

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

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.)

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.

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.

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

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