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REVIEW



# Epidemiology and risk factors for eosinophilic esophagitis: lessons for clinicians

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**ABSTRACT**

**Introduction:** The rapid expansion in the epidemiology of eosinophilic esophagitis (EoE) is being documented, along with cumulative research assessing environmental exposures associated with EoE and susceptibility due to genetic variants.

**Areas covered:** Incidence rates for EoE of 5–10 new cases per 100,000 inhabitants annually have shown an increase in recent reports of up to 20 in some countries; the highest prevalence being reported for Europe and North America, where EoE now affects more than 1 out of 1,000 people. EoE has been shown to be associated with several disorders, Th2-mediated atopies being the most common. Patients with EoE exhibit increased frequency of asthma, allergic rhinitis and eczema, and EoE has been considered as a late component of the atopic march. Risk variants in *TSLP, CAPN14* and *LRCC32* genes, among others, have all been related to EoE, and interact with prenatal and early life exposure potentially modifying abundance and composition of gut microbiome. Dysregulated interactions between bacteria and mucosal immunity emerge as leading causes of EoE.

**Expert opinion:** The expanding epidemiology of EoE, the resources needed and subsequent increasing healthcare costs require additional effort to optimize cost-effective management and unveil mechanisms that enhance the development of future preventive strategies.

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Eosinophilic esophagitis; epidemiology; prevalence; incidence; risk factors; environment

## 1. Introduction

Eosinophilic esophagitis (EoE) is a chronic inflammatory disease characterized by chronic or recurrent symptoms of esophageal dysfunction and eosinophilic infiltration of the esophageal mucosa [1]. Knowledge about the epidemiology of EoE has evolved from its first descriptions less than 3 decades ago [2,3] to systematic reviews [4,5] and recently published articles [6–8], which document that prevalence rates of EoE have increased rapidly over the last two decades, while the incidence has increased slowly but steadily. Although studies note differences in the epidemiology figures, this is most likely due to distinct definitions of the disease and the variable methodology used. Even so, in the last few years EoE has gone from being considered a rare disease to becoming a 'common' condition. It currently represents the second cause of chronic esophageal inflammation after gastroesophageal reflux disease (GERD) as well as the most common cause of dysphagia and food impaction among children and young adults [9,10].

This article aims to review the most recent evidence on the epidemiology of EoE, from changes in its frequency and the underlying reasons for this, to the potential risk factors proposed to explain the increasing recognition and expansion of EoE globally. The implications that the constant expansion of EoE have for clinical practice will also be discussed.

## 2. Epidemiology of EoE

Numerous studies carried out in North America, Europe and Australia over the last decade have attempted to estimate the real frequency of EoE. However, cases have been reported on all continents, making it a worldwide disease. Very different approaches have been taken in EoE epidemiological studies. These have included prospective, retrospective, biopsy records and population-based analyzes. The latter, which is undoubtedly the most appropriate design to assess the epidemiology of any disease, only accounted for a small percentage of the studies. Definition of the disease has also varied throughout its short life. Considering different cutoff points or thresholds in eosinophils per high power field or including patients who respond or not to proton-pump inhibitor (PPI) therapy are two variable parameters employed. Methodological rigor and/or risk of bias was found to be insufficient on occasion in some of the studies: Some risks of bias described include inappropriate sampling of study participants, differences in measurement of EoE in a standard and reliable manner for all participants or developing data analysis with insufficient coverage of the identified sample [5].

Although EoE affects individuals of any age and sex, all research, from case series to strictly-developed population-based studies, demonstrates that the most common age range is from 5 to 14 years-old in children and from 20 to 45 years old in adulthood. The disease is predominantly in

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**Article highlights**

- The prevalence figures for EoE have varied widely in recent years, depending on the definition used for the disease. However, the increasing trend in the number of patients diagnosed as suffering from this disease is unquestionable, with more than 1 out of 1,000 inhabitants being currently affected.
- The incidence rate for EoE in both children and adults is between 5 to 10 new cases per 100,000 inhabitants annually. Some recent studies, however, raise this rate to 20 new cases per 100,000 inhabitants annually. The increase in newly diagnosed cases of EoE exceeds the annual growth in the number of endoscopies performed.
- The increasing epidemiology of EoE has been interpreted in the context of expansion of immune-mediated disorders. In addition, increasing awareness among health professionals, generalization in the use of endoscopy and the recognition of PPI-responsive esophageal eosinophilia as EoE that responds to PPI, have contributed to elevating the epidemiology of this disease.
- Identifying risk factors for EoE is key to understanding the reasons underlying the increasing epidemiology of EoE. Several genetic susceptibility variants in components of the immune system, epithelial barriers and prenatal and early childhood exposures have been related to the risk of developing EoE. Most also predispose to concomitant Th-2 mediated allergies in the same patients, so disease-specific risk factors need to be further investigated.
- The continuous increase in the incidence and prevalence of EoE and its spread to all continents, the high costs of its management and complication of untreated cases will escalate costs for health systems in the near future. Identifying the interplay between risk factors and implementing preventive action constitute the major challenge over the coming years.

