

# The Epidemiology of Eosinophilic Esophagitis: An Ongoing Enigma

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**E**osinophilic esophagitis (EoE) is a relatively new diagnosis. Although considered a rare disease in the past, EoE has gained increasing attention in the last 15 years due to rising prevalence and interest. However, data on the epidemiology of the disorder are scarce. Eosinophilic esophagitis is characterized by upper gastrointestinal (GI) symptoms associated with esophageal eosinophilia and basal cell hyperplasia [2].

Landres et al. [1] initially described EoE in 1978. Current data indicate that its prevalence is increasing. A recent study suggests that it may affect up to 3.8% of symptomatic patients who had a biopsy taken during esophagogastroduodenoscopy (EGD) [3]. The most common presenting symptoms among teenage and adult patients are solid-food dysphagia (33–70%), chest pain (25%), gastroesophageal reflux disease (GERD)-like symptoms (23–27%), and abdominal pain (~25%). Food impaction requiring endoscopic removal occurs in 33–54% of adult EoE patients. Studies have shown that up to 15% of all patients undergoing upper endoscopy for dysphagia are found to have EoE [4–8]. Although not pathognomonic for EoE and not part of the diagnostic criteria, some endoscopic features such as fixed or transient esophageal rings, longitudinal furrows, esophageal strictures, and mucosal edema or fragility are common findings that may support the diagnosis of EoE in the appropriate clinical and histologic setting [9].

According to recent guidelines, the diagnosis of EoE requires symptoms suggestive of esophageal dysfunction,  $\geq 15$  eosinophils per high power field (eos/hpf) in at least one esophageal biopsy sample and exclusion of esophageal eosinophilia secondary to GERD [10].

In the past decade, epidemiologic data on eosinophilic esophagitis increased notably. While some reports and case

series suggest a rising prevalence, others contend that this observation is related to better recognition and an increase in histological diagnosis [11]. Sealock and co-authors [12] indicate that the disease's prevalence is low in the general population and higher in young adults with suggestive symptoms. In this article we review the current data pertaining to the epidemiology of EoE, including the number of patients, gender distribution, prevalence and associated risk factors. Of the 22 articles reviewed, 2 represented community-based studies, 14 were institution-based [Table 1], 3 described an association with climate, and 3 explored whether there was an association with celiac disease [Figure 1].

## COMMUNITY-BASED STUDIES

Ronkainen et al. [13] performed a prospective cross-sectional analysis to estimate the prevalence of EoE in Sweden. Upper endoscopy was performed in 1000 randomly selected adult residents from 2860 subjects who responded to the Abdominal Symptom Questionnaire in northern Sweden. This questionnaire assesses gastrointestinal symptoms, namely reflux, dys-

peptic and irritable bowel symptoms. Using  $\geq 20$  eos/hpf as the diagnostic criterion, 4 subjects (3 males, 1 female) had a definite

diagnosis of EoE. The resulting prevalence was 0.4% and the most common symptom was heartburn. Patients with  $\geq 15$  eos/hpf were diagnosed with probable EoE and the prevalence was 0.7%. Based on their analysis, no specific risk factors or allergic history were associated with EoE [13].

Straumann and Simon [14] completed a retrospective cross-sectional study evaluating subjects with different esophageal symptoms within a geographically and socioeconomically defined area in Switzerland of approximately 100,000 inhabitants. Patients with GERD were excluded from the study. Twenty-three patients were diagnosed between 1989 and 2004 using 24 eos/hpf as the diagnostic criterion. This resulted in a prevalence of 0.02% [confidence interval (CI) 0.01–0.03]. The average age at diagnosis was 34.3 years (range 13–55 years) and the majority of cases were males (n=21, 91.3%). Dysphagia was the most common symptom and more than half had a history of rhino-conjunctivitis. The average annual incidence was 1.4

**Eosinophilic esophagitis (EoE) is a relatively new diagnosis with increasing prevalence and interest in the last decade**

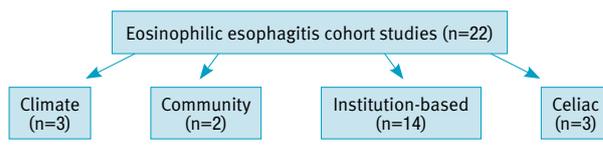
**Table 1.** Studies evaluating EoE prevalence based on current guidelines

