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Epidemiology of Eosinophilic Esophagitis

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Abstract

Great strides have been made in understanding the epidemiology of EoE over the past two decades. Initial research focused on case description and characterization of the burden of disease. Research is now shifting to risk factor ascertainment, resulting in new and intriguing etiologic hypotheses. This paper will review the current knowledge related to the epidemiology of EoE. Demographic features and natural history will be described, data summarizing the prevalence and incidence of EoE throughout the world will be highlighted, and risk factors for EoE will be discussed. EoE can occur at any age, there is a male predominance, it is more common in Whites, and there is a strong association with atopic diseases. EoE is chronic, relapses are frequent, and persistent inflammation increases the risk of fibrostenotic complications. The prevalence is currently estimated at 0.5–1 in 1000, and EoE is now the most common cause of food impaction. EoE can be seen in 2–7% of patients undergoing endoscopy for any reason, and 12–23% undergoing endoscopy for dysphagia. The incidence of EoE is approximately 1/10,000 new cases per year, and the rise in incidence is outpacing increases in recognition and endoscopy volume. The reasons for this evolving epidemiology are not yet fully delineated, but possibilities include changes in food allergens, increasing aeroallergens and other environmental factors, the decrease of *H. pylori* and early life exposures.

Keywords

Eosinophilic esophagitis; epidemiology; incidence; prevalence; risk factors; natural history

Introduction

Epidemiology is the study of patterns and causes of diseases in defined populations. It uses observational study designs, such as case-control or cohort studies, to make inferences about etiologies and risk factors for diseases. These results generate hypotheses that can

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subsequently be tested in experimental study designs, such as clinic trials. Over the past two decades, there have been great strides made in understanding the epidemiology of eosinophilic esophagitis (EoE). Case reports and case series provided initial descriptions of clinical characteristics of patients with EoE,¹⁻⁴ and then as larger cohorts were reported and natural history data accumulated,⁵⁻¹¹ formal disease definitions and guidelines were put forth.¹²⁻¹⁴ Epidemiologic techniques have been used to estimate the incidence and prevalence of EoE at the single center, regional, and national levels to provide an understanding of trends in the number of cases as well as the burden of disease attributable to EoE.¹⁵⁻²² The clear result of these studies is that EoE is rapidly increasing both in incidence and in prevalence. Investigations have also begun to determine potential etiologic factors that might explain this evolving epidemiology. This paper will review the current knowledge base related to the epidemiology of EoE. In particular, demographic features and natural history will be described, data summarizing the prevalence and incidence of EoE throughout the world will be highlighted, and risk factors for EoE will be discussed.

Demographic features

EoE has been reported throughout the lifespan, from infancy to almost 100 years of age.^{10,13,23} However, the majority of cases are in children, adolescents, and adults under the age of 50.^{10,13,22-24} There is a consistent gender discrepancy, with males affected three to four times more commonly than females, and EoE is also more frequently reported in Whites compared with other races/ethnicities.^{11,13,19,22,24-27} The reason for the male predominance is not known, and as more data accrues from larger centers with more diverse patient populations, increasing numbers of racial minorities have been identified with EoE.²⁸⁻³¹ While the majority of clinical, endoscopic, and histologic features are shared by EoE patients of different races, some data suggest that African-Americans with EoE may be diagnosed at earlier ages and are less likely to have typical endoscopic findings of EoE.^{28,31} EoE is also strongly associated with atopic disease and can run in families; both of these topics, as well as the clinical features and differences in the presentation between adults and children, are addressed in detail in other articles in this issue.