males, and most of cases are described in individuals of Caucasian origin.

### 2.1. Incidence

The literature provides widely variable incidence rates for EoE, although the latest studies have shown EoE affects around 5 to 10 new cases per 100,000 inhabitants annually, both for children and adults [8,11–14]. Other recent studies, however, raise this figures close to or greater than 20 new cases per 100,000 inhabitants annually [6,7,15]. This continued annual increase in the appearance of new cases has led to increased prevalence of EoE.

### 2.2. Prevalence

As a consequence of the steady increasing incidence of EoE and the fact that it predominantly affects young people and does not shorten life expectancy, the growth in the prevalence of the disease will continue for the foreseeable future before stabilizing. Noel el at carried out the first population-based study of EoE in the United States, published in 2004 [16]. They reported prevalence of 42.96 cases per 100,000 inhabitants. During the next decade, other studies similarly estimated prevalence ranging between 40 and 55 cases per 100,000 inhabitants [15,17–22]. These figures have been widely exceeded in studies published after 2016: Molina-Infante et al. reported the highest prevalence figure in that year of 81.7 cases per 100,000 inhabitants, and more recent research has found 100 cases per 100,000 inhabitants [7,8,23]. Robson et al reported EoE affecting 118.4 cases per 100,000 inhabitants in children from Utah, while simultaneously, Arias & Lucendo found in Spain EoE affecting 112 cases per 100,000 inhabitants in both children and adults, the highest prevalence published to date. Table 1 summarizes results from the main studies addressing population-based prevalence of EoE.

One of the main pieces of evidence that supports the prevalence of EoE truly increasing is studies which have evaluated the disease in the same geographical area at different points in time. Two such studies are in Olten County, Switzerland, where the prevalence of EoE went from 23 to 42.8 cases per 100,000 inhabitants between 2004 and 2009 [18,24], and in the Castilla-La Mancha region in central Spain where prevalence increased from 44.62 to 111.9 between 2011 and 2017 [8,17].

## 3. Reasons for the increasing prevalence of EoE

To explain these striking increases in the incidence and prevalence of EoE some hypotheses are proposed. To begin with, the increase in the frequency of EoE is not interpreted as an isolated phenomenon, but in the general context of an expansion of the epidemiology of immuno-mediated and allergic diseases, as the hygiene hypothesis classically proposed. In this general framework of a continued increase in the frequency of entities such as asthma, atopic dermatitis, rhinitis, inflammatory bowel disease and a multitude of food allergies, among others, during recent decades, EoE is one more such condition. According to the hygiene hypothesis, a more sterile environment restricts the immune system's exposure to the variety of antigens needed for its proper development and maturation, resulting in hyper-reactivity against its own or harmless antigens [24]. EoE is triggered and maintained by exposition to food allergens that are widely distributed in staple westernized diets [25,26]. The reasons why milk, wheat, eggs and legumes (the main foods involved in the origin of the EoE) have begun, in the last few decades, to trigger esophageal inflammation by eosinophils when they had been part of the human diet since the Neolithic period, are completely unknown.

The increasing expansion of EoE has been related to the parallel increase in the number of endoscopic examinations performed [27–30]. As a result of the diagnostic and therapeutic advances that these techniques have undergone, they have become a first-line choice for examining multiple diseases and conditions. However, several studies in the literature have demonstrated that the rise in the appearance of EoE preceded the use of endoscopic procedures [8,12,31,32].