Author [ref]	Study type		Patients			Interventions	Main results
	Design	Duration	N* EoE^	EoE patients' age (years)	Gender		
Kerlin et al. [15]	Prospective cross-sectional study	2 years	29 14	Mean 32	M 100%	EGD with proximal and distal biopsies in patients with food bolus impaction	<ul style="list-style-type: none"> <li>• 50% of patients with food bolus impaction had EoE (&gt; 15 eos/hpf, all with typical endoscopic features)</li> </ul>
Mackenzie et al. [16]	Prospective cross-sectional study	2 years	61 31	Mean 42	M 64.5% F 35.5%	EGD and distal and mid-esophageal biopsies of patients with dysphagia	<ul style="list-style-type: none"> <li>• EoE (&gt; 20 eos/hpf) prevalence of 12%</li> <li>• Asthma and food allergy risk factors for EoE</li> <li>• 42% w/o classic EGD findings</li> </ul>
Prasad et al. [5]	Prospective cross-sectional study	1 year	222 33	Mean 45	M 66.7% F 33.3%	EGD and mid-esophageal biopsy of patients with dysphagia	<ul style="list-style-type: none"> <li>• EoE (&gt; 20 eos/hpf) prevalence of 15%</li> <li>• 30% of patients with EoE had normal appearing mucosa on endoscopy</li> </ul>
Ramakrishnan and Chong [17]	Retrospective cross-sectional study	5 years	892 28	Median 33 Mean 34.9	NA	Reviewed biopsies of patients with diagnosis of GERD	<ul style="list-style-type: none"> <li>• EoE (&gt; 25 eos/hpf) prevalence of 3% in patients with previous GERD diagnosis and symptoms of bolus impaction/dysphagia</li> </ul>
Veerappan et al. [20]	Prospective cross-sectional study	7 months	400 25	Median 41	M 80% F 20%	Outpatient EGD and biopsy for various indications	<ul style="list-style-type: none"> <li>• EoE (&gt; 20 eos/hpf) prevalence of 6.5%</li> <li>• Asthma and classic EoE findings on EGD are strong predictors</li> </ul>
Shi et al. [21]	Retrospective cross-sectional study	4 years	3490 12	Median 50	M 58.3% F 41.7%	Reviewed biopsies from EGD for various indications	<ul style="list-style-type: none"> <li>• EoE (&gt; 15 eos/hpf) prevalence of 0.34%</li> <li>• Dysphagia and GERD-like symptoms are the most common clinical findings</li> </ul>

\* Total number of subjects

^Subjects diagnosed with EoE

**Figure 1.** Current studies evaluated



cases per 100,000 (range 1–6). However, although this study was performed in a population-based center, the cohort consisted of symptomatic subjects [14].

**INSTITUTION-BASED STUDIES**

Kerlin et al. [15] performed a prospective cross-sectional study of patients presenting with acute food bolus obstruction between 2002 and 2004 in Australia. A total of 43 patients were enrolled and 29 biopsies were obtained. Fourteen patients with a mean age of 32 years (range 19–62) were diagnosed with EoE. Using the criterion of > 15 eos/hpf, approximately 50% of the patients who underwent biopsy at the time of upper endoscopy for food bolus impaction were found to have EoE (48.2%, CI 31.4–65.6). All were males and no clear risk factors were identified. The study sample size was small and thus may overestimate the prevalence of EoE in acute food bolus impaction [15].

Mackenzie and colleagues [16] undertook a similar prospective cross-sectional study to evaluate the prevalence of EoE in

dysphagia and/or acute food bolus obstruction in patients at the Veterans Administration (VA) and University of Utah Health Sciences Center between 2005 and 2007. EGD was performed in 261 patients with dysphagia or food bolus obstruction. Based on > 20 eos/hpf, EoE was diagnosed in 31 patients with a mean age of 42 ± 15 (P < 0.001). The overall prevalence was 12%. The prevalence did not vary significantly between patients with food impaction or dysphagia (16.7% vs. 11.5% respectively, P = 0.52). The results showed no significant difference in the prevalence of EoE between male and female patients (males 10.8% vs. females 14.5%, P = 0.41), but most cases were males, reflecting the population at the VA hospital. Presence of asthma or food allergies denoted clear risk factors for EoE. Nonetheless, the cohort at the university hospital was younger compared to the VA. Additionally, GERD was not excluded in all patients prior to obtaining biopsies. Finally, routine stomach and duodenal biopsies to exclude eosinophilic enteritis were not performed [16].

