

# Environmental factors and eosinophilic esophagitis



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The incidence and prevalence of eosinophilic esophagitis (EoE) have markedly increased over the past 2 decades, outpacing increased detection of the disease. Although genetic susceptibility markers for EoE have begun to be elucidated, the rate at which EoE has increased in incidence suggests environmental factors predominate. Despite many advances in understanding of the pathogenesis of EoE, the cause of EoE is unknown. This article reviews the emerging data related to environmental risk factors for EoE. Many of these environmental factors are rooted in the theoretical framework of the hygiene hypothesis, specifically mediation of disease development through dysbiosis. Other hypotheses are based on associations that have been observed in studies of non-EoE allergic disease. We describe the evidence that early-life exposures, including antibiotic use, acid suppression, and cesarean delivery, can increase the risk of disease. We also describe the evidence that infectious agents, such as *Helicobacter pylori*, are inversely associated with disease. Current evidence on geographic risk factors, such as population density, climate zone, and seasonality, is reviewed. We also describe behavioral factors that have been evaluated. Limitations of the existing research are discussed, and recommendations for future areas of research, including assessment of gene-environment interaction, are presented. (J Allergy Clin Immunol 2018;142:32-40.)

**Key words:** Environment, early life, microbiome, epigenetics, gene-environment interaction

## Abbreviations used

alpha-gal:	Galactose-alpha,1,3-galactose
aOR:	Adjusted odds ratio
CTD:	Connective tissue disorder
EoE:	Eosinophilic esophagitis
HSV:	Herpes simplex virus
NSAID:	Nonsteroidal anti-inflammatory drug
PPI:	Proton pump inhibitor

Eosinophilic esophagitis (EoE) is an immune-mediated<sup>1-6</sup> chronic disease associated with significant morbidity, including dysphagia, food impactions, and, in the pediatric population in particular, food intolerance and faltering growth.<sup>7-13</sup> Disease management can be challenging. No pharmacologic therapies have been approved for the treatment of EoE, and current treatments necessitate dietary elimination strategies, topical steroids, or elemental formula diets. Most patients with EoE have evidence of concomitant atopic illness. However, although specific foods elicit clinical and histologic manifestations of disease for many patients, EoE is not believed to be an IgE-mediated disease.<sup>14,15</sup>

The incidence and prevalence of EoE have increased dramatically since its initial recognition as a unique disease entity just 2 decades ago.<sup>16-20</sup> In the 1990s, when EoE was first described, disease incidence was estimated at just 0.4 cases/100,000/y. Current estimates of disease incidence and prevalence vary but are generally described to be approximately 10 cases/100,000/y, with a prevalence of 50 to 100 cases/100,000.<sup>17,20-23</sup> The economic burden of EoE is substantial. In the United States, where as many as approximately 400,000 persons are affected,<sup>24</sup> the estimated annual health care costs associated with EoE are \$1.4 billion.<sup>25</sup>

Although some of this increase can be attributed to increased awareness and surveillance of the disease, incident diagnoses have outpaced the increase in upper endoscopies.<sup>17,20,26</sup> Candidate and genome-wide association studies have identified possible susceptibility genes associated with disease development<sup>27-30</sup>; however, given the rate at which disease incidence has increased, environmental factors are likely implicated in disease pathogenesis. Furthermore, a twin and family study of EoE identified a stronger concordance for EoE between dizygotic twins than in siblings, suggesting that not only do environmental factors contribute but also shared environmental factors experienced in early life might be important to disease cause.<sup>31</sup>

To date, the body of evidence to support the contribution of environmental factors in patients with EoE is still under development, with considerable gaps in knowledge. Much of the existing evidence has focused on early-life factors implicated in patients with other allergic diseases, infectious disease factors, geographic factors, and behavioral factors, with limited data on the contribution of genetic and epigenetic factors in relation to

