoor months. A similar study found that 33% of patients were diagnosed in the spring and only 16% were diagnosed in the winter, and the temporal correlation with grass pollen counts was compelling.[47] A study in Olmstead County, Minnesota, examined all patients with EoE from 1976 through 2005 and found that significantly more patients were diagnosed in late summer and early fall.[48] A study of 234 children with EoE assessed rate of diagnosis between months and inflammation severity based on histopathologic characteristics of biopsy tissue.[49] This study found not only that winter had significantly fewer newly diagnosed cases of EoE than did other seasons but also 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 aOR of 1.13 (95% CI, 1.03-1.24), and the relationship persisted through several sensitivity analyses. However, an adequately powered, single-center registry study did not 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 the seasonality of EoE diagnosis are generally limited in that they assess the timing of diagnosis rather than actual onset of disease.

Early-Life Exposures

We identified 3 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 drug use in infancy, group B streptococcal infection, nonexclusive breast-feeding, and others.[39] Although antibiotic drug 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 toward increased risk with other exposures, particular cesarean delivery. A subsequent and larger case-control study replicated these findings with respect to antibiotic drug exposure and found a statistically significant effect of cesarean delivery.[43] A further case-control study did not replicate the effects of childhood antibiotic agents and cesarean delivery and found no effect of smoking or breast-feeding duration.[40]

DISCUSSION

Eosinophilic esophagitis is defined as an allergen/immune-mediated condition.[1,6] Although the current model of EoE pathogenesis holds that an allergic exposure triggers a T_H2-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 variety 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 variety 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 found an etiologic environmental risk factor in a large population that was prospectively assessed.

Data on climate and seasonality, although mixed, suggest that trends related to climate zone, seasonality, or aeroallergens may affect 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 affect 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 although multiple hypotheses are possible, further research is needed to explicate the underlying reasons for this trend. The studies on early-life exposures, although 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 reported,[51] but why these might be important in some patients with EoE and not in others remains to be determined. Interestingly, emerging data with component-resolved diagnostics find 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 herein do not yet prove causality of any particular exposure.

When interpreting the results of this study, there are several limitations to acknowledge. Because we were concerned with nondietary 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 the search to articles that aimed to provide clinical evidence of the pathogenesis

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or etiology of EoE. Therefore, these 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. Although it is possible that we may have missed some studies, the study design assessing multiple literature sources with 2 independent data abstractors was comprehensive.

CONCLUSION

We identified 19 articles assessing environmental risk factors for EoE, and several trends were identified. Studies that directly supported 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 drug 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.

Abbreviations and Acronyms: **aOR** = adjusted odds ratio; **AR** = allergic rhinitis; **CHOP** = Children's Hospital of Philadelphia; **EE** = esophageal eosinophilia; **EGD** = esophagogastroduodenoscopy; **EoE** = eosinophilic esophagitis; **FBOE** = food bolus obstruction events; **GE** = gastroenterology; **GERD** = gastroesophageal reflux disease; **HPF** = high-power field; **NA** = not applicable; **NR** = not reported; **OR** = odds ratio; **PPI** = proton pump inhibitor; **PRISMA** = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **ref.** = referent group; **UNC** = University of North Carolina

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