In a prospective cross-sectional study, Prasad et al. [11] also analyzed the prevalence of EoE in dysphagia patients in Olmsted County between 2005 and 2006. Of the 222 patients who underwent EGD with biopsies, 33 were diagnosed with EoE according to > 20 eos/hpf [11]. This translates into a prevalence of 15% in dysphagic patients (CI 6%–12%), which is similar to the Utah study [16]. Male predominance was statistically significant (14% males vs 5% female, P = 0.003). Interestingly, 10 EoE patients (9.8%) had a normal appearing mucosa on endoscopy. This further supports the importance of obtaining esophageal biopsies in all symp-

**Most studies have identified a male predominance and higher prevalence in regions with a cold climate, although there are conflicting data regarding the effect of seasonal variation and association with celiac disease**

tomatic patients regardless of mucosal appearance. This study might have underestimated the prevalence of EoE since not all patients with dysphagia and normal mucosa on endoscopy were biopsied. Furthermore, most patients who were biopsied were young, which could have biased the study to overestimate prevalence as it did not include a representative sample of the whole population. No clear mean or range age was documented, but people younger than age 47 had a higher prevalence (14% vs. 3%,  $P < 0.001$ ).

Ramakrishnan and Chong [17] retrospectively reviewed 892 biopsies taken from patients previously diagnosed with GERD in London (UK) between 2002 and 2006. Twenty patients were diagnosed with EoE using  $> 25$  eos/hpf as the criterion, showing a prevalence of 2.2% in patients previously diagnosed with GERD (CI 1.5–3.4) and a mean age of 34.9. The study did not find any gender predominance, nor did it detect specific risk factors such as allergy history. Moreover, it did not report whether patients were on proton-pump inhibitors (PPIs) for GERD or had undergone 24 hour pH monitoring in the past.

Foroutan et al. [18] analyzed the association between EoE and refractory GERD in a prospective cross-sectional study. A

total of 68 patients underwent EGD and biopsy following an 8 week course of PPI. Using  $> 15$  eos/hpf or eosinophilic microabscess as diagnostic criteria, six patients with a mean age of  $41.2 \pm 3.3$  were found to have EoE, showing a prevalence of 8.8% (CI 4.1–17.9). All subjects diagnosed with EoE had a history of atopy ( $P < 0.001$ ). Unlike most reports, this study showed a slight female predominance with M:F ratio of 1:1.5. This ratio is not likely to be representative owing to the small sample size ( $n=68$ ) rather than environmental factors [18].

Similarly, García-Compeán and team [19] determined the prevalence of EoE in patients with refractory GERD in a prospective cross-sectional study from Mexico between 2007 and 2009. Six of the 150 enrolled patients met the criterion for EoE ( $> 15$  eos/hpf), yielding a prevalence of 4% (95% CI 2.4–5.6%). No statistical difference in relation to gender was observed. The study also found that patients with EoE had a significantly higher frequency of unexplained dysphagia than those without [6/6 (100%) vs. 24/144 (16.6%), respectively ( $P < 0.001$ )]. Moreover, patients with EoE were more likely to carry a diagnosis of atopy than those without [4/6 (66.6%) vs. 32/144 (22%), respectively ( $P = 0.029$ )]. Using logistic regression analysis, the authors found the following factors to significantly predict the presence of EoE: age under 45 years [odds ratio (OR) 4.8, 95% CI 2.4–8.6], dysphagia (OR 12.2, 95% CI 4.3–19.4), and history of atopy (OR 3.4, 95% CI 1.5–7.4)].