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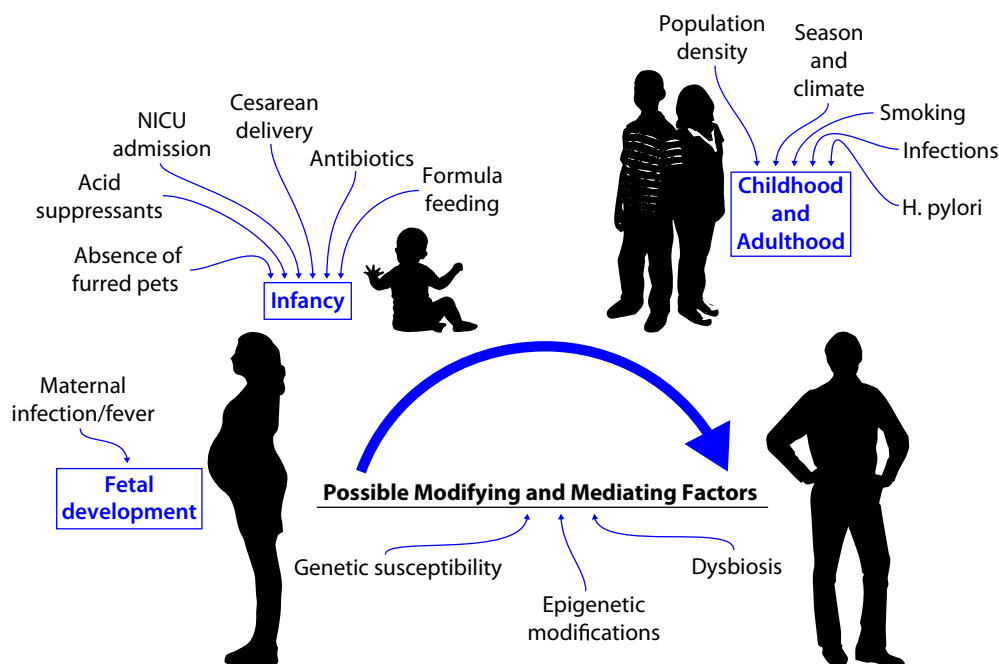


FIG 1. Candidate risk factors for development of EoE. NICU, Neonatal intensive care unit.

these environmental factors (Fig 1). This article describes the evidence thus far and provides recommendations for future directions to address these gaps in knowledge (Table I).

## ALLERGIC DISEASES, THE HYGIENE HYPOTHESIS, AND THE MICROBIOME

Given the high proportion of patients with EoE with concomitant atopic disease, it is not surprising that the focus of much of the research on environmental factors and EoE has focused on factors implicated in other atopic diseases. As with EoE, the incidence and prevalence of other atopic diseases have also been increased in recent decades. One of the prevailing theories to explain this increase, the hygiene hypothesis, asserts that an overly hygienic environment, although important in the reduction of infectious disease, might have untoward effects on the host-microbiome balance necessary for immune system development. However, this theory has been met with scrutiny and has been adapted recently with advances in our ability to characterize the human gut microbiome.<sup>32-35</sup> Evidence supports the role of the microbiome in establishing immune function health, but it is not necessarily an aseptic environment that is to blame but rather the absence of certain necessary commensal bacteria. Although the microbiome research field is still relatively underdeveloped (ie, technology for characterizing species continues to evolve and our capacity to analyze the complexity of the microbiota remains relatively crude),<sup>36-42</sup> numerous studies have identified differences in microbiota diversity and patterns of relative abundance in association with atopic disease.<sup>43</sup> A challenge in the literature is establishing the temporality of the association, specifically whether the differences observed are attributable to the disease process itself or whether differences in the microbiota lead to the cascade of events that elicit disease development (eg, microbiota-host interactions and alterations in barrier function

that contribute to aberrant immune response and loss of antigen tolerance).<sup>44-47</sup>

Although much of the microbiota research initially focused on gut microbiota, the field has expanded to include assessment of the entire human microbiome. Differences in the esophageal microbiome have been described between patients with EoE, patients with gastroesophageal reflux disease, and healthy control subjects,<sup>48</sup> but again, it is unknown whether these differences are driven by disease or whether they preceded disease development. With treatment, the differences between patients with EoE and healthy control subjects has been suggested to diminish, although not completely.<sup>37</sup>

Studies evaluating the use of synbiotics to prevent atopic disease have yielded varied results,<sup>49-51</sup> likely because our understanding of the microbiome and microbiota interactions is relatively immature, establishing which synbiotics confer protection remains elusive.<sup>52</sup> For patients with EoE, a single study conducted in a murine model identified a beneficial effect of the probiotic *Lactococcus lactis* NCC 2287 on esophageal inflammation.<sup>53</sup> Because only a few studies of the esophageal microbiome have been conducted, this is an area where further research is needed to establish the significance, if any, of the esophageal microbiome in disease pathogenesis.