Natural History

EoE is considered a chronic disease.¹²⁻¹⁴ Data from the placebo arms of randomized clinical trials³²⁻³⁸ and prospective and retrospective cohort studies^{5-7,10,11,39-41} show that EoE does not tend to spontaneously resolve or “burn-out”. Specifically, the endoscopic signs and esophageal eosinophilia persist in the absence of treatment. Moreover, if treatment is stopped, symptoms, endoscopic signs, and esophageal eosinophilia recur in the vast majority of patients over a period of several months.^{8,41-45} There are as of yet no published reports of EoE transforming into hypereosinophilic syndrome, extending to involve other areas of the GI tract, or causing a malignancy.^{6,7,10,11,40}

Recent data have supported the concept that EoE may progress from an inflammatory-predominant phenotype (primarily seen in children) to a fibrosis-predominant one (seen in adults).^{13,46-48} These data help to explain the clinical differences between adults and children,^{11,39,49,50} and are consistent with basic science work showing that esophageal

remodelling and deposition of fibrosis are key pathogenic features of EoE.^{51,52} The hypothesis is that in children, eosinophilic inflammation in the esophagus manifests with white plaques or exudates, decreased vascularity or mucosa edema, and linear furrows, but without esophageal rings or strictures, and causes symptoms such as pain, heartburn, and failure to thrive. With ongoing inflammation, however, subepithelial collagen is deposited, esophageal rings, narrowing, and strictures develop, and symptoms become dysphagia predominant.

A retrospective cohort study of patients in Switzerland explored this issue by assessing diagnostic delay – how long patients experienced symptoms prior to the EoE diagnosis and before any treatment – as a proxy for ongoing inflammation.⁵³ There was a very strong association between increasing diagnostic delay and the prevalence of strictures at diagnosis. For example, only 17% of those with less than 2 years of symptoms prior to diagnosis had strictures compared with 71% with more than 20 years of symptoms. They calculated that for every increased decade of untreated EoE, there was a doubling of odds of having an esophageal stricture. Another study assessed the same issue by examining endoscopically-defined phenotypes of EoE and noted nearly identical results, with the odds of having a fibrostenotic EoE phenotype doubling with each increasing decade of age.⁴⁸ These natural history data provide important information for patients, show long term consequences of EoE, and support the need for treatment of this condition.

Prevalence

The prevalence of a condition is defined by how many total cases exist during a given time frame in a specified location, and is a useful measure of the burden of that disease. EoE has been described in many places throughout the world including North America, Europe, South America, Australia, Asia, and the Middle East, but the prevalence appears to be highest in the U.S., Western Europe, and Australia as compared with Japan or China.^{17–22,54–62} As of yet, there are no reported EoE cohorts in sub-Saharan Africa or India.

The prevalence of EoE depends on the population that is studied, the definition of EoE that was used (and whether the study was conducted before the recognition of proton pump inhibitor-responsive esophageal eosinophilia [PPI-REE]),^{13,14} and the study methodology (prospective vs retrospective), and this contributes to variation in the range of prevalence estimates (Tables 1 and 2). While the majority of prevalence estimates are derived from single-centers with defined catchment areas,^{15,16,18,20,58,59,63,64} there are some studies that have used either population-based techniques or national databases to attempt to generate more accurate or generalizable estimates.^{17,21,22,65–67} Because EoE is chronic and non-fatal, studies universally report an increasing prevalence of EoE regardless of the geographic location.^{54,68}

Prevalence of EoE in the general population

How common is EoE? In reviewing data assessing the prevalence of EoE in general populations (Table 1), a reasonable answer is 0.5–1 cases/1000 persons. The majority of estimates in the U.S. range from 40–90 cases/100,000 persons.^{15,18,19,22,63,65} The largest

study in the U.S. examined administrative health claims data and found the prevalence to be 57/100,000, or approximately 152,000 cases, with a range from 39–153/100,000 (106,000–411,000 cases), based on the case definition that was used.^{22,69} These are consistent with the most recent estimates from Australia (89/100,000),⁵⁸ Switzerland (43/100,000),²⁰ Spain (45/100,000),⁵⁹ and Canada (34/100,000).⁶⁷ Additionally, these prevalence estimates are of the same order of magnitude of pediatric Crohn's disease and ulcerative colitis, and are beginning to approach the prevalence of IBD overall,⁷⁰ a remarkable observation given that EoE was essentially unknown two decades ago.