The definition of EoE changed after the release of the 2017 evidence-based guidelines for the management of the disease [1] and was included in the updated consensus on diagnostic criteria for EoE published one year later [33]. According to this definition, patients with proton-pump inhibitor (PPI)-responsive esophageal eosinophilia should be considered within the spectrum of EoE. However, since this condition was based on the response to a single drug, it did not constitute an appropriate disease descriptor and should be abandoned. Patients who had esophageal eosinophilia and esophageal symptoms resolved with PPI therapy were demonstrated to have phenotypic, molecular, mechanistic, and

Table 1. Individual population-based studies (identified by First author and year of publication) that have evaluated the prevalence of eosinophilic esophagitis in patients of all ages. Modified from Navarro P et al [5].

| Author, year | Country | Study Period | Reference Population | EoE Cases | Population type | Prevalence/100,000 hab |
|---|---|---|---|---|---|---|
| Noel R et al. 2004 | USA | 2000–2003 | - | 103 | Children | **42.96** |
| Cherian S et al. 2006 | Australia | 1995, 1999, 2004 | - | 285 | Children | **8.9** |
| Gill R et al. 2007 | USA | 1995–2004 | 600,000 | 44 | Children | **7.3** |
| Prasad G et al. 2009 | USA | 1976–2005 | 120,000 | 78 | All | **55** |
| Dalby K et al. 2010 | Denmark | 2005–2007 | 256,164 | 6 | Children | **2.3** |
| Hruz P et al. 2011 | Switzerland | 1989–2009 | 90,000 | 46 | Adults | **42.8** |
| Ally M et al. 2014 | USA | 2008–2009 | 10,180,515 | 987 | All | **9.7** |
| Dellon E et al. 2014 | USA | 2009–2011 | 11,569,217 | 6513 | All | **56.7** |
| Dellon E et al. 2015 | Denmark | 1997–2011 | - | 763 | All | **13.8** |
| Giriens B et al. Allergy. 2015 | Switzerland | 1993–2013 | 743,317 | 179 | All | **24.1** |
| Kim S et al. 2015 | USA | 2008–2013 | 3,486,069 | 1561 | All | **44.8** |
| Maradey-Romero C et al. 2015 | USA | 2011–2014 | 9,559,570 | 4840 | All | **50.6** |
| Mansoor E et al. 2016 | USA | 2010–2015 | 30,301,440 | 7840 | All | **25.9** |
| Gokhale M et al. 2017 | USA | 2013–2014 | 25,700,908 | - | - | **104** |
| Syed A et al 2017 | USA | 2009–2013 | 27,183,310 | 5370 | Adults | **19.75** |
| Gonsalves LO et al. 2018 | Brasil | 2004–2014 | 253,706 | 63 | Children | **24.8** |
| La Orden-Izquierdo E et al. 2018 | Spain | 2002–2013 | 485,355 | 254 | Children | **52.3** |
| Warnes MJ et al. 2018 | The Netherlands | 1996–2016 | 16,655,799 | 2161 | All | **12.97** |
| Molina-Infante J et al. 2018 | Spain | 2007–2016 | 167,620 | 137 | Adults | **81.73** |
| Robson J et al. 2019 | USA | 2011–2016 | 895,205 | 1060 | Children | **118.4** |
| Arias A et al. 2019 | Spain | 2006–2017 | 103,636 | 117 | All | **111.9** |

therapeutic features indistinguishable from EoE patients who did not respond to PPIs [34,35], with the evidence suggesting that PPIs were better classified as a treatment for esophageal eosinophilia that may be due to EoE rather than as a diagnostic criterion. The immediate consequence of this change in the definition was to include a large group of patients who were ruled out in other previous epidemiological studies as being affected by the disease, immediately increasing the incidence and prevalence of EoE in those studies using the new definition, and thus bringing the numbers closer to those reported for Crohn's disease or ulcerative colitis [36]. EoE prevalence estimates according to the several diagnostic criteria to define the disease are shown in Figure 1.

Finally, (irrespective the above reasons), the best knowledge about EoE acquired over the last decade has been reflected in the publication and updating of numerous clinical guidelines [1,37–40]. These have contributed to the fact that more and more professionals from different medical disciplines now recognize this disease in a growing number of patients with compatible symptoms, guiding them to accurate diagnosis and bringing to light a very high proportion of undiagnosed and hidden cases. However, the disease continues to have a significant diagnostic delay [12,41–43], which undoubtedly contributes to the development of esophageal strictures and derived complications. Subepithelial fibrous remodeling as a consequence of chronic esophageal inflammation has been demonstrated in children and adults with EoE. Eosinophil-associated tissue remodeling is a common process found in several conditions in which chronic eosinophilic inflammation is the common hallmark, including bronchial asthma [44], hypereosinophilic syndrome [45], eosinophilic gastroenteritis [46], and lastly, EoE [47]. All share structural changes within the affected tissue, including subepithelial fibrosis, which ultimately alter the functionality of the affected organs. Uncontrolled remodeling due to ongoing inflammation in EoE may adversely affect esophageal function, leading

to dysmotility, esophageal rigidity, progressive dysphagia and food impaction and, finally, stricture formation. Esophageal strictures constitute one of the most severe