## EARLY-LIFE FACTORS AND EoE

EoE can develop in infancy but is observed more frequently later in childhood and sometimes into adulthood. Thus it might not be readily apparent how factors experienced in early life could contribute to disease development later in life. However, early life is a period of unique developmental susceptibility, and immune maturation might be sensitive to early-life experiences.<sup>54,55</sup> Furthermore, it has been suggested that EoE might be part of the atopic march continuum, appearing later in the cascade of atopic illnesses frequently coexisting in childhood.<sup>56</sup>

**TABLE I.** What is unknown?

Potential for interaction between environmental factors and EoE
Epigenetic modifications and the environment in relation to EoE
Factors that might contribute to dysbiosis of the gut microbiota, such as diet, in relation to EoE
Examination between early-life factors and EoE and whether associations are mediated by dysbiosis
Temporal association between esophageal microbiome in association with EoE
Association between acid suppressant use in early life and EoE
Improved understanding of how geographic factors can contribute to disease pathogenesis

### Antibiotic use, cesarean delivery, and other microbiome-altering factors

Colonization of the microbiome occurs in early life and after the age of 2 or 3 years becomes relatively stable.<sup>57</sup> Changes in the microbiome can be observed at older ages with dietary changes, use of probiotics and antibiotics, illness, and other exposures, but these changes have been characterized generally as transient and self-limited. Because early life is important in development of the microbiome and, consequently, development of the immune system,<sup>44-47</sup> numerous studies have examined early-life experiences that can shape microbiota colonization.<sup>58</sup> Many factors are now described to alter the diversity and/or relative abundance of the microbiota in early life, factors including cesarean delivery, preterm delivery, neonatal intensive care unit admission, choice of infant feeding, maternal and infant use of antibiotics, and others.<sup>39,59-73</sup> It is this body of literature that has informed studies evaluating the contribution of early-life factors in relation to EoE.

To date, 5 case-control, single-center studies have been conducted examining the contribution of early-life factors and the development of EoE. Four of these included pediatric patients only,<sup>74-77</sup> and 1 study examined adult patients.<sup>78</sup> With the exception of 1 study, which observed only a weak inverse association between postnatal environmental tobacco smoke exposure and EoE in the pediatric population,<sup>76</sup> all 4 other studies, which were conducted at 3 different centers, identified associations between early-life factors and EoE development.<sup>74,75,77,78</sup> For the pediatric studies, although not all of the studies examined the same factors and although differences in associations were observed between studies, factors identified were consistent with those that have been demonstrated to alter microbiota colonization in the gut, including supplemented breast-feeding or formula feeding (possible protective effect for breast-feeding observed), neonatal intensive care unit admission, antibiotic use in infancy, cesarean delivery, ownership of a furred pet in the home in infancy (protective association observed), and infant use of acid suppressants (further described below). Perhaps the strongest and most consistent evidence of an association (positive association indicated in 4 of the 5 studies) has been observed for antibiotic use in infancy (Fig 2).

### Acid suppressants

Acid suppressants, specifically proton pump inhibitors (PPIs), are routinely used to aid in the diagnosis and treatment of EoE because patients with clinical symptoms and histologic evidence consistent with EoE diagnosis ( $\geq 15$  eosinophils/high-power field on biopsy) can experience clinical and histologic improvement

after treatment with a PPI. Paradoxically, acid suppressants, including PPIs, have been demonstrated to alter gut permeability.<sup>79-81</sup> This increased permeability can compromise oral tolerance, and in both animal models and human studies, acid suppressants have led to inhibition of dietary protein digestion and development of IgE antibodies in response to the inhibited protein or proteins.<sup>82,83</sup> In observational studies acid suppressants, when used during pregnancy, have been associated with increased risk of atopy in offspring.<sup>84</sup>