Veerappan et al. [20] performed a prospective cross-sectional study to investigate the prevalence of EoE in outpatients who underwent routine upper endoscopy for various indications at Walter Reed Army Medical Center, Washington, DC

between March and September 2007. Based on  $> 20$  eos/hpf, 400 patients with a median age of 50 years (range 19–92) were enrolled of whom 25 were diagnosed with EoE. The prevalence was 6.5% (25/385, CI 4.3–9.4%, 20/25 males, 18 patients  $<$  age of 50, 11 patients had seasonal allergies) [20]. This prevalence was significantly higher than that of a known prevalence in an asymptomatic Swedish community (0.4%) [13]. This study showed no significant difference with respect to race and demonstrated that EoE patients were significantly more likely to present with dysphagia.

de Sá et al. [21] also evaluated the prevalence of EoE in refractory GERD patients in a prospective study in Brazil. Only 1 of 103 patients who underwent EGD with biopsy was found to have EoE. This patient was male, age 23 years, and had a history of allergic rhinitis.

YN Shi et al. [22] completed a retrospective cross-sectional study that reviewed biopsies from patients who underwent EGD for various esophageal symptoms between 2006 and 2010 in China (Sun Yat-sen University). Of the 3490 esophageal biopsies performed, 12 patients had EoE based on  $> 15$  eos/hpf, demonstrating a prevalence of 0.34%. The median age of the

12 identified patients was 50 years (range 29–71 years) and the ratio of male to female 7:5. Dysphagia was the predominant reason for upper endoscopy (4/12, 33.3%). However, this study might have underestimated the prevalence of EoE since biopsies were not consistently obtained with each EGD. No allergic specific risk factors were identified [22]. Fujishiro and co-authors [23] evaluated 23,346 Japanese subjects as part of a prospective multicenter study to determine the prevalence of EoE in those who underwent EGD due to symptoms or as part of an annual medical checkup. Patients were enrolled between July and December 2010. Seventeen cases of EoE were diagnosed based on endoscopic appearance and the presence of  $> 20$  eos/hpf on biopsies. According to this study, the prevalence of EoE in Japanese patients was calculated to be 17.1/100,000. No gender predominance was noted and the mean age at diagnosis was 63 years. The authors acknowledge inclusion bias as a limitation that may have affected their results [23].

Altun et al. [24] performed a cohort study to determine the prevalence of EoE in Turkey. They enrolled 311 patients who presented for EGD due to different esophageal symptoms. EoE was diagnosed in 8 patients, reflecting a prevalence of 2.6%. Among patients with EE, 50% ( $n=4$ ) were women and 50% ( $n=4$ ) were men with a mean age of  $40.2 \pm 8$ . Interestingly, heartburn was the most common symptom and all those with EoE had a variable history of allergies [24].

Joo et al. [25] conducted a prospective cross-sectional study in Korea to determine the prevalence of EoE in patients who presented for EGD due to various esophageal symptoms. Of the 122 patients enrolled, 8 were diagnosed with EoE

### Data regarding the worldwide epidemiology of EoE are scarce and more studies exercising strict diagnostic guidelines are needed

using > 15 eos/hpf as the diagnostic criterion for EoE with M:F ratio of 5:3 and mean age of  $41.1 \pm 16.4$ , demonstrating a prevalence of 6.6%. When comparing EoE-positive with EoE-negative patients, a past history of GERD (62.5% vs 28.9%,  $P = 0.048$ ), allergic rhinitis (37.5% vs 7.9%,  $P = 0.007$ ) and atopic dermatitis (25.0% vs 4.4%,  $P = 0.015$ ) were significantly common in EoE patients. Epigastric pain was the most common symptom (61.5%) [25].

Arias and Lucendo [26] conducted a retrospective study and reviewed patient records from the gastroenterology and pathology departments of two hospitals in central Spain between 2005 and 2011. EoE was diagnosed based on > 15 eos/hpf, absence of eosinophilic infiltration of gastric and duodenal mucosa, exclusion of GERD by either 24 hour pH manometry, or presence of eosinophilic infiltration despite 8 weeks of PPI and exclusion of secondary etiology of esophageal eosinophilia. A total of 41 patients were found to have EoE. The mean age at diagnosis was 29.4 years (SD 10.8 range 16–53), 38 patients were males (95%) and 2 were females (5%). The most common presenting symptoms were food impaction (80%) and dysphagia (67.5%). A history of atopy was noted in 80% of the patients. Between 2005 and 2011 the period prevalence of EoE was 44.6 cases per 100,000 [26].

