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Epidemiology and Natural History of Eosinophilic Esophagitis

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Abstract

Eosinophilic esophagitis (EoE) has emerged over the past 2 decades as a major cause of upper gastrointestinal morbidity. Over this time, the epidemiology of EoE has also rapidly evolved. EoE has transformed from a rare case-reportable condition to disease that is commonly encountered in the gastroenterology clinic, hospital emergency room, and endoscopy suite. The incidence and prevalence are increasing at rates that outpace increased disease recognition. Current incidence estimates range from 5 to 10 cases per 100,000, and current prevalence estimates range from 0.5 to 1 case per 1000. We review the data and potential reasons behind this increase, examine risk factors, and identify important areas for research into disease etiology. The article also discusses the progression of EoE from an inflammatory to fibrostenotic phenotype. An accurate view of the natural history of EoE is central to discussions with patients regarding disease prognosis and decisions about long-term use of medical, endoscopic, and diet therapies. Progressive remodelling appears to be gradual, but not universal, and the duration of untreated disease is the best predictor of stricture risk. Ultimately, prospective, long-term outcome studies focusing on multiple aspects of disease activity are needed to fully understand the natural history of EoE.

Keywords: Incidence; prevalence; progression; fibrosis

Eosinophilic esophagitis (EoE) is an allergen/immune-mediated disease characterized by symptoms of esophageal dysfunction and eosinophilic infiltration of the esophageal mucosa in the absence of secondary causes of eosinophilia.[1, 2] The first cases of EoE were first reported in the late 1970s,[3, 4] but the disease as it is recognized today was described in 3 case series in the early and mid-1990s.[5-7] Since then, EoE has transformed from a rare case-reportable condition to a disease that is commonly encountered in the clinic and endoscopy suite,[8] and a major cause of upper gastrointestinal morbidity and increasing health care costs.[9] Over this time, our understanding of the epidemiology of EoE has also rapidly evolved. The incidence and prevalence are increasing at rates that outpace increased recognition,[10-12] indicating the importance of environmental rather than genetic changes.[13, 14] Descriptive epidemiology research in EoE has also matured, and there is now a focus on identifying etiologic factors. Although we know much about the pathogenesis of EoE,[15] we do not fully understand why EoE develops in an individual patient.[16] We review the incidence and prevalence of EoE, present potential reasons for the increase in EoE, examine possible risk factors, and discuss the natural history and possible progression of this chronic condition.

Epidemiology

Incidence of EoE and time trends

The incidence of EoE has been investigated several population-based studies, conducted primarily in North America and Europe.[11, 12, 17-25] Using the most recent time point from these studies, incidence rates range from a low of 2.1/100,000/year in the Netherlands[22, 26] to a high of 12.8/100,000/year in Ohio in the United States[17] (Supplementary Table 1). A meta-analysis calculated an overall pooled incident rate of 3.7/100,000/year (95% CI, 1.7–6.5), though there was substantial heterogeneity.[27] In this study, the incidence rate was higher in adults (7.0/100,000/year) than in children (5.1/100,000/year). When interpreting the published incidence data, it is important to recognize differences among studies performed at different centers and during different time periods. For example, proton pump inhibitor (PPI)-responsive esophageal eosinophilia may not have been excluded in some studies (there is controversy over this topic)[28] and or case-finding approaches might have been used.

All studies that have examined incidence rates of EoE over time have concluded that the incidence of EoE is increasing rapidly (Figure 1A; Supplementary Table 1). In the first report

investigating this issue, incidence increased 40% over a 4 year period (2000–2003).[17] In similar analyses, incidence increased approximately 27-fold[20] and 5-fold at 2 other North American centers.[23] In European studies, rates of increase ranged from 6-fold to more than 100-fold.[11, 12, 18, 19, 22, 24, 25] Although it is tempting to attribute this rapid change only to an associated increase in recognition of and knowledge about EoE, this is not the only explanation. Several studies have examined changes in rates of endoscopy with biopsy over the same time period as the change in rates of EoE, and have found that the increase in EoE incidence outpaces the relatively modest increase in rates of biopsy.[10-12, 20, 29] In addition, other studies have retrospectively pulled archived esophageal biopsy blocks to determine if cases of EoE were previously present but missed.[30, 31] Although cases of EoE were found, they were identified at rates that are far below what are currently observed. It therefore appears that the incidence of EoE is truly increasing, and is just not an artifact of increasing surveillance and detection. This information has major implications for understanding the etiology of EoE.

Prevalence of EoE

The prevalence of EoE has been investigated worldwide, but most population-based studies have been conducted in North America and Europe,[11, 12, 17-24, 32-40] with select studies in Australia and Asia.[41, 42] In a study in Scandinavia and a study in China, researchers performed upper endoscopies using a population-based sampling frame of asymptomatic individuals in the community.[33, 42] They found a rate of esophageal eosinophilia (defined as 15–20 eosinophils per high-power field) of approximately 400/100,000. These findings should be interpreted with caution, because the studies included patients who would not meet diagnostic criteria for EoE. Other studies attempted to identify all known EoE cases within a specific population catchment area. If we use the most recent time point from these studies, prevalence values range from as low as 2.3/100,000 in Denmark[21] to as high as 90.7/100,000 in Ohio (Supplementary Table 2).[17] A meta-analysis estimated an overall pooled EoE prevalence of 22.7/100,000 (95% CI, 12.4–36.0), with a higher rate in adults (43.4/100,000; 95% CI, 22.5–71.2) than in children (29.5/100,000; 95% CI, 17.5–44.7), though there was substantial heterogeneity in these estimates.[27] EoE is a chronic disease, so prevalence rates have increased steadily at all sites that have examined changes over time (Figure 1B).

