

# Epidemiology of Eosinophilic Esophagitis: Really a Novel and Evolving Disease?

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## Keywords

Eosinophilic esophagitis · Incidence · Prevalence · Epidemiology

## Abstract

**Background:** Eosinophilic esophagitis (EoE) has been described as a chronic allergen/immune-mediated disease characterized by symptoms of esophageal dysfunction and eosinophilic infiltration of the mucosa. **Summary:** Over the past decades, EoE has been increasingly recognized in various geographical areas with a high socioeconomic development (mostly industrialized countries) and has evolved from an unknown to a clinically distinct disease with increasing prevalence and incidence. An average age at diagnosis between 30 and 50 years and a male predominance have been consistently observed. In both children and adults, EoE is clearly associated with allergies, predominantly food – but also aeroallergens. Most EoE patients present with a personal allergic background such as asthma, rhinoconjunctivitis, and oral allergy syndrome. **Key Message:** Knowledge of epidemiological characteristics is crucial for identifying risk factors and understanding of the pathogenic mechanisms.

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## Introduction

Thirty years ago, eosinophilic esophagitis (EoE) was described as a new immune-mediated inflammatory disorder of the esophagus characterized by esophageal symptoms in combination with a dense esophageal eosinophilia [1, 2]. Over the past 3 decades, an increasing incidence and prevalence has been described in the literature. However, most of the epidemiological information on EoE was based on retrospective evaluation of pathology reports with reexamination of biopsy specimens, analysis of endoscopy databases or surveys [3–9]. In recent years, population-based epidemiological information from geographically confined regions with longitudinal analysis has provided more substantial information on the characteristics and course of the disease. The aim of the current review was to address epidemiological key characteristics, such as the incidence and prevalence of EoE, and to describe demographic characteristics of EoE and disease associated factors.

## Prevalence of Esophageal Eosinophilia

Following the updated 2018 guidelines, EoE should be diagnosed when symptoms of esophageal dysfunction and at least 15 eosinophils per high-power field on esophageal biopsy are present after a comprehensive assessment of

non-EoE disorders that could cause or potentially contribute to esophageal eosinophilia [10]. Generally, eosinophils are present in the mucosa of all segments of the digestive tract, except the esophagus [11, 12]. Therefore, the presence of eosinophils in the esophagus is commonly associated with disease and requires a process of differential diagnosis. Data from a population-based study found a prevalence of 4.8% of any esophageal eosinophils in the distal part of the esophagus in the general population and was associated with erosive esophagitis and hiatal hernia [12]. This suggests that eosinophils may be present in the esophagus in the general population and may not generally be associated with EoE. Besides EoE, eosinophilic infiltration of the esophagus has been reported in patients having gastroesophageal reflux disease, Barrett's esophagus, and rare conditions such as drug-induced esophagitis, bacterial and parasitic infection, vasculitis, Crohn's disease, and eosinophilic gastroenteritis with affection of the esophagus [11].

#### *Global Incidence and Prevalence of EoE*

In 2016, one of the first systematic reviews for EoE with a total of 13 population-based studies from North America, Europe, and Australia was published: a pooled prevalence rate of 22.7 cases per 100,000 inhabitant-years and a pooled incidence rate of 3.7 cases per 100,000 inhabitant-years was calculated [13]. A steady increase in EoE incidence and prevalence rates has been observed comparing studies conducted before and after 2008, and higher prevalence rates in American compared to European studies have been shown. The variability may be partly explained by differences in access to endoscopic resources and physician awareness. Data on the epidemiology of EoE in Central and South America, Asia, and North Africa are still scarce.

A recent systematic review showed comparable data: a slightly higher pooled prevalence of 34.4/100,000 and a pooled incidence of 7.7/100,000 in adults and 6.6/100,000 in children, respectively, was calculated [14]. A steady increase in the incidence and prevalence of EoE over time was observed as well. This trend was further confirmed by another meta-analysis including a total of 40 studies from 15 different countries and around 150,000 EoE patients, showing a steadily increasing global EoE prevalence between 1976 and 2022 [15]. In addition, a higher incidence and prevalence of EoE in high-income regions of North America and Europe compared to middle- and low-income regions was observed in this analysis.

