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Environmental factors and eosinophilic esophagitis

Elizabeth T. Jensen, MPH, PhD[1,2] and **Evan S. Dellon, MD, MPH**[2]

[1]Division of Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics, Wake Forest Baptist Medical Center, Winston-Salem, NC

[2]Center for Esophageal Diseases and Swallowing, Division of Gastroenterology and Hepatology, University of North Carolina School of Medicine, Chapel Hill, NC

Abstract

The incidence and prevalence of eosinophilic esophagitis (EoE) have markedly increased over the past two decades, outpacing increased detection of the disease. While 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 the understanding of the pathogenesis of EoE, the etiology of EoE is unknown. This paper 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 may increase 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.

Keywords

environment; early life; microbiome; epigenetics; gene-environment

Introduction

Eosinophilic esophagitis (EoE) is an immune-mediated,[1–6] chronic disease associated with significant morbidity, including dysphagia, food impactions, and in the pediatric population

Corresponding Author: Evan S. Dellon, MD, MPH, CB#7080, Bioinformatics Building, 130 Mason Farm Rd., UNC-CH, Chapel Hill, NC 27599-7080, Phone: (919) 966-2513, Fax: (919) 843-2508, edellon@med.unc.edu.

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in particular, food intolerance and faltering growth.[7–13] 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, while specific foods elicit clinical and histologic manifestations of disease for many patients, EoE is not believed to be an IgE-mediated disease.[14, 15]

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

While some of this increase may be attributable to increased awareness and surveillance of the disease, incident diagnoses have outpaced the increase in upper endoscopies. [17, 20, 26] Candidate and genome-wide association studies have identified possible susceptibility genes associated with disease development; [27–30] however, given the rate at which the 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 that shared environmental factors experienced in early life may be important to disease etiology.[31] To date, the body of evidence to support the contribution of environmental factors in EoE disease is still under development, with considerable gaps in knowledge. Much of the existing evidence has focused on early life factors implicated in other allergic diseases, infectious disease factors, geographical factors, and behavioral factors, with limited data on the contribution of genetic and epigenetic factors in relation to these environmental factors (figure 1). This paper describes the evidence thus far, and provides recommendations for future directions to address these gaps in knowledge.

Allergic diseases, the hygiene hypothesis, and the microbiome

Given the high proportion of EoE patients 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 increased in recent decades. One of the prevailing theories to explain this increase, the hygiene hypothesis, asserts that an overly hygienic environment, while important in the reduction of infectious disease, may have untoward effects on the host-microbiome balance necessary for immune system development. However, this theory has been met with scrutiny and has been recently adapted with advances in our ability to characterize the human gut microbiome.[32–35] 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. While the microbiome research field is still relatively underdeveloped (technology for characterizing species continues to evolve, and our capacity

to analyze the complexity of the microbiota remains relatively crude),[36–42] numerous studies have identified differences in microbiota diversity and patterns of relative abundance in association with atopic disease.[43] 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 (e.g. microbiota-host interactions, alterations in the barrier function that contribute to aberrant immune response and loss of tolerance to antigens, etc.).[44–47]

While much of 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 (GERD), and healthy controls,[48] but again, it is unknown whether these differences are driven by disease or whether they preceded disease development. With treatment, the differences between EoE cases and healthy controls has been suggested to diminish, although not completely.[37] Studies evaluating the use of synbiotics to prevent atopic disease have yielded varied results.[49–51] Likely, because our understanding of the microbiome and microbiota interactions is relatively immature, establishing which synbiotic(s) confers protection remains elusive.[52] For EoE, a single study conducted in a murine model identified a beneficial effect of the probiotic Lactococcus lactis NCC 2287 on esophageal inflammation.[53] 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 more frequently is observed later in childhood and sometimes into adulthood. Thus, it may 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 may be sensitive to early life experiences.[54, 55] Furthermore, it has been suggested that EoE may be part of the atopic march continuum, appearing later in cascade of atopic illnesses frequently co-existing in childhood.[56]

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 becomes relatively stable.[57] Changes in the microbiome may be observed at older ages with dietary changes, use of probiotics, antibiotics, illness, and other exposures, but these changes have been generally characterized as transient and self-limited. Because early life is important in the development of the microbiome, and, consequently, development of the immune system,[44–47] numerous studies have examined early life experiences that may shape microbiota colonization.[58] Many factors are now described to alter the diversity and/or relative abundance of microbiota in early life; factors including cesarean delivery, preterm delivery, neonatal intensive care unit (NICU) admission, choice of infant feeding, maternal and infant

use of antibiotics, and others.[39, 59–73] It is this body of literature that has informed studies evaluating the contribution of early life factors in relation to EoE.