The association between acid suppressant use and development of EoE has only been evaluated minimally. One study examined EoE among patients prescribed a PPI after an initial upper endoscopy and described that there was no evidence of an increase in absolute EoE cases after repeat endoscopy or evidence that an increasing PPI dose was associated with an increased proportion of EoE diagnoses on repeat endoscopy.<sup>85</sup> Conversely, a small case series of three patients described development of EoE after initial diagnoses of reflux esophagitis or infectious esophagitis treated with a PPI.<sup>86</sup> In the most recent case-control study of early-life factors and EoE, a positive association was observed between reported use of an acid suppressant in infancy and EoE diagnosis at age 3 years or older.<sup>77</sup> Although intriguing, the association observed could be attributable to protopathic bias or symptoms of EoE leading to use of a PPI in infancy, with delayed diagnosis at age 3 years. Thus additional mechanistic research is needed to evaluate these associations further.

### INFECTIOUS RISK FACTORS FOR EoE

#### *Helicobacter pylori*

Perhaps providing support for the hypothesis that the increase in prevalence described for atopic conditions can be driven in part by changes in the environment that decrease infectious disease, *Helicobacter pylori* has been inversely associated with atopic conditions, including allergic rhinitis, atopic dermatitis, and asthma.<sup>87</sup> This same inverse association has also been observed for EoE in both pediatric and adult studies, with a reduction in EoE risk in the absence of *H pylori*.<sup>88-91</sup> This relationship also fits the temporality noted for the increase in EoE over the past 2 decades and is supported by a possible mechanism. Specifically, *H pylori* is thought to polarize toward more of a T<sub>H</sub>1 immune response, and absence of *H pylori* can polarize toward a T<sub>H</sub>2 response.<sup>88</sup> However, this mechanism has yet to be tested experimentally.

#### Herpes simplex virus

Case reports and case series have suggested a possible association between herpes simplex virus (HSV) esophagitis and EoE.<sup>92-94</sup> In one series of 3 pediatric patients with atopy, HSV esophagitis was diagnosed initially, and there was no evidence of EoE, but EoE developed within 2 months of the HSV diagnosis.<sup>93</sup> A case series of 5 adults with HSV esophagitis showed histologic and clinical symptoms consistent with an EoE diagnosis.<sup>95</sup> Similarly, a retrospective assessment of 11 immunocompetent patients with HSV esophagitis identified 5 patients with eosinophilic infiltrate consistent with EoE at follow-up biopsy.<sup>96</sup> Although these reports suggest HSV esophagitis can co-occur with EoE in some patients, observational studies are needed to evaluate the potential for a temporal association.

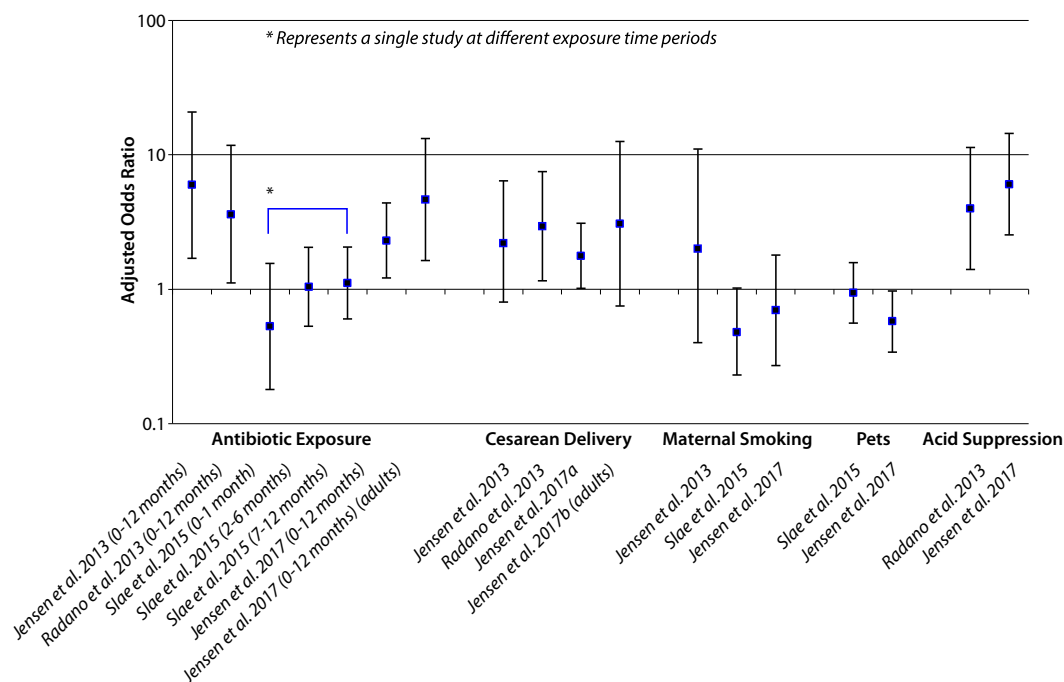


FIG 2. Early-life factors evaluated in association with EoE.