#### *Time Trends in Incidence and Prevalence of EoE in Geographically Confined Regions*

In Canton of Vaud (Switzerland), a steady increase over the past 10 years up to an incidence of 6.3/100,000 and a cumulative prevalence of 24.1/100,000 in 2013

was demonstrated [16]. This observation confirmed earlier studies from the confined region of Olten County (Switzerland), with increasing cumulative incidence (7.4/100,000) and prevalence rates (42.1/100,000) [17]. Similar findings have been observed in a confined region in Spain with a cumulative incidence rate reaching 10/100,000 and a cumulative prevalence rate of 106/100,000 persons/year (children and adult rates combined) [18]. Two independent nationwide analyses in North America reported estimated prevalence rates of 50.6/100,000 [19] and 25.9/100,000 [20], respectively. The difference between the two US-American studies may be due to differences in the case definition and unequal population sizes. In the second analysis, only patients with a diagnosis of EoE and a history of proton pump inhibitor use were included, to avoid cases of proton pump inhibitor-responsive esophageal eosinophilia.

Recently, a systematic review and meta-analysis on the incidence and prevalence of EoE in Europe showed an overall prevalence across all studies of 32.7/100,000 and an incidence of 4.1/100,000 with the highest incidence values reported from confined areas of Spain [21]. All studies that reported longitudinal trends in EoE incidence showed an increase over time, more marked in recent years. These findings of increasing incidence and prevalence rates were also confirmed in register-based pathology reports from the Netherlands, Sweden, and Denmark [22–24]. Generally, it seems that the incidence rates were lower in nationwide studies compared to regional or center-based studies. This cannot be explained solely by increased awareness for the disease amongst health care professionals in different regions worldwide, as the epidemiological trend behaved disproportionately compared to the increase in esophageal biopsies over time [25]. As this awareness has only grown in the last 10–20 years, the numbers of EoE diagnoses have risen at different points in time. On the other hand, different methods of data collection and evaluation may also play a role, for example, the inclusion or exclusion of patients with proton pump inhibitor-responsive esophageal eosinophilia. Retrospective studies on old biopsy blocks did not reveal a considerable amount of missed EoE diagnoses in previous time periods [25]. Furthermore, it should also be considered and further investigated whether EoE develops differently in different regions due to genetic and environmental factors. Independently of these considerations, an increase in the incidence and overall prevalence of EoE cases in Europe over the last 30 years was demonstrated.

**Table 1.** Epidemiological characteristics of EoE patients

Characteristic	Comment
Age: 30–50 years old	Adults are more often affected than children
Gender: male	Male-to-female ratio of about 3:1
Ethnicity: Caucasian	Caucasians are more often affected than African Americans, Hispanics or Asians
Clinical history: allergic disorders	Asthma, allergic rhinitis, atopic dermatitis, or food allergies are most common
Diagnostic delay (initial diagnosis)	Associated with a higher risk for complicated disease

### *Diagnostic Delay and Risks*

A recent population-based study calculated a median diagnostic delay of 4 years in adult patients and 2 years in pediatric patients and found that the median diagnostic delay did not change significantly over the past 10 years [16]. This is of clinical relevance as Danish cohort data indicated that the complicated EoE phenotype is associated with a longer diagnostic delay [26].

This finding is supported by a recent analysis that showed decreased esophageal distensibility and compliance in adult EoE patients with longer symptom duration prior to their diagnosis [27]. The association between reduced distensibility and increased symptom duration supports the findings of a previously reported prediction model that the risk of developing fibro-stenotic disease more than doubles per decade of life [28]. It also fits with prior clinical studies assessing longitudinal course of EoE, which concluded that the prevalence of esophageal strictures correlates with the duration of untreated disease [29–31]. Thus, reduced esophageal distensibility can be associated with diagnostic delay and can have an important impact on disease progression in patients with EoE.