To date, five 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,[74–77] one study examined adult patients.[78] With the exception of one study, which observed only a weak inverse association between postnatal, environmental tobacco smoke exposure and EoE in the pediatric population,[76] all four other studies, conducted at three different centers, identified associations between early life factors and the development of EoE.[74, 75, 77, 78] For the pediatric studies, while not all of the studies examined the same factors and differences in the associations were observed between studies, factors identified were consistent with those factors that have been demonstrated to alter microbiota colonization in the gut, including supplemented breastfeeding or formula feeding (possible protective effect for breastfeeding observed), NICU 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 (figure 2).

Acid suppressants

Acid suppressants, specifically proton pump inhibitors (PPIs), are routinely used to aid in the diagnosis and treatment of EoE as patients with clinical symptoms and histologic evidence consistent with EoE diagnosis (≥15 eosinophils/high power field on biopsy) may experience clinical and histologic improvement following treatment with a PPI. Paradoxically, acid suppressants, including PPIs, have been demonstrated to alter gut permeability.[79–81] This increased permeability may compromise oral tolerance and in both animal model and human studies, acid suppressants have led to inhibition of dietary protein digestion and development of IgE antibodies in response to the inhibited protein(s).[82, 83] In observational studies, acid suppressants, when used during pregnancy, have been associated with increased risk of atopy in offspring.[84]

The association between acid suppressant use and development of EoE has only been minimally evaluated. One study examined EoE among patients prescribed a PPI after an initial upper endoscopy and described that following repeat endoscopy, there was no evidence of an increase in absolute EoE cases nor evidence that increasing PPI dose was associated with increased proportion of EoE diagnoses on repeat endoscopy.[85] Conversely, a small case series of three patients described development of EoE following initial diagnoses of reflux esophagitis or infectious esophagitis treated with a PPI.[86] 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 or older.[77] While 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. 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 may 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.[87] This same inverse association has also been observed for EoE, in both pediatric and adult studies, with reduction in EoE risk in the absence of *H. pylori*.[88–91] This relationship also fits the temporality noted for the increase in EoE over the past two decades, and is supported by a possible mechanism. Specifically, *H. pylori* is thought to polarize towards more of Th1 immune response, and absence of *H. pylori* may polarize towards a Th2 response.[88] However, this mechanism has yet to be tested experimentally.

Herpes simplex virus

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

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, as this is an infectious vector that causes a food allergy. Sera biobanked from adult EoE cases (n=50) and controls (n=50) were evaluated for IgE sensitization to alpha gal. While a high proportion of cases and controls were observed to have evidence of sensitization, no differences were observed between cases and controls.[97]

Mycoplasma pneumonia

A case series of 12 EoE patients found a high proportion (83%) of IgG positivity for *Mycoplasma pneumonia* with serological testing.[98] However, without characterization of seroprevalence of *M. pneumonia* in controls, the association with EoE cannot be determined.

Geographic risk factors for EoE

Geographic factors, while likely not directly causal for EoE, could offer insight into other environmental factors that may 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 controls and 508 allergy controls observed a higher proportion of EoE cases arising from suburban areas, as compared to allergy controls (aOR: 2.1; 95% CI: 1.2, 3.5). However, when comparing EoE cases to GI controls, no association between residence was observed. Another study surveyed gastroenterologists and allergists on eosinophilic gastrointestinal disease patients, and found that EoE was more common in patients with a rural residence.[22] In a study of 14,381 cases and 89,754 controls 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. As compared to the most populous residence, there was a 40% increase in 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. While no difference was observed in the incidence of EoE diagnoses, differences in symptoms were reported, with a higher proportion of urban residents reporting dysphagia (p=0.047) and a higher proportion of rural residents reporting heartburn or reflux (p=0.04).[99]