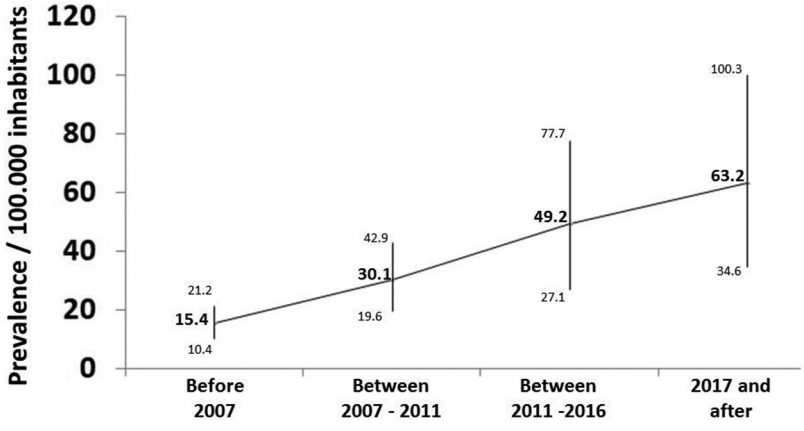


Figure 1. Prevalence rates for EoE with 95% confidence intervals (in patients per 100,000 inhabitants), resulting from meta-analyses of individual studies grouped according to the diagnostic criteria for EoE used in each study.

complications of EoE that develop as a result of a long-standing untreated eosinophilic inflammation. Despite patient age and delayed diagnosis being recognized as determining factors for fibrotic esophageal strictures [42,48,49], not every patient with

prolonged EoE evolution develops such strictures. Esophageal strictures are less commonly found in pediatric cases of EoE, likely due to the limited progression of the disease. Preventing the evolution of the disease toward fibrostenosant phenotypes requires its early diagnosis and effective treatment, since for each extra decade of a patient with untreated EoE, the possibility of finding strictures in the esophagus doubles [42,48,49].

## 4. Risk factors

Clearly defining and identifying risk factors independently associated with the development of EoE is a key aspect in understanding the continuous increase in the number of patients who have developed the disease in recent decades and is recognized as essential in the implementation of potential preventive strategies and therapeutic measurements. Several studies have started to investigate potential risk factors for EoE in recent years. Among these, geography, including population density and weather, has been proposed as one such factor. A negative correlation has been shown between population density and risk of EoE when rural and urban areas were compared [50]. However, climate areas, which are the major determinant for aeroallergen distribution, have extensively been analyzed for the association between EoE and geography [47,48], in the sense that cold climate zones are associated with increasing odds of EoE compared with tropical and arid zones [51].

### 4.1. EoE predominates in young male caucasian subjects

Male sex is one of the first risk factors identified as leading to EoE in earlier case series. It is well established and repeatedly documented in epidemiological studies that EoE is diagnosed more frequently among male subjects, who have at least a two-fold higher risk of suffering from EoE [5]. The male predominance (~70%) traditionally described in EoE [4,5], implying that currently unidentified sexual chromosome-related genes or hormonal factors may be involved in the development of the disease, have been explained by a mutation in the X chromosome affecting two chains of the IL-13 receptor (IL-13 Ra 1 and 2 located in position Xq13.1–q28), which would remain uncorrected by the Y chromosome genes in males [52]. More recently, a single nucleotide polymorphism in the gene encoding for the TSLP receptor (TSLPR) located in the pseudoautosomal region on Xp22.3 and Yp11.3 has been shown to be directly involved in male predominance of EoE [53].

EoE may affect humans at any age with a predominance for the Caucasian race, where the disease has been shown much more frequently than in other population groups [54–56]. However, the vast majority of studies have been carried out in developed countries of the northern hemisphere, where the white population of Caucasian origin is predominant. Although population-based studies are lacking in other populations, evidence shows that EoE is becoming a relevant disease in Asia, South America, and North Africa.