### **Demographic Characteristics of Patients with EoE**

#### *Age Distribution*

Most studies report the highest prevalence and incidence rates of EoE in middle-aged adults (30–50 years of age, Table 1) [32]. Nationwide US-American and Dutch studies confirmed the peak prevalence in this age range for both genders [33]. In the USA, the prevalence rate was highest in the pediatric population (<18 years) with 25.1 as well as in the adult population (18–65 years) with 30.0, but lower in the elderly population (>65 years) with 12.8 cases per 100,000 patients, respectively [20]. Most analyses confirm a higher incidence and prevalence of EoE in adults compared to children. For example, a pooled prevalence of 42–53/100,000 inhabitants for adults and 29–34/100,000 inhab-

itants for children was found in the most recent worldwide systematic analyses [13–15]. It is unclear whether the low percentage of elderly diagnosed with EoE is due to an atypical disease presentation or EoE is truly less prevalent in this age group. Another factor could be that EoE is less frequently considered as differential diagnosis in elderly patients, as it is commonly thought to be a disease of younger age [19]. In addition, it should be considered that elderly patients often belong to a patient group that is less represented and investigated in clinical studies.

#### *Gender and Social Parameters*

The observation that male gender is a risk factor for the development of EoE both in adults and children was confirmed in many studies [32]. In the most recent global systematic review from 2023, the risk of developing EoE was found to be 3.4 times higher for men compared to women [15]. This finding could also be reproduced for patients in the USA with Caucasian males being the majority of EoE cases [19, 20]. Corresponding OR rates of 2.5, for example, in the Netherlands [22] and 2.8 in Switzerland [16] underline the increased relative risk of developing EoE among male patients.

One of the latest Swiss studies on gender-specific differences in EoE was published in 2022 and analyzed prospectively collected data of 266 adult patients. A higher endoscopic and histologic disease activity in male compared to female patients was observed, although no differences in subjective symptom severity and in EoE-associated quality of life could be demonstrated [34]. A retrospective study of 755 medical records of US-American EoE patients showed that males were diagnosed at younger age and had higher odds of having abnormal endoscopic findings compared to women [35].

#### *Symptoms of Esophageal Dysfunction*

In a systematic review in 2018, a total of 27 studies from different countries around the world (USA, Australia, Japan, Slovenia, Italy, Spain, Switzerland,

**Table 2.** Symptoms associated with EoE

Age group	Symptoms
Adults	Solid food dysphagia, food impaction, non-swallowing associated chest pain, heartburn, atypical presentation of exercise-induced chest pain
Children	Emesis, abdominal pain, reflux-like symptoms, nausea, regurgitation, food refusal, failure to thrive

and UK) have been included and showed that the most commonly described symptoms by pediatric EoE patients were emesis and abdominal pain (Table 2). In adults, the most common symptoms were solid food dysphagia and food impaction [36]. Other symptoms include reflux-like symptoms, nausea, food refusal and failure to thrive in children and non-swallowing associated chest pain or heartburn in adults [32, 37–39]. Clinicians should also be aware of atypical manifestations of EoE, for example, exercise-induced chest pain, particularly in younger male patients [40]. In a systematic search on differences of EoE patients in Asian compared to Western countries, similar disease characteristics were found [41].

### Associated Disease Contributing Factors

#### *Allergic Predisposition*

Allergic and atopic disease such as food allergies, bronchial asthma, allergic rhinitis, and atopic dermatitis are more common in EoE patients compared to the general population [42, 43]. A positive history of concurrent atopic disease has been described in 50–60% of EoE cases [32]. In a retrospective database analysis from 2009 to 2013 in the USA the following rates of concurrent diseases up to 12 months post-diagnosis were observed: atopic rhinitis in 44.7%, asthma in 27.1%, atopic dermatitis in 25.2%, and food allergies in 16.9% with almost two-third of all patients suffering from at least one of these 4 conditions [43].

Sensitization to ingested, cutaneous, and/or inhaled allergens plays an important role in the development of EoE and there is a strong consensus regarding food allergens such as milk, eggs, wheat, and soy as potential triggers for EoE [44]. Different dietary treatments show a significant and positive influence on the course of the disease. Dietary treatment options like amino acid-based

elemental diets and allergy test result-directed food eliminations, but especially one-food (1-FED) up to six-food elimination diets (6-FED) showed high rates of histological remission in patients with EoE [45–47]. The removal of one or more ingested food types, can cause resolution of disease in >50% of adult and pediatric patients. A recent multicenter trial on 6-FED (milk, wheat, egg, soy, fish/shellfish, and peanut/tree nuts) and 1-FED (milk) proved the efficacy of these approaches in terms of histological and endoscopic remission as well as clinical improvement [48].