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).[100] Climate zones can be closed 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, as diagnosis is known to lag far behind initial onset of symptoms. While some of these studies suggest an association between season and EoE,[20, 101–105] some studies have indicated no association.[106–108] Diagnostic delay may contribute to some of these inconsistencies, but geographic and climate differences may also contribute as aeroallergans (type, count, and temporal variability) are known to vary across climate zones. A recent study of seasonality and pollen counts conducted in 36 EoE patients 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, London planetree), *Fagus* (beech), Poaceae (grass pollen family), and *Ambrosia* (ragweed). Symptoms of EoE correlated with peak levels of grass pollen.[109] Another study examined seasonality and EoE, taking into account climate zone, again using the national pathology data described above. As expected, this study identified differences in the relationship between seasonality and EoE by climate zone, with strongest evidence of seasonal variation in EoE diagnoses in temperate and cold climates. Summer months were associated with higher EoE diagnose, however peak diagnoses by month differed according to climate zone.[110]

Behavioral risk factors for EoE

Smoking and alcohol have been associated with GERD and non-steroidal anti-inflammatory drugs (NSAID) use has been associated with atopic illnesses[111–113] and other inflammatory gastrointestinal illnesses including microscopic colitis.[114] Only one study has thus far examined these factors in EoE. In a single center case-control study (n=115 incident cases and 225 controls) who had undergone upper endoscopy for symptoms of esophageal dysfunction, data on smoking behaviors, alcohol use and NSAID use was collected through patient questionnaire, administered prior to 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 attenuated with adjustment for age, sex, race, education level, smoking, and atopy (aOR: 1.6; 95% CI: 0.8, 3.1).[115] Other potential confounders, specifically factors that could be associated with smoking behaviors and diagnosis of EoE were not assessed.

Genetic 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 (e.g. siblings of EoE patients). To date, only one study has investigated genetic susceptibility markers in relation to environmental factors. This study, while small (n=248), observed that breastfeeding conferred a protective effect for EoE, among those with the susceptibility gene variant at rs6736278 (CAPN14).[116] More studies are needed to examine how environmental factors may 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,[117–119] and environmental factors have been associated with changes in epigenetic methylation and histone modification patterns.[120, 121] Epigenetic modifications in EoE have been minimally explored in EoE,[122] yet offer the potential to improve our understanding of how environmental factors infer increased (or decreased) risk of disease. 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 while 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 that EoE patients experience, and the disease, in a proportion of patients (~30%), 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's ulcerative colitis, rheumatoid arthritis, IgA deficiency, multiple sclerosis, CVID, and autoimmune thyroid disease.[123–125]

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

Conclusions and future directions

While 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 (e.g. asthma), may 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 may increase risk for atopy.[129–131] 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 where temporality of the association can be firmly established. A prospective assessment would also provide the opportunity to assess whether certain individuals (i.e. atopic) 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 if this is a correlative or causative relationship. Other infectious factors, including HSV esophagitis and *M. pneumonia*, warrant investigation in robustly designed, case-control or case-cohort studies from which appropriately selected controls can provide a comparison for evaluation.

Studies on geographic factors have described the association between season and climate, and generally suggest 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 (e.g. particulate matter, pollutants, seasonal agricultural factors) could contribute. Studies of population density provide mixed evidence, although the largest of the studies conducted to date suggests risk is higher 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 may include.

A single center study has been conducted on behavioral factors in adults, but this study suggests that there may be opportunities to mitigate risk even in adulthood. This is an area of research that merits additional development, however an on-going challenge will be establishing disease duration and whether exposures preceded disease development. Likely, adult patients presenting with long-standing fibrostenotic disease may 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 development of EoE would be extremely challenging. Existing, population-based databases may be used, although often with concomitant loss in detailed exposure data. Consortia, specifically assembling cases across multiple sites into a shared resource for study, may 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 may prove challenging to study even in this higher risk population. Large sample sizes will be needed to investigate whether there are differences in the 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 I the associations observed. Hypotheses and associations generated by epidemiologic studies will need to be evaluated in *in vivo* an *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 that are 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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Abbreviations

EoE	Eosinophilic esophagitis
GERD	Gastroesophageal reflux disease
PPIs	Proton pump inhibitors
NICU	Neonatal intensive care unit
HSV	Herpes simplex virus
NSAID	Non-steroidal anti-inflammatory drugs
CTD	Connective tissue disorders
TEF	Tracheo-esophageal fistulae
CAPN14	Calpain-14