### Galactose-alpha-1,3-galactose

In a case-control design study IgE sensitization to tick-borne galactose-alpha,1,3-galactose (alpha-gal) was evaluated in relation to EoE because this is an infectious vector that causes a food allergy. Sera biobanked from adults with EoE ( $n = 50$ ) and control subjects ( $n = 50$ ) were evaluated for IgE sensitization to alpha-gal. Although a high proportion of cases and control subjects were observed to have evidence of sensitization, no differences were observed between cases and control subjects.<sup>97</sup>

### *Mycoplasma pneumoniae*

A case series of 12 patients with EoE found a high proportion (83%) of IgG positivity for *Mycoplasma pneumoniae* with serologic testing.<sup>98</sup> However, without characterization of seroprevalence of *M pneumoniae* in control subjects, the association with EoE cannot be determined.

### Geographic risk factors for EoE

Geographic factors, although likely not directly causal for EoE, could offer insight into other environmental factors that might be implicated in disease development.

### Population density/geographic differences

To date, 4 studies have examined population density or rural versus urban residence in relation to EoE. The first, a single-center, case-control study of 508 cases, 508 gastroenterology specialty clinic control subjects, and 508 allergic control subjects observed a higher proportion of patients with EoE arising from suburban areas compared with allergic control subjects (adjusted odds ratio [aOR], 2.1; 95% CI, 1.2-3.5). However, when comparing patients with EoE with

gastroenterology clinic control subjects, no association between residence was observed. Another study surveyed gastroenterologists and allergists on patients with eosinophilic gastrointestinal disease, and found that EoE was more common in patients with a rural residence.<sup>22</sup> In a study of 14,381 cases and 89,754 control subjects identified in a pathology database containing patients from throughout the United States, a dose-response inverse relationship was observed between population density and increased risk of EoE. Compared with the most populous residence, there was a 40% increase in the risk of EoE observed for the least populous area of residence (aOR, 1.4; 95% CI, 1.1-1.8). Another study examined EoE incidence and clinical symptoms of EoE according to rural versus urban residence in 57 patients with EoE in Iowa. Although no difference was observed in the incidence of EoE diagnosis, differences in symptoms were reported, with a higher proportion of urban residents reporting dysphagia ( $P = .047$ ) and a higher proportion of rural residents reporting heartburn or reflux ( $P = .04$ ).<sup>99</sup>

### Climate zone/seasonality

The same national pathology database described above was also used to examine the association between climate zone and EoE. Relative to the temperate climate zone, this study reported an increased risk for EoE for patients residing in a cold climate zone (aOR, 1.4; 95% CI, 1.3-1.5).<sup>100</sup> Climate zones can be closely linked to local vegetation patterns and might implicate certain aeroallergens, but this requires further study.

Numerous single-center studies have examined seasonality in relation to EoE, although a challenge in such studies is determining symptom onset because diagnosis is known to lag far behind initial onset of symptoms. Although some of these studies suggest an association between season and EoE,<sup>20,101-105</sup>



some studies have indicated no association.<sup>106-108</sup> Diagnostic delay can contribute to some of these inconsistencies, but geographic and climate differences can also contribute because aeroallergens (type, count, and temporal variability) are known to vary across climate zones. A recent study of seasonality and pollen counts conducted in 36 patients with EoE in the New York City area identified increased patient reporting of symptoms in summer months (July-September) and increased diagnoses in the Fall (October-December). Counts from 11 different pollen taxa were examined, including *Acer* (maple), *Betula* (birch), *Populus* (poplar), *Ulmus* (elm), *Quercus* (oak), *Carya* (hickory), *Fraxinus* (ash), *Platanus* (sycamore and London planetree), *Fagus* (beech), Poaceae (grass pollen family), and *Ambrosia* (ragweed). Symptoms of EoE correlated with peak levels of grass pollen.<sup>109</sup> Another study examined seasonality and EoE, taking into account climate zone, again by using the national pathology data described above. As expected, this study identified differences in the relationship between seasonality and EoE by climate zone, with the strongest evidence of seasonal variation in EoE diagnoses in temperate and cold climates. Summer months were associated with higher EoE diagnosis; however, peak diagnoses by month differed according to climate zone.<sup>110</sup>