EoE prevalence estimates vary with location (Figure 2). The prevalence tends to be on the same order of magnitude in Western Europe, North America, and Australia,[12, 17, 19, 20, 22, 23, 35, 37-41, 43-45] but much lower in Japan and China.[46-50] The disorder has also been reported in South American, Korea, Turkey, and the Middle East,[43, 51-55] but there are still no reports from sub-Saharan Africa or India.[56] The differences between high prevalences in Western countries and low prevalences in Eastern countries, despite similarities in clinical presentation and molecular features,[57, 58] provides a platform for future investigations of etiologic mechanisms, especially those that focus on environmental factors.

In additional to geographic variations in prevalence, the prevalence of EoE differs among clinical populations (Figure 3; Supplementary Table 3). An overall estimate of the prevalence of EoE is 0.5–1 cases per 1000 persons, yet EoE is detected in 2.4%–6.6% of patients undergoing endoscopy for any indication,[51, 53, 59-61] and this rate is much lower in Japan and China (less than 0.4% of cases).[46, 47, 50] In studies assessing patients undergoing endoscopy for an indication of dysphagia, rates are higher, ranging from 12% to 23%.[62-66] The highest proportions of EoE, frequently above 50%, occur in patients presenting with an esophageal food bolus impaction—EoE is now the most common cause of esophageal food bolus impactions in patients presenting to emergency departments.[67-79] EoE has also be detected in 1%–8% of patients undergoing endoscopy for symptoms of refractory reflux or heartburn,[43, 54, 60, 65, 80-83] 6% of patients undergoing endoscopy for non-cardiac chest pain,[84] 4% of patients undergoing endoscopy for abdominal pain,[85] 4% of patients with refractory aerodigestive symptoms,[86] and 5% of patients with IgE-mediated food allergies.[87]

Risk factors

There is intense interest in learning why the incidence and prevalence of EoE are increasing.[13, 88-90] Although some genetic factors have been associated with EoE,[15] the rapid trends in EoE incidence indicate a role for environmental factors in disease risk.[14] In a study of a large administrative database in the United States, prevalence increased steadily with age, to a peak value in individuals 30–44 years old. Prevalence then sharply decreased among older individuals;[37] this trend was also observed from a population-based study in the Netherlands.[22] These observations raise the question as to whether environmental changes starting 40–50 years ago contributed to disease development. One often-proposed theory is the hygiene hypothesis,

which suggests that humans are losing immune tolerance from being raised in clean environments. This hypothesis is supported by the general increase in a number of allergic and autoimmune conditions.[91] However, data also support a number of more specific etiologic factors (Table 1).

Because EoE is an allergic condition, several environmental allergens have been implicated. First, food allergens trigger EoE and the disease can be put into remission by removal of specific foods, either via elimination diets or hypoallergenic elemental formulas.[7, 92, 93] However, it is still not clear why foods that were tolerated over the course of human evolution would now induce EoE; the effects of farming practices, genetic modification, mass production, packaging, and other related factors have not been examined. Environmental or aeroallergens can also induce EoE—there are links between pollen season and EoE flares, seasonality of diagnosis of EoE (with more cases diagnosed during times of increase aeroallergens), and cold or arid climate zones.[10, 16, 20, 94-100] Odds of EoE are higher in rural areas with lower population density,[35, 101, 102] which might be explained by vegetation, pollution, or other environmental exposures.

Recently, early-life exposures have been investigated as potential risk factors for EoE.[103] The first report on this topic found that antibiotics taken during the first year of life substantially increased the odds of subsequent diagnosis of pediatric EoE, and that several other factors, including Cesarean delivery and preterm birth, might also be associated with EoE.[104] These results were replicated in 2 additional studies,[105, 106] but were not found in a third.[107] Although the mechanism of these early-life factors is not known, an intriguing possibility is that they affect the microbiome—this is an area of active research.[103, 108]

Infectious risk factors for EoE have also been studied. The strongest data to date show an inverse association between *Helicobacter pylori* and EoE; this relationship has been confirmed at several centers in different locations worldwide.[109-113] This is of particular interest because the time of discovery of *H pylori* (in the early 1980s), along with the subsequent widespread treatment and decrease in prevalence of this infection, match the trend of increase in diagnosis of EoE. *H pylori* infection appears to produce a T-helper 1 cell-mediated response, so lack of *H pylori* might predispose people to a T-helper 2 cell-mediated immune response. [109] Lack of *H pylori* has also been associated with other atopic disorders,[114] but there are no direct data to indicate a role for *H pylori* in pathogenesis of EoE. EoE might also be associated with herpes

simplex virus[115-117] or mycoplasma pneumoniae,[118] but the mechanisms by which these would contribute to pathogenesis have not been studied—in contrast to an infectious complication of a topical steroid treatment for EoE. One study found a high rate of galactose-alpha-1,3,galactose sensitization, which is conveyed by a tick bite, in patients with EoE, but individuals without EoE (controls) had similarly high sensitization rates.[119]

Several other risk factors and conditions have also been associated with EoE. Oral and sublingual immunotherapy have been reported to induce EoE,[120-123] and a recent systematic review estimated that EoE could develop in 2.7% of patients undergoing oral immunotherapy.[124] This was an interesting observation, as it mimics the mechanism of induction of EoE in animal models.[125] PPIs have been proposed as a possible factor, given that they were introduced in the 1980s, their increase in use coincides with the rise of EoE, and PPI use has been associated with formation of new food-specific IgE antibodies.[126] However, there is no direct evidence to support this hypothesis. Recently, borderline low levels of vitamin D were reported in a cohort of patients with EoE,[127] but no data comparing vitamin or micronutrient levels in EoE cases vs controls were presented. Finally, a number of other conditions, including celiac disease,[128-132] connective tissue disorders,[133] and autoimmune processes, have been associated with EoE.[134, 135] However, there have not been mechanistic studies of these associations, with the exception of patients with Loeys-Dietz syndrome (and its associated mutation in the transforming growth factor beta gene), who develop eosinophilic gastrointestinal disorders.[133, 136]