Despite EoE has been reported throughout the life span, most cases occur in children, adolescents, and adults younger than 50 years. Available data mostly coming from retrospective and population-based studies coincide with peak incidence in older children [8,9] while the majority of cases in adults are clinically apparent at the age of 30–45 years [8,12,15].

### 4.2. EoE predominates in atopic subjects

Atopy has been linked to EoE from the initial reports of the disease and it is currently recognized as a factor in the appearance of the disease. Since these initial reports it has been found that most patients with EoE also presented with a personal and/or family history of bronchial asthma or allergic rhinitis; atopic dermatitis; hypersensitivity to drugs, blood eosinophilia; or elevated serum total and specific IgE levels [57]. IgE-mediated food allergy is also common among EoE patients and alters its clinical presentation during childhood [58]. Overall, atopic manifestations are 3 to 5 times more common among patients with EoE compared to control subjects with endoscopically excluded EoE, according to a recent systematic review: a higher frequency of rhinitis (OR 5.01; 95% CI, 2.9 – 8.9), bronchial asthma (OR 3; 95%CI, 2 – 4.6) and atopic eczema (OR 2.9; 95%CI 1.9 – 4.3) was found among patients with EoE [59]. Recently, a retrospective analysis of a pediatric cohort has suggested that EoE is a late manifestation of the 'allergic march' –the natural history of allergic manifestations during childhood– in some individuals, with a peak of incidence which appears after that of atopic dermatitis, IgE-mediated food allergy and bronchial asthma [60]. There was also a cumulative effect of multiple preceding allergic conditions in the rate of subsequent EoE diagnosis, which was higher in individuals with more than one preceding allergic condition. This study provided the first evidence that atopy may predispose to EoE.

### 4.3. Pollen and EoE: less and less associated

Despite EoE being identified as a particular form of food allergy from the earlier descriptions of the disease – able to be almost totally resolved clinically and histopathologically after removing all food antigens from patients' diets [61] – positive results to airborne antigens in EoE patients of all ages are repeatedly described, separate to sensitization to food antigens [62,63]. Some reported cases suggested EoE was triggered by aeroallergens [64–66], including several environmental allergens that cross-react with food allergens [67,68]. It was also found that experimental accumulation of eosinophils in the esophagi and other gut segments could be reproduced in murine models through exposure to aeroallergens [69–71]. In addition, several studies in adults and children noted seasonal variations in the diagnosis of EoE: Using the month of presentation as a surrogate marker for disease activity, peaks of new diagnosis [71–73] and even esophageal food bolus impaction [74] occurred more during the months with higher

pollen concentrations, which was directly interpreted as aero-allergen-triggered EoE.

EoE is well characterized as a chronic disease, for which diagnostic delay is quite common [41,42] often due to patients minimizing symptoms through modified eating behavior. In contrast, since endoscopy is often performed after waiting lists, equating the onset of symptoms with the time of endoscopy performance is, somewhat deceiving. In addition, IgE-mediated immediate reactions are of minimal to no relevance, in the pathophysiology of EoE [75]. In 2015, a systematic review with meta-analysis on the seasonality of the initial diagnosis or recrudescence [i.e., food bolus impaction) of EoE was carried out on data from the 18 studies and a total of 16,846 EoE patients then available [76]. No overall statistical differences in the annual seasonal distribution of newly diagnosed EoE cases were observed. Similarly, a homogenous distribution of episodes of EoE recrudescence throughout the year was noted when all studies were combined. Recently, large series of incident diagnoses of EoE covering periods over 10 years found the appearance of new EoE cases homogeneously distributed throughout the seasons [6,8,12], and well-designed prospective studies found that pollen season did not influence the response to dietary therapy in either children or adults with EoE [77–79]. Cases of more common bolus impaction during summer and Autumn in patients with EoE are still reported, however [80]; outdoor season leads to different eating habits that might increase the risk of suffering from meat bolus impaction, which eventually lead to EoE diagnosis. Likewise, parents may gain increased awareness on their children's symptoms during summer holidays due to spending more time together [81].

### 4.4. Does helicobacter pylori have something to say?

Helicobacter pylori (H. pylori] infects approximately 50% of the global population, with a wide variation between regions and countries [82]. Primary infection mostly occurs during childhood and inadequate sanitation practices, low social class, and crowded or high-density living conditions seem to be related to a higher prevalence of H. pylori infection [83]. An inverse association between rising EoE and declining H. pylori patterns has been reported in the literature in the past [84–87], as the prevalence of H. pylori decreased in westernized countries [88,89] it was suggested that H. pylori infection had a protective role against the development of EoE. H pylori exerts immunomodulatory properties by polarizing the immune system toward a Th1 response, thus conferring protection against Th2-mediated allergic disorders [90], as already shown in asthma [91,92].