## BEHAVIORAL RISK FACTORS FOR EoE

Smoking and alcohol have been associated with gastroesophageal reflux disease, and nonsteroidal anti-inflammatory drug (NSAID) use has been associated with atopic illnesses<sup>111-113</sup> and other inflammatory gastrointestinal illnesses, including microscopic colitis.<sup>114</sup> Thus far, only 1 study has examined these factors in patients with EoE. In a single-center case-control study of 115 incident cases and 225 control subjects who had undergone upper endoscopy for symptoms of esophageal dysfunction, data on smoking behaviors and alcohol and NSAID use were collected through a patient questionnaire administered before endoscopy and diagnosis. This study observed a decreased risk of EoE among those who had ever smoked (aOR, 0.5; 95% CI, 0.2-0.9) and a decreased risk of EoE for current NSAID use (aOR, 0.4; 95% CI, 0.2-0.8). Current alcohol use was moderately associated with EoE, but the estimate was attenuated with adjustment for age, sex, race, education level, smoking, and atopy (aOR, 1.6; 95% CI, 0.8-3.1).<sup>115</sup> Other potential confounders, specifically factors that could be associated with smoking behaviors and diagnosis of EoE, were not assessed.

## GENETICS AND EPIGENETICS AND THE ENVIRONMENT

### Gene-environment interaction

Studies of gene-environment interaction offer the potential to identify novel genes, exposures, or both whereby risk is only conferred in the presence or absence of the other. These studies could offer increased mechanistic understanding of disease and also help identify modifiable environmental factors for disease prevention in those with underlying genetic susceptibility for disease (eg, siblings of patients with EoE). To date, only 1 study has investigated genetic susceptibility markers in relation to environmental factors. This study, although small (n = 248), observed that breast-feeding conferred a protective effect for EoE among those with the susceptibility gene variant at rs6736278.<sup>116</sup> More studies are needed to examine how environmental factors

can interact with underlying genetic susceptibility to increase or decrease risk of disease.

## Epigenetic modifications and environmental factors

Epigenetic assessments have elucidated novel mechanistic pathways in the development of childhood asthma and allergy,<sup>117-119</sup> and environmental factors have been associated with changes in epigenetic methylation and histone modification patterns.<sup>120,121</sup> Epigenetic modifications in patients with EoE have been explored minimally in patients with EoE<sup>122</sup> yet offer the potential to improve our understanding of how environmental factors infer increased (or decreased) disease risk. These evaluations could provide mechanistic insights that are important in the development of therapeutic targets for disease treatment.

## EoE phenotypic heterogeneity

It should be noted that although most of the research on environmental factors in the development of EoE has been informed primarily by risk factors demonstrated to be associated with atopic disease, there is heterogeneity in the comorbid conditions experienced by patients with EoE, and in a proportion of patients (approximately 30%), the disease does not appear to be associated with having other atopic conditions. Indeed, for some patients with EoE, there appears to be increased co-occurrence of autoimmune conditions, including celiac disease, Crohn disease/ulcerative colitis, rheumatoid arthritis, IgA deficiency, multiple sclerosis, common variable immunodeficiency, and autoimmune thyroid disease.<sup>123-125</sup>

EoE has also been associated with tracheoesophageal fistulae, although even in those with co-occurring EoE and tracheoesophageal fistulae, 70% were indicated to have at least 1 or more additional atopic conditions. Additionally, EoE has been associated with inherited connective tissue disorders (CTDs), with 3.3% of patients with EoE having a CTD (Marfan syndrome, Marfanoid-related syndrome, Ehlers-Danlos and related syndromes, and Loeys-Dietz syndrome) at one center (compared with a prevalence of approximately 0.02% in the general population).<sup>126-128</sup> Again, the co-occurrence of atopy was similar in those with and without a co-existing CTD. Environmental etiologic studies of EoE conducted thus far have not differentiated EoE based on atopic co-occurrence or the presence of other comorbid conditions.