Natural History

An accurate view of the natural history of EoE is central to discussions with patients about their prognosis and in making decisions about long-term use of medical, endoscopic, and diet therapies. Recommendations for maintenance therapy are based not only on prevention of disease relapse, but also on preventing the future consequences of EoE.[1, 2] If it appears that a patient with EoE is likely to undergo spontaneous remission or experience minor consequences, the risks of long-term therapy may outweigh the benefits. Since the initial characterization of EoE in the early 1990s, investigators have approached this topic from different provider perspectives and with distinct methods. Most studies have been retrospective, single-center experiences describing variable outcome metrics. Moreover, most studies included patients who received multiple treatments for EoE, including PPI therapy, elimination diet, steroids, and

esophageal dilation. In analyzing results of these studies, it is important to consider the age of the patients included and their perspectives. EoE is a relatively new disease, so uncertainties about the progression and long-term consequences of EoE can cause anxiety in patients.[137]

Two of the most informative studies of EoE progression came from a single-center study of adults in Switzerland.[138, 139] The perspective of 1 of the first investigators to describe EoE, combined with a systematic and comprehensive approach to data collection, provided valuable insights. Once study, published 15 years ago, continues to provide the best characterization of EoE progression in adults.[138] It followed 30 adults for a mean 7.2 years in the absence of medical therapy for EoE. Dysphagia and esophageal eosinophilia persisted in nearly every patient. Interestingly, the intensity of dysphagia was reduced over the follow-up period in 37% of patients, was stable in 37%, and worsened in 23%. Similarly, histopathologic findings of eosinophil density and basal zone hyperplasia decreased in most patients, although the eosinophil density increased in 20%. Subepithelial fibrosis increased on follow up in 6 of 7 biopsies (86%) evaluated for this marker of esophageal remodeling. Endoscopic abnormalities were stable but the severity of esophageal stenosis was not measured. No patient developed generalized eosinophilic infiltration of the gastrointestinal tract or an esophageal neoplasm.

The study highlighted the chronic nature of EoE in adults but also the absence of clinical progression over the follow-up period. However, there are 2 important limitations to the study. First, one third of the cohort underwent esophageal dilation. Although dilation is not expected to alter esophageal eosinophilia, it can reduce dysphagia, which could account for the substantial proportion of patients with stable or improved symptom outcomes. Esophageal dilation also makes it difficult to accurately determine stricture recurrence. Second, 50% of patients altered eating behaviors to compensate for perceived difficulties with rough-textured foods or hurried eating habits. Dietary modification may have reduced the burden of dysphagia reported.

A second study from the same center provided important insights into disease progression—it has been the only randomized study of topical steroid withdrawal performed in patients with EoE.[139] In this study, 28 patients who had achieved histologic remission following a randomized, controlled trial of swallowed budesonide were randomly assigned to groups given either budesonide (0.5 mg daily, 25% of the induction dose) or placebo. In patients given placebo for 1 year, peak esophageal eosinophil counts increased from 0.7 to 65 eosinophils per high-power field. At week 50, 64% of the patients given placebo had symptom relapse, at a median 3

months following withdrawal of budesonide. As in the previous study, an increase in subepithelial fibrosis was detected in the placebo group, although this increase was not statistically significant.

Three different centers have examined long-term outcomes of EoE using a cross-sectional study design that involved collection of survey questionnaires in children and adults diagnosed with EoE at an earlier time point.[140-142] All 3 studies found that most patients with EoE had mild to no symptoms several years after diagnosis. Importantly these studies assessed only symptom outcomes—they did not report endoscopic or histologic follow-up outcomes.

The first study, performed at the University of Pennsylvania, reported survey results from 53 of 140 patients with EoE over the age of 17 (mean age 21) who had been diagnosed in childhood (most during adolescence).[140] Several years after their diagnosis of EoE, only 4% of patients had a positive symptom score for dysphagia, based on the Mayo Dysphagia Questionnaire, and 37% reported dysphagia during the month prior to the questionnaire. Half of the patients were actively taking PPIs, whereas 76% were following an allergy-directed diet. These proportions were typical of local practice patterns.

Using a similar study design, researchers at Indiana University surveyed 58 young adults (mean age 21) with EoE who had been diagnosed in childhood.[141] After a mean follow-up period of 8 years, nearly half of the patients (47%) reported symptom resolution, despite the fact that two-thirds of the cohort did not receive active therapy for EoE (10% received topical steroids, 17% took PPIs). One third of patients reported dysphagia more than once each month and only 2% reported worsening of symptoms.

A study performed at the Mayo Clinic surveyed 59 adults (mean age, 56 years) who had been diagnosed with EoE more than 10 years ago;[142] 65% were taking PPIs and 7% received topical steroids. Twenty-eight percent of the subjects reported dysphagia in the month before the survey began, although 37% reported dietary restrictions. One limitation to this study is that the adults surveyed accounted for only a small proportion of the total EoE cases at the institution.

Two retrospective studies provided a more pessimistic view on the progression of EoE in adults.[143, 144] One study used the Swiss EoE Database to demonstrate that the prevalence of esophageal strictures increased with longer durations of untreated disease.[144] The study included 200 adults (median age, 39 years) with EoE and defined untreated disease duration as the time period from symptom onset to the diagnosis of EoE. Strictures developed in 17% of patients with

a delay in EoE diagnosis of 0–2 years, in 31% with a delay of 2–5 years, in 38% with a delay of 8–11 years, in 64% with a delay of 14–17 years, and in 71% with a delay of more than 20 years. Neither age at symptom onset nor degree of esophageal eosinophilia were associated with the presence of a stricture.