#### *EoE and Seasonal Distribution*

In contrast to food allergens, the influence of aero-allergens has not yet been conclusively clarified. There are indications that airborne antigens play a disease modifying role in the pathogenesis of EoE [49] and some reports suggest a seasonal variation with EoE being more frequently diagnosed in the spring and summer season [50–52]. This is further supported by the observation that EoE varies by climate zones in the USA [53]. A retrospective case series of 1,180 EoE patients found that 14% had a history of exacerbation by aeroallergens, and 20% of those had biopsy-confirmed seasonal variation of esophageal eosinophilia [54]. Mild but consistent seasonal variance with an accumulation of diagnoses (EoE and esophageal eosinophilia) in the summer months – whereby climatic and geographic differences were considered – have been reported previously [55].

A confirmation of a seasonal dependency of EoE would be an indicator that external seasonal factors, in particular, pollen could play a substantial role in the pathogenesis of this Th2-type inflammation. Indeed, one study found a significant association between peak grass pollen count and diagnosis of EoE in spring, but only a coincident association with peak tree or weed pollen counts [56]. It is important to consider that there is a substantial gap between onset of symptoms (= likely onset of disease) and endoscopic, respectively, histologic diagnosis. Also, the onset of disease often does not correlate with the date of diagnosis.

Taken together, there is currently no solid proof that either the first onset of EoE or the course of its inflammation show a seasonal variation, or that pollen exposure could play a significant pathogenic role. The current evidence does not support causality in inhaled allergen exposure and the genesis nor exacerbation of EoE in humans, although there is a possibility that inhaled allergen sensitization could play a disease modifying role in EoE in the context of cross-reacting food allergens [49]. To answer this question, prospective studies are needed

using a systematic assessment of the course of symptoms as well as the inflammatory activity of EoE with a correlation to the pollen exposure.

#### *EoE and Autoimmune-Related Conditions*

An association between EoE and celiac disease (CeD) has been suggested in several case series and cohort studies [57–60]. A prevalence of EoE in patients with CeD of 2.5–5.0% was reported in children (<18 years of age) and adults in independent reports [57, 58, 61, 62]. However, in a population-based approach with 1,000 randomly selected adults from the general population, no increased risk of CeD was found among subjects with esophageal eosinophilia, EoE or gastroesophageal reflux disease [63]. Current data do not support a true association between EoE and CeD including data from a systematic review [64]. Furthermore, gluten-free diets do not appear to induce remission of coexisting EoE in several reports and HLA DQ2 and DQ8, the predisposing alleles for CeD, were not found to be increased in adult EoE patients compared to controls [57, 61, 65]. However, it was reported that gluten-free diet resolved EoE findings in some patients, suggesting possible shared pathophysiology in some cases [66].

It has been suggested that patients with EoE had an increased risk for other autoimmune-related diseases, including ulcerative colitis and Crohn's disease [67, 68]. An interesting propensity-matched analysis of IBD patients revealed that, when comparing patients with and without EoE, the relative risk for immune-mediated comorbidities was significantly higher for CeD, IBD-

related inflammatory conditions, eczema, and asthma. Patients with a concurrent diagnosis of EoE and IBD had a higher composite risk of IBD-related complications and lower risk of food bolus impaction [69].

#### **Conclusion**

During the last 3 decades, the prevalence and incidence rates for EoE have steadily increased in various regions worldwide and EoE evolved from a novel to a clinically distinct disease. Better understanding of epidemiological characteristics and the clinical presentation of EoE is crucial for identifying risk factors and understanding the pathogenic mechanisms. In consequence, this will lead to identification of preventive measures and will improve treatment strategies.

#### **Conflict of Interest Statement**

The authors have no conflicts to declare regarding this article.

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#### **Author Contributions**

R.M. and P.H. contributed equally to the writing of this article.

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