Several studies, however, provide estimates that are outside of this range. In Northern Sweden, data from a population-based study assessing the prevalence of Barrett's esophagus was reanalyzed and found a prevalence of 400/100,000 for EoE.¹⁷ These patients were largely asymptomatic and while they had esophageal eosinophilia, may not have met current diagnostic criteria for EoE.^{13,14} A study in the U.S. military found a prevalence of 10/100,000, but this might have been an underestimate due to the specialized population assessed or to low sensitivity of the administrative code for EoE.^{66,69} Studies from the Netherlands and the southern region of Denmark have also reported lower prevalences of EoE.^{21,64} It is unknown if these results are due to practice patterns in those countries or a true difference in the prevalence of disease.

Prevalence of EoE in patients undergoing endoscopy

While these prior studies assessed the overall prevalence of EoE, depending on the specific patient population seen in health care settings the prevalence may be orders of magnitude higher (Table 2). For example, a prospective study which collected esophageal biopsies on consecutive patients undergoing upper endoscopy for any indication found that 6.5% of patients were diagnosed with EoE.²⁶ Other studies with a similar design found comparable rates, from 2.4% to 6.6%.^{71,72} Given that there are approximately 6.9 million upper endoscopies performed annually in the U.S.,⁷³ endoscopists should expect to commonly encounter EoE in the procedure suite.

EoE is even more common in patients undergoing upper endoscopy for symptoms of dysphagia. In three prospectively studies conducted in this focused patient population, the prevalence of EoE ranged from 12–22%.^{25,74,75} Not every patient in these studies with a finding of esophageal eosinophilia, however, would meet current diagnostic guidelines with exclusion of PPI-REE, because patients were enrolled prior to the recognition of this phenomenon. A recent study conducted in an esophageal referral center reported an EoE prevalence of 23% for patients undergoing endoscopy for dysphagia, after excluding those patients with PPI-REE.⁷⁶ In that study, esophageal eosinophilia itself was seen in 40% of those undergoing upper endoscopy for dysphagia, before a PPI trial was conducted. Given that approximately 20% of all upper endoscopies performed are for an indication of dysphagia,⁷³ EoE must be highly suspected in this population.

In the most extreme form of dysphagia, esophageal food bolus impaction requiring a visit to an emergency department and urgent endoscopy, EoE is now the most frequent condition identified. In this setting, between 46–63% of patients with food impaction will have EoE.^{77–80} These data, however, are somewhat limited because less than half of patients with

food or foreign body impactions will have esophageal biopsies to evaluate for esophageal eosinophilia,^{78,80} so EoE in this setting may still be underdiagnosed. If patients have a bolus impaction and no biopsies are obtained, it is reasonable to perform a follow-up procedure to identify the underlying etiology.

The prevalence of EoE in patients undergoing endoscopy for other upper GI symptoms has also been described. For patients with heartburn-predominant symptom who don't respond clinically to PPI therapy (PPI-refractory reflux), EoE has been identified as the cause 1%-8% of the time.^{26,42,61,76,81-84} In adults with non-cardiac chest pain, one study found that EoE was the etiology in 6%.⁸⁵ In children undergoing upper endoscopy for abdominal pain, the frequency of EoE was 4%,⁸⁶ and in children undergoing multispecialty evaluation for refractory aerodigestive symptoms, it was also 4%.⁸⁷

While these epidemiologic data have utility for understanding how common EoE is, building a differential diagnosis for patients undergoing endoscopy, and measuring the burden of disease attributable to EoE, they also imply a practical point. Because EoE is common in patients undergoing endoscopic procedures, practitioners should strongly consider the diagnosis and obtain esophageal biopsies to evaluate for it. Currently guidelines recommend obtaining biopsies for all patients presenting with dysphagia, regardless of the endoscopic appearance.¹²⁻¹⁴ There is also a recent analysis that suggests if the clinical probability of EoE is at least 8-10%, obtaining biopsies in patients with PPI-refractory reflux is also cost-effective.⁸⁸

Incidence

The incidence of a condition is how many new cases occur during a given time frame in a specified location, and is a measure of the number of people newly affected by a disease. The incidence of a condition can be low (a small number of new cases), but the prevalence can be relatively high if the condition is chronic and does not impact longevity. Additionally, the incidence of a condition can be roughly equivalent to the prevalence for a condition that is either short-lived or highly morbid.