Data from the University of North Carolina substantiated this concept in 379 patients with EoE (mean age, 25 years) who were classified, based on endoscopic features, into inflammatory, fibrostenotic, or mixed inflammatory/fibrostenotic phenotypes.[143] Patients with an inflammatory phenotype were significantly younger than those with a mixed or fibrostenotic phenotype. The risk of developing a fibrostenotic phenotype doubled for every decade of life, and odds of developing fibrostenosis increased 5% for each year of symptoms prior to diagnosis. A study of 64 adults followed at the University of South Florida identified a greater duration of delayed diagnosis in patients with more severe esophageal strictures.[145] The time period of delayed diagnosis increased from 5 years for strictures over 16 mm in diameter, to 11 years for strictures 10–16 mm, to 15 years for strictures less than 10 mm.

Based on these data, we created a conceptual model for progression of EoE, from development of inflammation to fibrostenosis, assessed through a combination of endoscopic and histologic outcomes (Figure 4). Medical and diet therapies to reduce mucosal inflammation would have greater utility in patients with earlier-stage disease, whereas dilation would provide more benefit patients with strictures.

Two of the leading pediatric centers for treatment of EoE performed retrospective studies to determine long-term outcomes. Children's Hospital of Philadelphia reviewed 330 pediatric cases of EoE with more than 1 year of follow-up data; the mean follow-up period was 3.2 years.[146] Most patients at this center were actively treated with dietary elimination in addition to PPIs, in combination with medical therapy of concomitant allergic rhinitis and asthma. Only 3% of patients had histologic remission without continuing diet therapy and 10% had evidence for development of tolerance to foods previously identified as triggers of their EoE. Most of a subset of 24 patients who had elected to not treat their EoE had ongoing symptoms and eosinophilia, whereas 17% had progression to dysphagia after a mean follow-up time of 6 years.

Another approach to understanding the natural history of EoE was undertaken by Cincinnati Children's Hospital, where biopsies taken from a time period prior to the recognition of EoE were reanalyzed for presence of esophageal eosinophilia.[147] From this cohort, 42 children

completed survey questionnaires regarding symptoms. Dysphagia was present in half of the patients at a mean time point of 15 years after their index endoscopy. Retrospective analyses of biopsies showed findings consistent with EoE, indicating interval progression in patients with unrecognized disease.

Studies have therefore reached conflicting conclusions on EoE progression. However, their findings can be reconciled by considering differences in study design and methods. Symptom-focused outcome studies have indicated a relatively benign course of the disease, with absent or only mild dysphagia in most patients, with or without use of medical or dietary therapy directed at EoE. Several years after a diagnosis of EoE, approximately 30%–50% of children transitioning to adulthood reported symptoms of dysphagia. Although patient-reported outcomes are central to the management of EoE, patients typically adapt to the slow, progressive structuring by means of modification in eating behaviors. Avoidance of specific food textures (meat, crusty bread), increased use of liquids with meals, prolonged meal times, and meticulous mastication can reduce occurrence of dysphagia from esophageal strictures.

With progressive but very gradual esophageal remodeling, esophageal stenosis would be expected to affect fewer than 50% of patients; patients would develop a mild degree of stricture over fewer than 10 years. Longer term follow-up studies might reveal more substantial effects on the prevalence and severity of dysphagia. In addition, data from trials of patients with EoE have demonstrated that even short-term medical therapy can provide several months of symptom relief.[148, 149] Likewise, esophageal dilation can relieve symptoms of dysphagia for more than 1 year, even in the absence of anti-inflammatory therapy,[150] and patients who undergo esophageal dilation at baseline who have an initial histologic response to anti-inflammatory treatment require fewer dilations at later time points than patients without a histologic response.[151] Even sporadic use of therapy during a follow-up period could therefore reduce symptoms, even in patients not taking therapy at the time of a cross-sectional survey.

The studies reporting long-term reductions in symptoms often included patients who maintained PPI therapy. Numerous studies have demonstrated the long-term effectiveness of PPI therapy in reducing symptoms and eosinophilia (in 30%–70% of patients with symptomatic esophageal eosinophilia).[152] It is therefore important to remember that study outcomes can be affected by the effectiveness of PPIs, rather than spontaneous improvement in disease activity.

Contrary to symptom-based studies, studies focusing on endoscopic outcomes have reported progression of significant fibrostenoses in most patients with over a decade of untreated EoE.[143-145, 153] These studies used the time since symptom onset, rather than time since diagnosis of EoE, as a surrogate for duration of untreated disease. Although this method is subject to problems of recall accuracy, the longer time off EoE-directed treatment likely depicts a more accurate estimation of disease progression. Moreover, these studies have reported objective outcomes based on endoscopic detection of strictures rather than assessments of symptoms, which are subjective and affected by eating behavior. On the other hand, inclusion of patients with severe fibrostenoses referred to tertiary care centers may introduce selection bias, with unintentional exclusion of patients who never sought medical care due to stable or improved symptoms over time. Studies of another objective measure of disease activity, findings histopathology analyses, have uniformly corroborated the chronicity of EoE.[138, 139] Spontaneous resolution of esophageal eosinophilia is uncommon in EoE, although the degree of eosinophilia may wane even in the absence of active therapy.

Future Directions

The evolution of the epidemiology of EoE over the last 2 decades is remarkable, as the incidence and prevalence have increased rapidly. EoE is now commonly encountered in the endoscopy suite and clinic, is the leading cause of food impaction, is a major cause of dysphagia, and accounts for significant health-related costs. The implications of the emergence of EoE are 2-fold. First, if current incidence and prevalence trends hold, EoE may no longer be considered a rare disease. Furthermore, the cause of the continued increase in EoE cases over the last 2–3 decades is still largely unexplained, and this directly effects epidemiology research of EoE. While the descriptive epidemiologic features of EoE have been well characterized, little is known about the etiologic epidemiologic features. It is important to learn why specific individuals develop EoE, what the initial triggers are, what changes in the environment might be responsible for the increasing incidence of EoE, and what factors predispose to its development.