More recently, a study from the Netherlands by Van Rhijn et al. [27] determined the incidence of EoE in children and adults between 1996 and 2010. The authors presented a retrospective cross-sectional study of histopathological reports of esophageal eosinophilia. Of 8838 reviewed pathology reports, 674 patients were found to have EoE. Between 1996 and 2010 the annual incidence rate of EoE increased from 0.01 to 1.31 per 100,000. Whether this represents a true rise or is the result of increased understanding and detection of the disease is unknown. Higher incidences were seen in both males and females between the ages of 20 and 29. The incidence of EoE did not appear to vary with seasons. The study did not strictly adhere to the current diagnostic guideline and included patients whose exact eosinophil count was unknown, rendering the diagnosis of EoE uncertain in certain cases. That report constitutes the largest incidence study and reveals a clear rise in incidence of EoE in both children and adults [27].

Lee and collaborators [28] investigated the prevalence of EoE in both rural and urban settings in patients with non-PPI-responsive esophageal eosinophilia. The cohort comprised 20,718 patients, of whom 57 (0.28%) had biopsy-proven EoE ( $\geq 20$  eos/hpf) despite  $\geq 4$  weeks of high dose PPI. Of those with EoE, 29 (50.9%) lived in a rural area versus 28 (49.1%) in urban areas. In fact, there was no significant difference in the incidence of EoE between these populations. A male predominance was appreciable with a male:female ratio of 2:1 (39 males, 68.4%; 18 females, 31.6%). The mean age at the time of diagnosis was 26.7. Despite the lack of variation based on living environment, the authors contend that

various allergens in particular environments may predispose patients to EoE and that treatment should take into account the residential location of the patient [28].

Recently, Weinbrand-Goichberg et al. [20] described their experience with eosinophilic esophagitis in patients between the ages of 11 months and 20 years old who were referred to the Failure-to-Thrive clinic or for a gastroenterological opinion from 2000 to 2010. A diagnosis of EoE was established based on the presence of typical symptoms, endoscopic features and  $\geq 15$  eos/hpf on biopsy. Of the 7500 patients included, 30 were found to have EoE. Food hypersensitivity was detected in 17 patients, and 10 patients had asthma, allergic rhinitis, or both. Presenting symptoms varied depending on the age group. Those under 3 years of age displayed failure to thrive while those who were older displayed classical symptoms. The study supports a high index of suspicion to diagnose EoE in children with low intake failure to thrive [29].

#### **INFLUENCE OF CLIMATE AND SEASONAL VARIATION ON EOE PREVALENCE**

Almansa et al. [30] determined the effect of seasons on the epidemiology of EoE. The authors retrospectively reviewed the medical records of patients who underwent EGD for different esophageal symptoms. A total of 4146 medical records were reviewed. EoE was diagnosed in 41 patients based on > 20 eos/hpf, showing a prevalence of 0.98% (CI 0.7–1.3%). The mean age of the patients (30 males, 11 females) was 51.9 years. All patients had a variable history of allergies. Dysphagia was the most common presenting symptom. More patients were diagnosed during the ‘outdoor’ seasons – spring ( $n=18$ , 44%) and summer ( $n=10$ , 24%) – than during fall ( $n=7$ , 17%) and winter ( $n=6$ , 15%) ( $P < 0.019$ ), indicating that EoE could be due to aeroallergens [30]. Prasad et al. [11] also noted a majority of cases diagnosed in the late summer/fall period, suggesting a possible environmental trigger. Wang et al. [31] corroborated this seasonal variation in pediatric patients diagnosed with allergic EoE. Their retrospective analysis performed over a 6 year period identified 134 children with allergic EoE. Compared with summer, spring and fall, fewer cases of allergic EoE were diagnosed during winter [31].