The association between H pylori and EoE was investigated through a large multicenter prospective study in Spain involving 404 EoE patients all ages and 404 matched non-EoE controls [93], all naïve to H pylori eradication therapy and off PPI therapy. Overall there was no difference in H. pylori prevalence between cases and controls (37% vs. 40%; $p = 0.3$) neither in children (42% vs. 46%, $p = 0.1$) nor in adults (36% vs. 38%, $p = 0.4$). Atopy, however, was inversely associated with H. pylori infection in EoE patients (OR 0.85; 95%CI 0.75–0.98). More recently, a systematic review with meta-analysis polled results of 11 individual studies and showed that H pylori exposure vs non-exposure was associated with a 37% reduction in odds of EoE overall [94], irrespective of patients' age. However, prospective studies were less likely to show an association between H pylori exposure and EoE. Most studies did not provide information on previous eradication therapies for H pylori infection among EoE patients, thus preventing obtaining definitive conclusions on this matter.

### 4.5. Familiar association in cases: genes or the environment?

Family association in cases has also been shown throughout the literature, with 7% –8% of EoE patients reporting having other family members affected by the same disease, most commonly, siblings [95]. The risk of EoE among familiar clustering has been directly related to the proximity of the relationship between affected members, which was maximum in the case of first-degree relatives of a proband (ranging between 1.8% and 2.4%) compared to the general population (0.05%). Moreover, in a twins' cohort, the risk of heritability of EoE was 41% for monozygotic twins, 22% in dizygotic twins and 2.4% among siblings of different ages [96]. Numerous genetic susceptibility variants have been shown to contribute to EoE, including variants at 5q22 (TSLP), 2p23 (CAPN14), and 11q13 (LRCC32), but the magnitude of association for disease susceptibility is shown to be modest (<2-fold) [97], similar to that seen in other allergic and immunological diseases for which the environment plays a major role. In addition, most EoE risk loci are outside of the coding regions of genes, suggesting a key role for gene regulation in patients with EoE, which is consistent with most other complex immune-mediated diseases.

Recently, genetic and functional evidence supporting the association of genetic variants genetic variants involved in mitochondrial dysfunction with EoE has been provided [98]. Two mutations in the dehydrogenase E1 and transketolase domain-containing 1 (*DHTKD1*) gene were identified in patients with EoE, which alter endogenous DHTKD1 expression and/or impair mitochondrial function. The loss of DHTKD1 increased production of reactive species of oxygen and induced the expression of *viperin*, a gene previously shown to be involved in production of Th2 cytokines in T cells. This finding underscore the level of genetic complexity of EoE and present evidence that mitochondrial dysfunction contributes to variable disease phenotype.

Instead of placing more weight on genetics in the heritability of EoE, the twin's cohort analysis [96] revealed a powerful role for common environment (81.0%) compared to additive genetic heritability (14.5%) and supported the idea that members of the same family living together are more exposed to common environmental factors, especially in the case of twins. In fact, sharing identical genetic backgrounds (as in monozygotic twins) is not enough for both to develop EoE, as it is largely the shared environment that determines the association with the disease. Additional evidence of the weight of environmental factors in determining the appearance of EoE is seen in the results of a subsequent study showing that the risk of suffering EoE was 7.2 times higher

Table 2. Risk factors found to be associated to Eosinophilic Esophagitis in case-control studies. Bold letter denotes statistically significant differences.