EoE development involves chronic inflammation that leads to progressive fibrostenosis in many but not all patients. This process is gradual, allowing many patients to adopt coping strategies to circumvent or underestimate symptom detection. In addition to coping strategies, genetic factors and behavior factors contribute to variation in the severity and effects of disease

progression. For now, the duration of untreated disease appears to be the single best predictor of stricture risk. Treatment with elimination diets or medical therapy might slow disease progression, but there are few data to support this concept, and factors that predict progression have not been identified. Spontaneous remission does occur, but it appears to be uncommon, based on data collected over the short time period that EoE has been studied. Prospective long-term outcome studies, focused on multiple aspects of disease activity, are needed to fully understand EoE progression.

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Figure Legends

Figure 1. (A) Time trends in EoE incidence from estimates in population-based studies. **(B)** Time trends in EoE prevalence from estimates in population-based studies.

Figure 2. Worldwide prevalence of EoE from estimates in population-based studies.

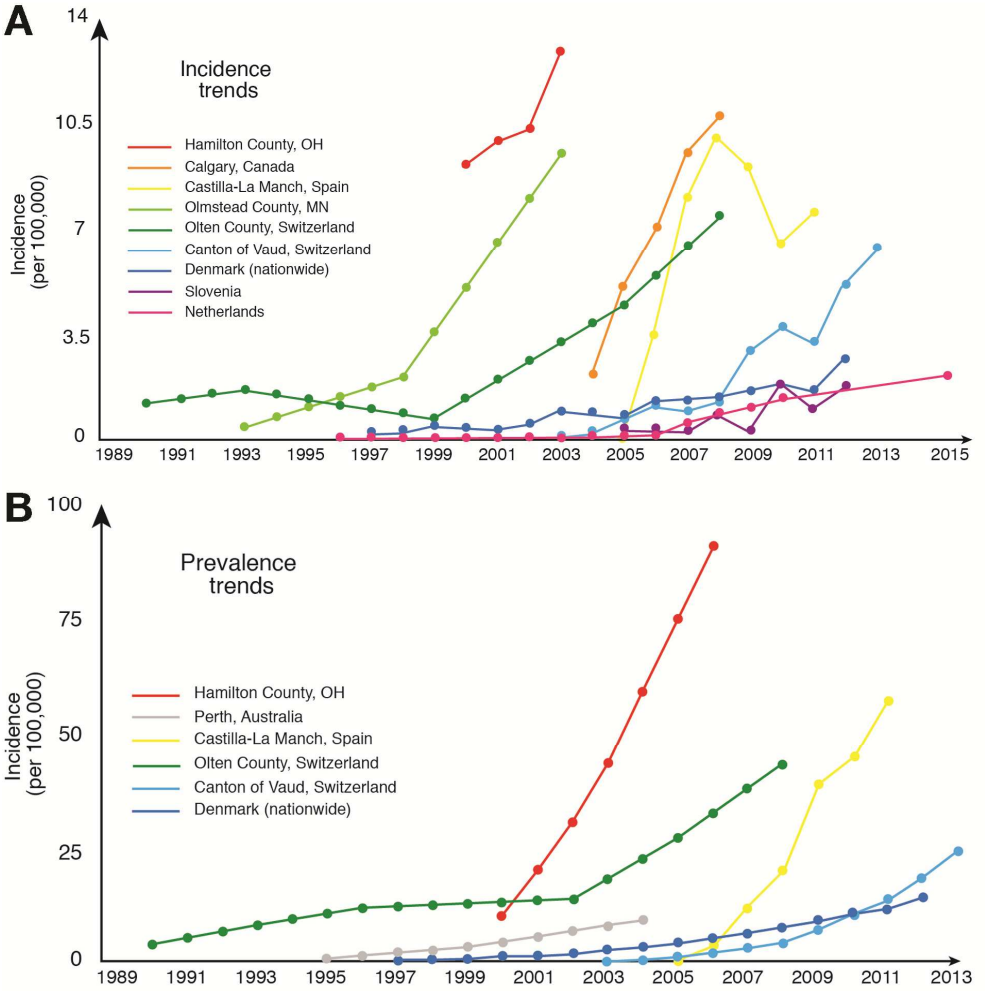
Figure 3. Prevalence of EoE in special populations including patients undergoing endoscopy for any reason, for dysphagia, for food bolus impaction, or for symptoms of refractory reflux.

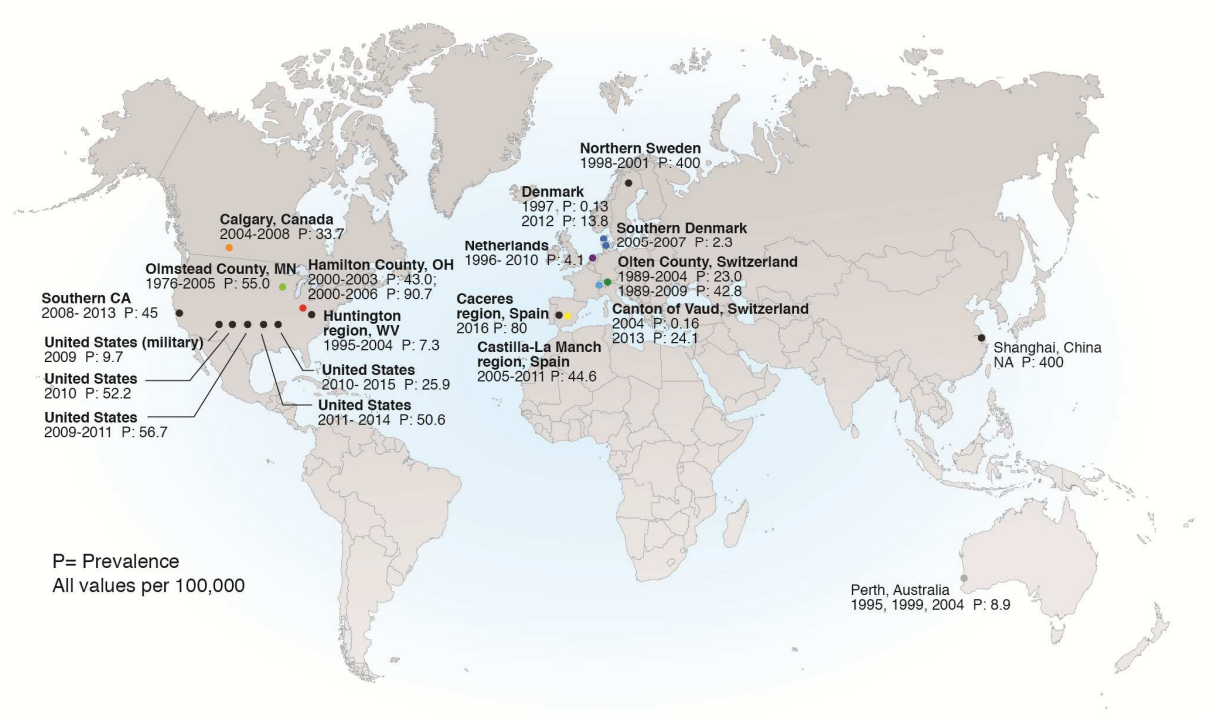
Figure 4. Progression of EoE from inflammation to fibrosis.