In order to study the incidence of a condition, it is necessary not only to detect all new (incident) cases, but to ensure that existing (prevalent) cases are not falsely counted as new cases. In EoE, this has been accomplished primarily at referral centers in regions where the patient population and catchment area is well defined,^{15,19,20,59,64} but there are some emerging regional and national data as well.^{21,67} The majority of the reports estimate the incidence of EoE from 6-13 cases/100,000 persons (Table 3). The two studies that report lower incidence rates, from the Netherlands and the southern Denmark, were the same ones that reported lower prevalences rates.^{21,64}

Increasing incidence and risk factors

Studies are consistent in showing that the incidence of EoE has been rising rapidly. In a report from Hamilton County, Ohio, the incidence of EoE was noted to increase from 9 to 12.8/100,000 over a three year period.¹⁵ In a report from Olmstead County, Minnesota, no EoE cases were seen before 1990, but in the incidence rose from 0.35 to 9.5/100,000 over a

15 year period.¹⁹ Similar increases have been reported in Switzerland (1.2 to 7.4/100,000 over a 20 year period)²⁰ and in the Netherlands (0.01 to 1.3/100,000 over 14 years).²¹ This increasing incidence has also been reflected in temporal trends in the relative prevalence of dysphagia etiologies, with EoE becoming a more frequent cause of dysphagia over time.⁸⁹

Why is eosinophilic esophagitis increasing?

While these marked changes in EoE incidence account for its increasing prevalence, they also beg the question of why is the incidence itself increasing? While the answer is not known, there are a number of hypothesis.⁹⁰ One explanation is simply that EoE is increasing because of increasing recognition; the condition was always there but given the research and clinical interest in the condition, practitioners are more aware of EoE, have a higher degree of suspicion when performing endoscopy, take more esophageal biopsies, and are therefore more likely to make the diagnosis. The exponential increase in the number of publications related to EoE is a testament to the increased interest in EoE (from 0–1 publication per year prior to 2000, to >200 publications in 2013). Some data that support this theory show that the increase in incidence rates relatively closely matches the increase in endoscopy volume or biopsy rates.^{67,91} However, there are other studies where biopsy rates do increase 2–3 times over the study period, but the incidence of EoE outpaces that increase by several fold, indicating that increased recognition is not the only explanation.^{11,19,89,92} Additionally, in studies where archived pathology samples have been retrieved and reanalyzed, cases of probable EoE identified in the early 1980s and 1990s occur at lower rates than what is currently being observed.^{93,94}

There are other epidemiologic clues that provide insight. Recent data suggest that the prevalence of EoE steadily increases as age increases, peaks in the 35–45 age range, and then decreases (Figure 1).²² This is a counterintuitive observation for a chronic and non-fatal disease (where prevalence would be expected to continue to increase as age increases), and suggests a possible cohort effect. It is interesting to speculate whether something might have changed in the environment 40–50 years ago that began to affect children born after that time, but did not affect older individuals. In contrast, genetic changes would not be expected to impact a new disease over a relatively short time frame. This time frame is also consistent with decades-long symptom duration prior to EoE diagnosis in some older patients with EoE.^{23,48,90,95}

Allergen and hygiene hypotheses

There are a number of etiologic risk factors that have either been identified or hypothesized to contribute to the increase of EoE (Box 1). One possibility relates to EoE as an allergic disease (see also the article on allergic mechanisms in this issue of *Clinics*). All allergic diseases, including asthma, atopic dermatitis, allergic rhinitis, and food allergies, have been increasing in recent decades.⁹⁶ One global explanation for this is the hygiene hypothesis, which holds that because the environment in developed countries has become much more sterile, human immune systems are exposed to smaller variety of antigens, and tolerance is less likely to develop.⁹⁶ Thus, EoE as an allergen/immune-mediated disease would be rising in parallel with other allergic diseases.