Hurrell et al. [32] provided data regarding the influence of climate on the prevalence of EoE. They completed a retrospective cross-sectional study of esophageal biopsies obtained from a comprehensive U.S. pathology database between 2008 and 2010. A diagnosis of EoE required > 15 eos/hpf. Cases were those with EoE on biopsy; controls had normal esophageal biopsies. The authors assigned a Köppen-Geiger (K-G) climate class to each patient to determine whether there was any association between case-control status and the main K-G climate type (tropical, arid, temperate, or cold). The study included 233,649 patients who underwent esophageal biopsies. Mean age was 55.8 years and 46.2% were male. The authors found

that the cold climate zone contained the highest prevalence of patients with EoE (4.8%) compared with other climate zones. However, the most notable difference in prevalence was seen in patients aged 40 or younger, with no significant difference in EoE prevalence after the age of 50. The authors hypothesize that increased aeroallergens in a cold climate may contribute to increased prevalence noted in these regions. Due to the study's design, no conclusion regarding causality could be drawn [32].

**CELIAC DISEASE AND EOE**

Celiac disease is an immune mediated, gluten-sensitive disease of the small bowel distinct from EoE. The two are separate clinical and pathologic entities. Studies indicate that the prevalence of EoE is increased among pediatric patients with celiac disease [32-34]. It has been hypothesized that in addition to their gluten-sensitive enteropathy, a wheat or gluten allergy may serve as a trigger for EoE in these patients. Although there are fundamental differences in the pathophysiological mechanisms involved in eosinophilic esophagitis and celiac disease, these conditions may coexist and the prevalence is higher than anticipated [35]. Recently, Ludvigsson et al. [36] evaluated an adult population to determine whether there was any association between celiac disease, GERD and EoE. Of the 11 patients found to have EoE, none had celiac disease. The authors found no increased risk of celiac among patients with GERD, esophageal eosinophilia, or EoE [36].

**CONCLUSIONS**

This review article examined studies pertaining to the epidemiology of EoE in adult populations. In summary, the prevalence of EoE is highly variable. Many reasons may account for this wide disparity in numbers [Figure 2]. Several studies were performed before the guidelines to diagnose EoE were published in 2007. As such, studies that were completed prior to 2007 may have included patients with GERD who did not receive PPI therapy prior to undergoing EGD and biopsy. Thus, the

prevalence of EoE may have been overestimated. Additionally, not all studies adhered to > 15 eos/hpf as the cutoff criterion. This could have influenced sensitivity and overlooked several patients who should have been diagnosed with EoE. However, recent studies adopted current guidelines and reflect a more accurate prevalence [Table 1]. Factors such as patient population, gender, climate and presence of symptoms appear to influence the epidemiology of EoE. Most studies identified a male predominance and only a few showed no difference with respect to gender distribution. The prevalence of EoE appears to be higher in regions with a cold climate, although there are conflicting data on the influence of season. A few reports have suggested a higher prevalence during spring and summer but others did not describe such a variation. The prevalence seems to be higher in patients with dysphagia compared to PPI-resistant GERD or the general population. Most studies report that patients had a history of atopic disorders, suggesting that EoE may be a manifestation of a broader allergic response. The majority of studies relied on patient-reported history of atopy or allergy and lacked objective evidence such as immunoglobulin E levels or skin testing. Other aspects such as endoscopist bias in taking biopsies also likely affected results. Furthermore, eosinophilic gastroenteritis was not excluded in most studies. In closing, the prevalence of EoE is difficult to determine, and more studies exercising strict guidelines for number of biopsies, area of biopsies (normal vs. suspicious), and inclusion and exclusion criteria are needed to accurately determine the epidemiology of EoE in adult populations.

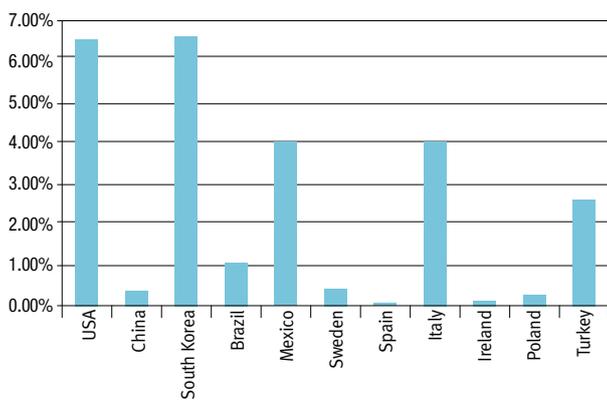
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**Figure 2.** Prevalence by country



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