| Author, year | Type Risk Factor | Risk Factor | | OR (95% CI) |
|---|---|---|---|---|
| Jensen E et al, 2013 [99] | Prenatal | Maternal smoking | | 2 (0.4–11) |
| | Intrapartum | Preterm birth | | 4.2 (0.7–46.4) |
| | | Group B streptococcus | | 2.2 (0.3–25) |
| | | Cesarean delivery | | 2.2 (0.9–6.4) |
| | Postnatal | No exclusive breast-feeding | | 3.5 (0.6–19.5) |
| | | **Antibiotic exposure** | | **6 (1.7–20.8)** |
| Radano et al, 2014 [103] | Intrapartum | **Cesarean delivery** | | **3.21 (1.20–8.60)** |
| | Postnatal | **Antibiotic exposure** | | **3.58 (1.27–10.13)** |
| | | **Acid suppression** | | **3.99 (1.4–11.38)** |
| Slae et al, 2015 [102] | Postnatal | Antibiotic exposure | 0–1 months | 0.53 (0.18–1.55) |
| | | | 2–6 months | 1.04 (0.53–2.05) |
| | | | 7–12 months | 1.11 (0.60–2.06) |
| | | Smoking exposure | | 0.53 (0.27–1.02) |
| | | Pets | | 1.01 (0.36–2.89) |
| Jensen E et al, 2018 [101] | Prenatal | **Maternal fever** | | **3.18 (1.27–7.98)** |
| | | Maternal smoking | | 0.70 (0.27–1.80) |
| | | Prenatal vitamins | | 0.85 (0.30–2.45) |
| | | Folic acid supplement use | | 1.56 (0.86–2.83) |
| | | **Pregnancy complications** | | **1.87 (1.12–3.12)** |
| | | **Preterm labor** | | **2.18 (1.06–4.48)** |
| | Intrapartum | **Cesarean delivery** | | **1.77 (1.01–3.09)** |
| | | Preterm birth | | 1.39 (0.71–2.72) |
| | Postnatal | NICU | | 1.92 (0.95–3.89) |
| | | Any breast-feeding | | 1.11 (0.60–2.05) |
| | | **Antibiotic exposure** | | **2.30 (1.21–4.38)** |
| | | **Acid suppression** | | **6.05 (2.55–14.4)** |
| | | **Pets** | | **0.58 (0.34–0.97)** |

OR (95% CI): Odds ratio (95% confidence interval)

among first-degree relatives, almost 2 times higher in second-degree relatives, and among spouses of EoE patients, 2.86 times higher [53].

Jensen et al [99] in 2013 first identified the link between specific environmental factors and the risk of developing EoE, firstly in children and subsequently expanded [100–103]: by analyzing a large single-center registry of EoE cases, the authors identified several prenatal and early childhood exposures associated with an increased risk of presenting the disease including preterm labor, cesarean delivery, non-exclusive breastfeeding, neonatal ICU admission, use of antibiotics and anti-secretive drugs during childhood [101]. These factors are almost identical to those already reported as being a predisposition to bronchial asthma in children [104]. However, it was found that having a furry pet in infancy reduced the odds of having EoE [101]. Table 2 details prenatal, perinatal and early life exposures related to the risk of developing EoE.

In a cohort of 127 EoE patients and 121 control subjects, a subsequent study integrated the previously obtained information, which identified genetic susceptibility variants that contributed to EoE, with environmental information [100]. It was found that breastfeeding and neonatal ICU admission showed a significant interaction with the rs6736278 variant within the *CAPN14* gene, thus breastfeeding had a strong protective effect in patients carrying the susceptibility genotype. On the other hand, admission to the neonatal ICU significantly increased the risk of developing EoE in those without the susceptibility gene variant at rs17815905 at the *LOC283710/KLF13* gene.

The early life factors examined in the previous studies are all related to dysbiosis in gut colonization during infancy and involve the esophageal microbioma in regulating the functioning of the esophageal immune system. Patients with EoE and non-EoE control exhibit differences in their esophageal microbiota in terms of abundance and composition [105–107], and evidence of activation of toll-like receptor dependent-signaling pathways in EoE support the potential implication of microbiota and the innate immune system in the pathogenesis of this disease [108]. The interacting gene polymorphisms already described might modify the interaction between esophageal microbiota with EoE-related immunological pathways, even before the onset of EoE. Further studies are required to confirm the associations described and to unveil the role of the microbiome in the pathogenesis of EoE, as well as the potential ways of restoring it into normal and correcting disturbances in gene-environment interactions in EoE.

### 4.6. Indoor exposures and building materials

Indoor sources of combustion, including gas cooking and heating devices emissions have a statistically significant association with the risk of onset and exacerbations of bronchial asthma in patients of all ages [109–111]. The same is being shown for rhinitis and eczema [112]. Some home building materials may contain chemical contaminants able to impair occupants' health [113,114]. The association of indoor and housing contaminants with EoE have been recently assessed in a single-center, case–control study [115]. EoE risk was positively associated with gas and forced air heating systems and independently associated with brick exteriors. The length of time from symptom onset to diagnostic endoscopy was similar to, but shorter than, the average duration that a patient lived in their house before EoE diagnosis. While EoE is commonly associated with bronchial asthma and other atopies, future studies should ascertain the contribution of indoor and building materials exposure to the appearance of each of these diseases.