Environmental hypotheses

Related to the hygiene hypothesis are theories that changing environmental factors are contributing to the rise in EoE. One factor is aeroallergens. There have been clear links in humans between pollen and other aeroallergen exposure either triggering EoE or correlating with EoE disease activity.⁹⁷⁻⁹⁹ Additionally, many studies have shown a link between the season of the year and EoE diagnosis, with EoE more commonly being diagnosed in summer or fall, times of potentially higher aeroallergen activity.^{11,19,100,101} Other environmental exposures such as air pollution or industrial exposures, have yet to be formally assessed.

Geographic risk factors have also been reported. Several studies have utilized a large nationwide pathology database containing hundreds of thousands of patients undergoing endoscopy with esophageal biopsy, and representing more than 14,000 cases of esophageal eosinophilia and EoE.^{102,103} Prevalence of esophageal eosinophilia was noted to vary by climate zone, with cases more commonly noted in arid and cold weather climates.¹⁰² This was an interesting finding because the climate zone classification used is closely linked to types of vegetation, again raising the question of allergen exposure, and also because other autoimmune and allergic diseases have geographic variation with a north-south gradient. A related study showed that esophageal eosinophilia appeared to be more common in rural areas with low population density.¹⁰³ While this may be counterintuitive (some allergic diseases such as asthma and atopic dermatitis are felt to be more common in urban areas), there are other studies on EoE that support this as well.^{65,104} This raises the question of whether vegetation or environmental exposures more likely to be found in rural areas are risk factors for EoE, but additional research is required to explore these possibilities.

Food allergens can also be considered environmental exposures. It is well-established that foods can trigger EoE and that allergen-free elemental formula or elimination of certain food allergens from the diet can result in clinical, endoscopic, and histologic remission (see also the article on dietary therapy of EoE in this issue of *Clinics*).^{4,5,45,105,106} However, it is less clear why foods that have been tolerated for much of human history are now allergic triggers in EoE. Whether this is because of recent changes in agricultural practices, decreased variety of foods, genetic modification of crops, pesticides, antibiotic or hormone use in livestock, or other factors such as packaging and transport of foods remains to be determined.

Helicobacter pylori hypothesis

When thinking about reasons that EoE may be increasing, it is possible that something being removed from the environment could also play a role. *Helicobacter pylori* is one such factor. Since its formal characterization in the early 1980s and subsequent association with peptic ulcer disease and gastric cancer, the prevalence of *H. pylori* has markedly decreased in the U.S. with ongoing treatment of this pathogen.¹⁰⁷ In a study examining more than 165,000 paired esophageal and gastric biopsy samples, there was a strong inverse relationship between *H. pylori* and esophageal eosinophilia; those who were more likely to have esophageal eosinophilia or EoE were less likely to have *H. pylori*.¹⁰⁸ This relationship has also been noted in two smaller studies in EoE,^{17,109} and is consistent with the observation that *H. pylori* is inversely associated with other atopic disorders such as asthma and

eczema.¹¹⁰ The mechanism by which *H. pylori* may be protective of EoE is not known, but it has been hypothesized that the infection polarizes the immune system towards a Th1 response, and the lack of infection might allow a Th2 response, less tolerance, and increased atopy.¹⁰⁸

Proton pump inhibitor hypothesis

Another potential ecological association to explain the increase in EoE is the parallel increase in use of PPI medications over the past three decades. This increase in use has also been noted in infants as a treatment for reflux and colic, which represents a major change in practice during a time when the immune system is developing.¹¹¹ While there is no direct evidence that PPI use has caused EoE in an individual patient, there are some intriguing mechanistic reasons that this could be a concern, especially given the multitude of effects that PPI have outside of their antisecretory action.^{112,113} Specifically, PPIs can increase upper GI tract permeability, potentially creating a new route of antigen exposure, and their use has also been associated with the development of new food-specific IgE antibodies.^{112,114–116} However, these data are balanced by two important points. First, many patients who are diagnosed with EoE have never taken a PPI previously. Second, convincing data show that PPIs have anti-inflammatory/anti-eosinophil effects both *in vitro*¹¹⁷ and *in vivo* where at least 30–40% of subjects with esophageal eosinophilia have symptomatic and histologic resolution after a PPI trial.^{76,118,119} Because of this, a PPI trial is now a required part of the EoE diagnostic algorithm.^{12–14} Therefore, before PPIs can be considered to be a cause of EoE, direct evidence will be required.