Table 1. Risk Factors for EoE and Disorders Associated with EoE

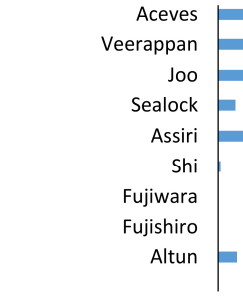
Risk factor	Comment
Aeroallergens[10, 16, 94-96, 98, 99, 154]	Might cause EoE or increase disease activity; can cross react with food allergens; may explain seasonal variation in diagnosis
Food allergens[7, 155, 156]	Directly trigger EoE; elimination can lead to disease remission
Helicobacter pylori[109-113]	Inversely associated with EoE; decrease in *H. pylori* prevalence has accompanied increase in EoE prevalence over the last 20 years; mechanistic data lacking
Infections (herpes simplex virus; mycoplasma)[115-118]	Associated with EoE; mechanistic data lacking
Oral or sublingual immunotherapy[120-124]	Causes or induces EoE in certain patients; baseline EoE status for reported cases usually not know prior to immunotherapy
Proton pump inhibitors[126]	Reported to induce IgE antibodies to certain foods
Cold or arid climates[100]	Increased odds of EoE in these climate zones, but not in temperate or tropical zones
Population density[35, 101, 102]	Odds of EoE increase as population density decreases
Early life factors[104-107]	Antibiotic use, Cesarean section, and preterm delivery increase the odds of pediatric EoE
Connective tissue disorders[133]	Ehlers-Danlos, Marfan Syndrome, and Loeys-Dietz syndrome have been associated with EoE
Celiac disease[128-132]	Associated with EoE; EoE is more common in patients with celiac disease than would be expected
Autoimmune conditions[134, 135]	Inflammatory bowel disease, rheumatoid

arthritis, IgA deficiency, multiple sclerosis, and Hashimoto's thyroiditis associated with EoE

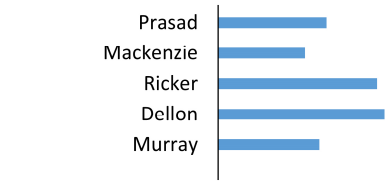

A
Incidence trends
Incidence (per 100,000)
14
10.5
7
3.5
0
Hamilton County, OH
Calgary, Canada
Castilla-La Manch, Spain
Olmstead County, MN
Olten County, Switzerland
Canton of Vaud, Switzerland
Denmark (nationwide)
Slovenia
Netherlands
1989
1991
1993
1995
1997
1999
2001
2003
2005
2007
2009
2011
2013
2015
B
Prevalence trends
Incidence (per 100,000)
100
75
50
25
0
Hamilton County, OH
Perth, Australia
Castilla-La Manch, Spain
Olten County, Switzerland
Canton of Vaud, Switzerland
Denmark (nationwide)
1989
1991
1993
1995
1997
1999
2001
2003
2005
2007
2009
2011
2013


Northern Sweden
1998-2001 P: 400
Denmark
1997, P: 0.13
2012 P: 13.8
Southern Denmark
2005-2007 P: 2.3
Calgary, Canada
2004-2008 P: 33.7
Netherlands
1996- 2010 P: 4.1
Olten County, Switzerland
1989-2004 P: 23.0
1989-2009 P: 42.8
Olmstead County, MN
1976-2005 P: 55.0
Hamilton County, OH
2000-2003 P: 43.0;
2000-2006 P: 90.7
Southern CA
2008- 2013 P: 45
Caceres
region, Spain
2016 P: 80
Canton of Vaud, Switzerland
2004 P: 0.16
2013 P: 24.1
Huntington
region, WV
1995-2004 P: 7.3
United States (military)
2009 P: 9.7
Castilla-La Manch
region, Spain
2005-2011 P: 44.6
Shanghai, China
NA P: 400
United States
2010- 2015 P: 25.9
United States
2010 P: 52.2
United States
2011- 2014 P: 50.6
United States
2009-2011 P: 56.7
P= Prevalence
All values per 100,000
Perth, Australia
1995, 1999, 2004 P: 8.9