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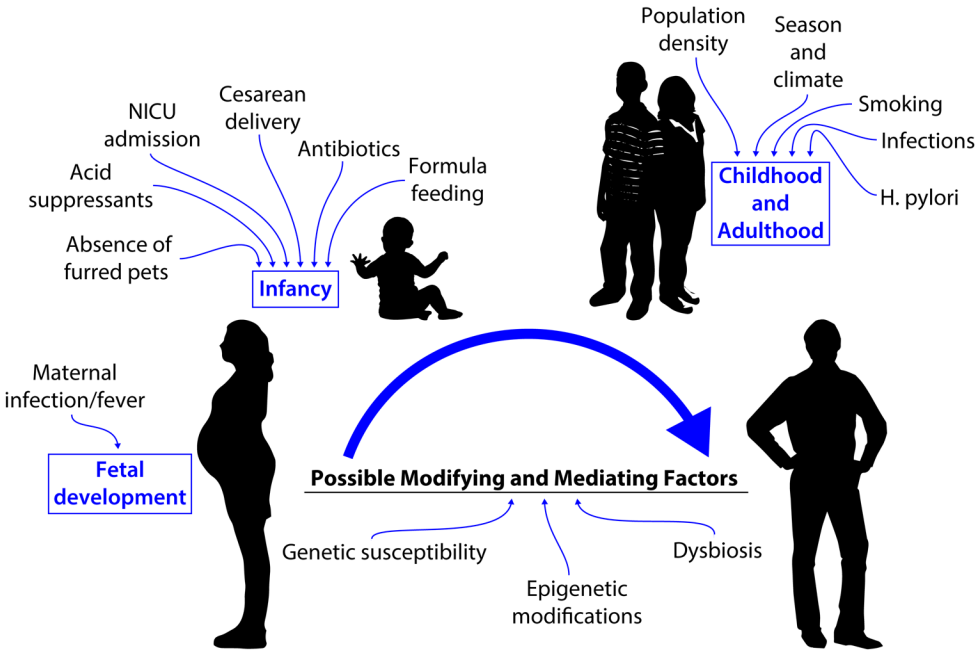

Figure 1.
Candidate risk factors for development of Eosinophilic Esophagitis

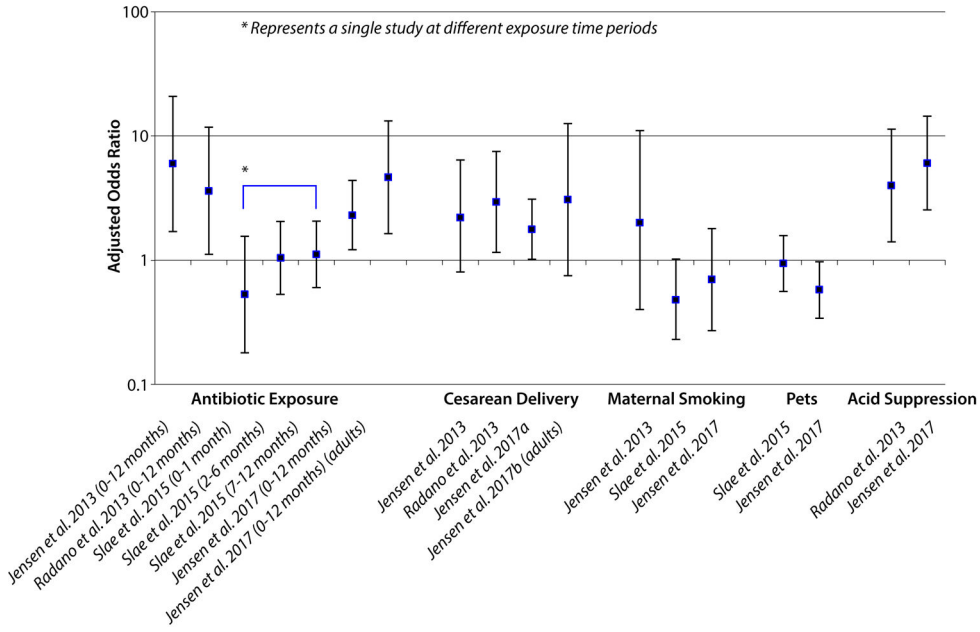

Figure 2.
Early life factors evaluated in association with Eosinophilic Esophagitis

Table 1

What is unknown?

Potential for interaction between environmental factors and EoE
Epigenetic modifications and the environment in relation to EoE
Factors that may 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 geographical factors may contribute to disease pathogenesis