Early life exposure hypotheses

A new area of investigation has started to examine early life exposures that might predispose to development of EoE. It has been noted that antibiotic exposure in early life increases the odds of developing other allergic diseases such as asthma or atopic dermatitis and inflammatory bowel disease, especially Crohn's disease.^{120–122} There are recent pilot data suggesting the same may be true in EoE, where exposures during the first year of life were assessed and the subsequent odds of pediatric EoE determined.¹²³ In this study, infants who received antibiotics were markedly more likely to have EoE than controls who did not, and there was also a trend for increased EoE in infants delivered by cesarian section, those who were born prematurely, and those who had non-exclusive breastfeeding. All of these factors could theoretically impact the early life microbiome, perturbations of which have been hypothesized to be a determinant of atopic disease.¹²⁴ Novel research techniques in EoE have begun to characterize the esophageal microbiome, but this has yet to be fully explored as a risk factor for EoE.¹²⁵

Other hypotheses

A final set of risk factors for EoE that have been recently identified are connective tissue and autoimmune disorders. A report in a large cohort of EoE patients found a subset with coexisting diseases such as Ehlers-Danlos, Marfan, and Loeys-Dietz syndromes, in which EoE was significantly elevated compared to expected rates in the general population.¹²⁶ Moreover, this association suggested potential genetic links that could be used to learn more

about the pathogenesis of EoE. In a preliminary study using administrative data, a similar relationship between EoE and connective tissue disorders were noted, and there was also a relationship with autoimmune diseases.¹²⁷

Summary

The epidemiology of EoE has become increasingly well understood over the past decade. The disease is well characterized clinically, and those features have informed diagnostic guidelines. EoE can affect patients of any age, but there is a male predominance, it is more common in Whites, and there is a strong association with atopic diseases. EoE is chronic, relapses are frequent with cessation of treatment, and new data suggest that unopposed inflammation and persistent symptoms with diagnostic delay increases the risk of fibrostenotic complications. The prevalence of EoE is rising substantially, and it is now the most common cause of food impaction in patients presenting to the emergency department, and is frequently encountered in the endoscopy suite. Approximately 0.5–1 in 1000 people are estimated to have EoE, a prevalence that is beginning to approach that of inflammatory bowel disease. Incidence estimates suggest that there are 1/10,000 new cases per year, and the rise in incidence is outpacing the increasing in recognition and endoscopy volume. The reasons for this evolving epidemiology are not yet fully delineated, but possibilities include changes in food allergens, increasing aeroallergens and other environmental factors, the decrease of *H. pylori* and early life exposures that may affect the microbiome. The study of the epidemiology of EoE has now shifted from case description to risk factor ascertainment, and new etiologic hypotheses have been raised that present exciting avenues for future epidemiologic and pathogenic research in this condition, with the ultimate goal of preventing the occurrence of EoE.

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Key points

- EoE affects patients of all ages, is more commonly seen in males and Whites, and is strongly associated with atopy.
- EoE is chronic, relapses are frequent after treatment is stopped, and diagnostic delay with persistent inflammation increases the risk of esophageal strictures and fibrostenotic complications.
- The prevalence of EoE is 0.5–1 cases/1000 persons.
- The incidence of EoE is approximately 10 cases/10,000 persons per year.
- Elucidating the reasons for the rapid rise in incidence and prevalence of EoE is an active area of research, and possibilities include changes food allergens and aeroallergens, other environmental factors, the decrease of *H. pylori* and early life exposures.

Figure 1.

Prevalence of EoE (cases per 100,000) in the United States as stratified by sex and by 5 year increments of age, in a study of an administrative health claims data. From Dellon ES, Jensen ET, Martin CF, Shaheen NJ, Kappelman MD. Prevalence of Eosinophilic Esophagitis in the United States. Clin Gastroenterol Hepatol 2013; with permission.