## CONCLUSIONS AND FUTURE DIRECTIONS

Although numerous studies have been conducted on environmental factors and EoE, this body of research remains relatively undeveloped. Consistent evidence has supported possible associations between antibiotics in infancy and development of EoE, but the studies conducted thus far have the potential for bias given the fact that use of antibiotics has been collected retrospectively through recall. Furthermore, there is a potential that these associations could reflect confounding by indication; specifically, some other factor associated with early-life antibiotic use, such as asthma, might also be associated with EoE. None of the studies examining antibiotic use examined infection as a possible contributing factor and antecedent for antibiotic use, although there are studies suggesting infections might increase atopy risk.<sup>129-131</sup> Thus it is unknown whether

antibiotics are the true causal agent in the associations observed for EoE or whether they are simply intermediates in some other mechanistic pathway.

Mechanistic and observational studies support a possible role for acid suppressants, particularly early-life use, in the development of EoE; however, this too must be explored more fully, ideally in a prospectively designed study in which temporality of the association can be firmly established. A prospective assessment would also provide the opportunity to assess whether certain subjects (ie, atopic subjects) are at increased susceptibility to EoE given exposure to acid suppressants.

Clear evidence supports an inverse association between *H pylori* and EoE, but this relationship has only been described through cross-sectional data, and it is unknown whether this is a correlative or causative relationship. Other infectious factors, including HSV esophagitis and *M pneumoniae*, warrant investigation in robustly designed, case-control, or case-cohort studies from which appropriately selected control subjects can provide a comparison for evaluation.

Studies on geographic factors have described the association between season and climate and suggest generally the potential that aeroallergens contribute to disease development. However, seasonality and climate are relatively crude proxy measures for aeroallergens, and associations observed do not preclude the possibility that other factors associated with climate and season (eg, particulate matter, pollutants, and seasonal agricultural factors) could contribute. Studies of population density provide mixed evidence, although the largest of the studies conducted to date suggests risk is greater in rural areas. Population density is certainly a proxy for some other contributory factor, and thus additional studies are needed to evaluate what these other factors might include.

A single-center study has been conducted on behavioral factors in adults, but this study suggests that there might be opportunities to mitigate risk even in adulthood. This is an area of research that merits additional development; however, an ongoing challenge will be establishing disease duration and whether exposures preceded disease development. It is likely that adults presenting with long-standing fibrostenotic disease might be less suitable for studying exposures experienced in adulthood. The challenge of establishing temporality is pervasive in the literature evaluating environmental factors and EoE.

One approach to addressing this issue establishing temporality would be to assemble a prospective longitudinal cohort for study of EoE. However, despite increasing incidence and prevalence, assembling a prospective cohort for evaluation of risk factors leading to EoE development would be extremely challenging. Existing population-based databases can be used, although often with concomitant loss in detailed exposure data. Consortia, specifically assembling cases across multiple sites into a shared resource for study, might be critical to building the sample sizes needed for developing this body of evidence further. Potentially, an existing cohort of children with atopy could be leveraged, but the relative uncommonness of EoE might prove challenging to study, even in this higher-risk population. Large sample sizes will be needed to investigate whether there are differences in observed risk factors according to EoE phenotype or comorbid disease presentation.

Another approach to evaluating the contribution of environmental factors in EoE would be designing a sibling pair study, specifically enrolling index cases and their siblings and evaluating

differences in the exposures experienced. This design would potentially offer improved control for possible confounders in the observed associations. Hypotheses and associations generated by epidemiologic studies will need to be evaluated in *in vivo* and *in vitro* models and in experimental animal models to dissect disease mechanisms and confirm causality.

In conclusion, there is much to be learned about environmental factors and EoE. As this area of research continues to mature, more robustly designed studies with appropriately selected comparator groups and well-characterized exposure and phenotypic data will continue to advance our capacity to identify exposures implicated in disease development. Integration of environmental factors data with omics-based data sources offers the potential to provide mechanistic insights and opportunities for disease mitigation through behavior or novel therapeutics.

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