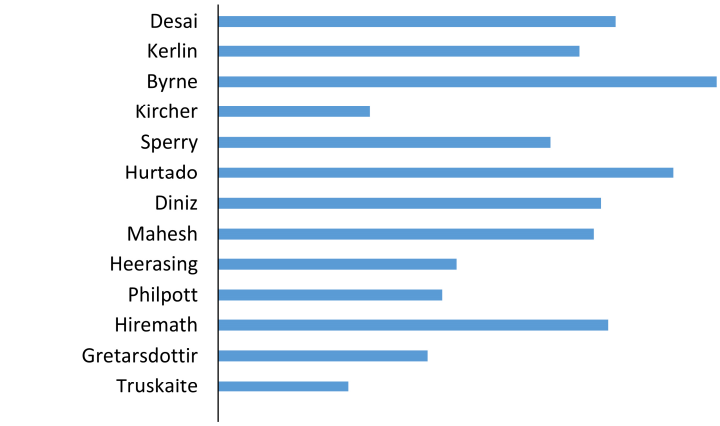
Patients undergoing endoscopy for any reason



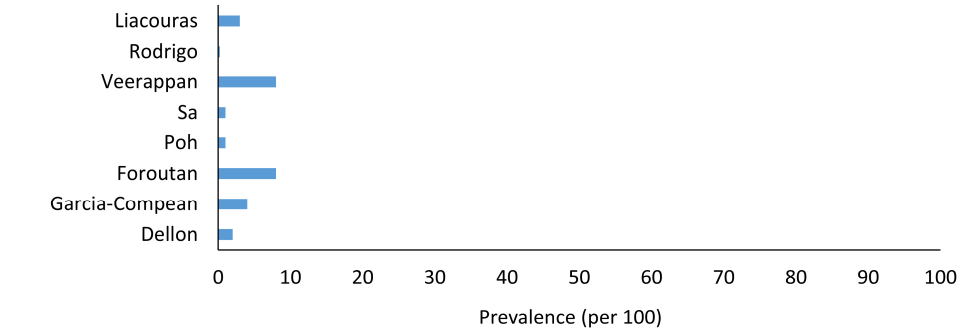
Patients undergoing endoscopy for dysphagia

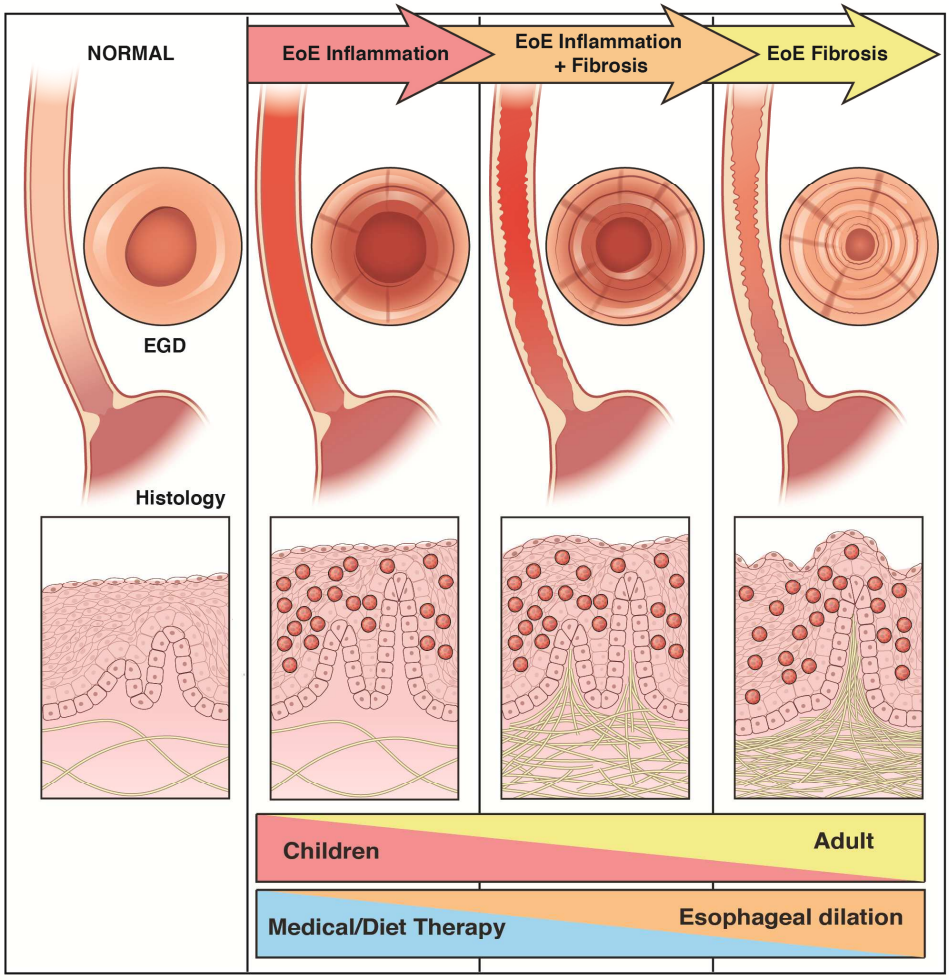


Patients undergoing endoscopy for food bolus impaction



Patients undergoing endoscopy for refractory reflux symptoms




NORMAL
EoE Inflammation
EoE Inflammation + Fibrosis
EoE Fibrosis
EGD
Histology
Children
Adult
Medical/Diet Therapy
Esophageal dilation

Supplemental Table 1. Population-based Estimates of EoE Incidence

Location	Population	Time frame	Incidence (per 100,000)	Reference
Hamilton County, OH	Pediatric	2000	9.1	[17]
		2001	9.9	
		2002	10.3	
		2003	12.8	
Olten County, Switzerland	Adult	1989-1991	1.2	[18, 19]
		1992-1994	1.6	
		1995-1997	1.1	
		1998-2000	0.7	
		2001-2003	0.7	
		2004-2006	4.4	
		2007-2009	7.4	
Olmstead County, MN	Adult and pediatric	1991-1995	0.35	[20]
		2001-2005	9.5	
Southern Denmark	Pediatric	2005-2007	1.6	[21]
Netherlands	Adult and pediatric	1996	0.01	[22, 26]
		2010	1.3	
		2015	2.1	
Calgary, Canada	Adult and pediatric	2004	2.1	[23]
		2008	10.7	