Table 1

Population-based estimates of the prevalence of EoE

Author	Location	Population	Time frame	Prevalence (per 100,000)
Noel; Buckmeier	Hamilton County, OH	Pediatric	2000–2003; 2000–2006	43.0; 90.7
Cherian	Perth, Australia	Pediatric	1995, 1999, 2004	89.0
Straumann; Hruz	Olten County, Switzerland	Adult	1989–2004; 1989–2009	23.0 42.8
Ronkainen	Northern Sweden	Adult	1998–2001	400
Prasad	Olmstead County, MN	Adult and pediatric	1976–2005	55.0
Gill	Huntington region, WV	Pediatric	1995–2004	73.0
Dalby	Southern Denmark	Pediatric	2005–2007	2.3
Spergel	United States	Adult and pediatric	2010	52.2
Ally	United States (military)	Adult and pediatric	2009	9.7
van Rhijn	Netherlands	Adult and pediatric	1996–2010	4.1
Syed	Calgary, Canada	Adult and pediatric	2004–2008	33.7
Arias	Castilla-La Manch region, Spain	Adult and pediatric	2005–2011	44.6
Dellon	United States	Adult and pediatric	2009–2011	56.7

Data from Refs 15–22,58,59,63–67.

Table 2

Prevalence of EoE in selected patient populations undergoing endoscopy

Author	Population	Time frame	Prevalence (per 100)
<i>Patients undergoing endoscopy for any reason</i>			
Veerappan	Adults	2007	6.5
Joo	Adults	2009	6.6
Sealock	Adults (VA population)	n/a	2.4
<i>Patients undergoing endoscopy for dysphagia</i>			
Prasad	Adults	2005–2006	15
Mackenzie	Adults	2005–2007	12
Ricker	Adults (non-obstructive dysphagia only)	2007–2009	22
Dellon	Adults	2009–2011	23
<i>Patients undergoing endoscopy for food bolus impaction</i>			
Desai	Adults	2000–2003	55
Kerlin	Adults	n/a	50
Sperry	Adults and pediatric	2002–2009	46
Hurtado	Pediatric	2005–2009	63
<i>Patients undergoing endoscopy for refractory reflux</i>			
Liacouras	Pediatric	1993–1995	3
Rodrigro	Adult	2002–2005	0.2
Veerappan	Adult	2007	8
Sa	Adult	2006–2008	1
Poh	Adult	n/a	1
Foroutan	Adult	2006	8
Garcia-Campean	Adult	2007–2009	4
Dellon	Adult	2009–2011	2
<i>Patients undergoing endoscopy for non-cardiac chest pain</i>			
Achem	Adult	2006–2007	6
<i>Patients undergoing endoscopy for abdominal pain</i>			
Thakkar	Pediatric	2007–2010	4
<i>Patients with refractory aerodigestive symptoms</i>			
Hill	Pediatric	2003–2013	4

Data from Refs 25,26,41,42,61,71,72,74–87.

Table 3

Population-based estimates of the incidence of EoE*

Author	Location	Population	Time frame	Incidence (per 100,000)
Noel	Hamilton County, OH	Pediatric	2003	12.8
Hruz	Olten County, Switzerland	Adult	2007–2009	7.4
Prasad	Olmstead County, MN	Adult and pediatric	2001–2005	9.5
Dalby	Southern Denmark	Pediatric	2005–2007	1.6
van Rhijn	Netherlands	Adult and pediatric	2010	1.3
Syed	Calgary, Canada	Adult and pediatric	2004–2008	11
Arias	Castilla-La Manch region, Spain	Adult and pediatric	2005–2011	6.4

* The estimated incidence of the most recent time point in each study is presented Data from Refs 15,19–21,59,64,67.

Box 1

Potential etiologic risk factors for EoE

-
- Aeroallergens
 - Food allergens
 - *Helicobacter pylori* (protective)
 - Proton pump inhibitors
 - Cold or arid climates
 - Population density (urban vs rural locations)
 - Early life factors (antibiotic use; cesarian section)
 - Connective tissue disorders
-

Data from Refs 4,45,65,97–100,102–105,108,109,112,123,126.