Castilla-La Manch region, Spain	Adult and pediatric	2005-2011	6.4*	[24]
Denmark (Nationwide)	Adult and pediatric	1997	0.13	[11]
		2012	2.6	
Slovenia	Pediatric	2005	0.24	[25]
		2006	0.25	
		2007	0.25	
		2008	0.76	
		2009	0.25	
		2010	1.78	
		2011	1.02	
		2012	1.8	
Canton of Vaud, Switzerland	Adult and pediatric	1993-2003	0	[12]
		2004	0.16	
		2005	0.61	
		2006	1.06	
		2007	0.89	
		2008	1.17	
		2009	2.87	
		2010	3.67	
		2011	3.19	
		2012	5.07	
		2013	6.3	
Caceres, Spain	Adult and pediatric	2012-2016	9.8	[45]

*The is the average incidence of the study timeframe

Supplemental Table 2. Population-based Estimates of EoE Prevalence

Location	Population	Time frame	Prevalence (per 100,000)	Reference
Hamilton County, OH	Pediatric	2000	9.9	[17, 32]
		2001	19.8	
		2002	30.2	
		2003	43.0	
		2006	90.7	
Perth, Australia	Pediatric	1995	0.5	[41]
		1999	3.1	
		2004	8.9	
Olten County, Switzerland	Adult	1989-1991	3.6	[18, 19]
		1992-1994	7.9	
		1995-1997	11.5	
		1998-2000	12.5	
		2001-2003	13.4	
		2004-2006	26.6	
		2007-2009	42.8	
Northern Sweden	Adult	1998-2001	400	[33]
Olmstead County, MN	Adult and pediatric	1976-2005	55.0	[20]
Huntington region, WV	Pediatric	1995-2004	7.3	[34]
Southern Denmark	Pediatric	2005-2007	2.3	[21]
United States	Adult and pediatric	2010	52.2	[35]

United States (military)	Adult and pediatric	2009	9.7	[36]
Netherlands	Adult and pediatric	1996-2010	4.1	[22]
Calgary, Canada	Adult and pediatric	2004-2008	33.7	[23]
Castilla-La Manch region, Spain	Adult and pediatric	2005	0	[24]
		2006	3.4	
		2007	11.4	
		2008	19.8	
		2009	38.3	
		2010	34.7	
		2011	44.6	
United States	Adult and pediatric	2009-2011	56.7	[37]
Shanghai, China	Adult (randomly selected in population)	n/a	400	[42]
Denmark (nationwide)	Adult and pediatric	1997	0.13	[11]
		2012	13.8	
United States	Adult and pediatric	2011-2014	50.6	[38]
Southern CA, US	Adult and pediatric	2008-2013	45	[39]
Canton of Vaud, Switzerland	Adult and pediatric	1993-2003	0	[12]
		2004	0.16	
		2005	0.77	
		2006	1.8	

		2007	2.7	
		2008	3.8	
		2009	6.6	
		2010	10.2	
		2011	13.2	
		2012	18.1	
		2013	24.1	
United States	Adult and pediatric	2010-2015	25.9	[40]
Caceres, Spain	Adult and pediatric	2012-2016	80	[45]

Note: Estimates where there is a date range are the cumulative prevalence over that date range

Supplemental Table 3. Estimates of EoE Prevalence in Selected Populations

Location	Population	Time frame	Prevalence (per 100)	Reference
Patients undergoing endoscopy for any reason				
San Diego, CA	Pediatric	1998-2002	5.1	[59]
Washington, DC	Adults	2007	6.5	[60]
Korea	Adults	2009	6.6	[51]
Houston, TX (military)	Adults	n/a	2.4	[61]
Saudi Arabia	Pediatric	2009-2012	4.8	[53]
Guangdong Province, China	Adults	2006-2010	0.34	[50]
Osaka, Japa	Adults	2010-2011	0.01	[46]
Japan	Adults	2010	0.02	[47]
Turkey	Adults	2010-2011	2.6	[52]
Patients undergoing endoscopy for dysphagia				
Rochester, MN	Adults	2005-2006	15	[62]
Salt Lake City, UT	Adults	2005-2007	12	[63]
Las Vegas, NV	Adults	2007-2009	22	[64]
Chapel Hill, NC	Adults	2009-2011	23	[65]
New Zealand	Adults	2012-2013	14	[66]
Patients undergoing endoscopy for food bolus impaction				
Detroit, MI	Adults	2000-2003	55	[67]
Brisbane, Australia	Adults	n/a	50	[68]
Salt Lake City, UT	Adults	1999-2004	69	[69]
Regensburg, Germany	Adults and adolescents	2000-2008	21	[70]
Chapel Hill, NC	Adults and pediatric	2002-2009	46	[71]
Denver, CO	Pediatric	2005-2009	63	[72]
Cincinnati, OH	Pediatric	1993-2009	53	[73]

Adelaide, Australia	Adults	1996-2010	52	[74]
Melbourne, Australia	Adults and pediatric	2012-2014	33	[75]
Melbourne, Australia	Adults	2002-2012	31	[76]
Houston, TX	Pediatric	2007-2013	54	[77]
Iceland	Adults and adolescents	2008-2013	29	[78]
Sweden	Adults	2011-2016	18	[79]
Patients undergoing endoscopy for refractory reflux				
Philadelphia, PA	Pediatric	1993-1995	3	[80]
Las Angels, CA	Adult	2002-2005	0.2	[81]
Washington, DC	Adult	2007	8	[60]
São Paulo, Brazil	Adult	2006-2008	1	[43]
Tucson, AZ (military)	Adult	n/a	1	[82]
Iran	Adult	2006	8	[54]
Monterrey, Mexico	Adult	2007-2009	4	[83]
Chapel Hill, NC	Adult	2009-2011	2	[65]