### 4.7. Systemic disease associations in EoE

Finally, the association of EoE with other systemic diseases such as celiac disease, inflammatory bowel disease (IDB), esophageal atresia, and connective tissue disorders has also been proposed in the literature [116], despite there still not being a defined common base from an epidemiological, clinical, molecular and genetic perspective.

The association of EoE and celiac disease was a controversial aspect that today appears to be solved. Short case series reported on an association between both entities [14,117–120], which could not be demonstrated in large population-based studies [121,122]; and two systematic reviews found no evidence to support such an association [123,124]. Patients with EoE do not show increased frequencies of HLA DQ2 or DQ8 alleles related to the risk of celiac disease [125]; and a gluten-free diet leads to symptomatic and histopathological remission of EoE in up to 40% of patients [123], which is almost the same effectiveness demonstrated for a wheat-free diet in EoE [78,79].

Eosinophilic infiltration in gastrointestinal tract tissues was recognized early on as a histopathological feature of inflammatory bowel disease [126]. Blood eosinophil numbers may be elevated in both IBD and EoE, in which the pro-inflammatory functions of eosinophils contribute to tissue damage [127]. An association between EoE and Crohn's disease has also been repeatedly described in small case series [128–132], with most recent studies suggesting a 5-fold increase in the occurrence of EoE among IBD patients. This gives rise to speculation about the true relationship between the two disorders, which share an idiopathic dysregulated mucosal immune response that causes inflammation. However, a recent population-based analysis from the Inform Diagnostics database, a national electronic repository of histopathology records distributed throughout the entire United States, found a statistically significant inverse relationship between EoE and Crohn's disease or microscopic colitis, but not ulcerative colitis [133]. IBD and EoE are highly prevalent disorders in westernized countries; recent estimates indicate that IBD now affects up to 240 patients/100,000 inhabitants in Europe and North America [133–135] whilst the prevalence of EoE has been estimated to be 110 patients/100,000 inhabitants in recent reports [6,8]. From an epidemiological point of view, we should expect the concomitance of both diseases in the same patients, even if they are completely independent disorders. Compared with IBD controls, patients who suffer from both EoE and IBD were diagnosed with IBD at a younger age and were more likely to be male than those with IBD alone. However, there were no differences in medical or surgical therapy for IBD between the 2 groups. Among those with IBD-EoE, patients for whom IBD was diagnosed first presented more commonly with dysphagia and endoscopically had evidence of esophageal rings compared with those who were diagnosed with EoE first [136]. However, most of the available studies have cross-sectional designs that potentially bias the results. Well-designed prospective studies are necessary to verify the true nature of the association between IBD and EoE.

A link between the prevalence of EoE and connective tissue disorders (CTDs), including Marfan, hypermobile Ehlers-Danlos, and joint hyper-mobility syndromes, has been suggested after finding an unexpectedly 8-fold higher risk of EoE in patients with CTDs after retrospective analyses of electronic medical record databases [137], and confirmed in a recent report [138]. The investigation of the molecular connection of this association proposed mutations in *fibrillin-1* (*FBN1*) and *TGFBR1* genes, which were related to an impaired epithelial barrier function and excessive TGF-b signaling [139], respectively, with both contributing to the EoE-CTD proposed phenotype. Further prospective research is needed to confirm the aforementioned syndromic association and to establish the particularities of EoE in these patients.

Finally, esophageal atresia and EoE have been linked in several case reports and short case series published in the last decade [140–142]. Esophageal atresia, with or without an associated tracheoesophageal fistula, is a relatively common congenital malformation, with a live-birth prevalence of 1.8 per 10,000 births [143]. It is usually repaired soon after birth with a postoperative survival rate of 95%, which indicates that the principal burden of the disease is accounted for by post-operative morbidity. Dysphagia occurs frequently in infants and children with a history of esophageal atresia repair, anastomotic structure being its most common cause. Strictures early in the life of these patients respond well to dilatations [116]. Later in life, dysmotility and peptic esophagitis have been found to contribute to the development of dysphagia, so in the long term, affected children are usually treated with PPI. EoE is also identified as a cause for dysphagia in patients with esophageal atresia, and under-recognition may lead to excessive use of anti-reflux therapy and an escalation of interventions, including fundoplication, as symptoms may be attributed to gastroesophageal reflux disease [144]. In the literature, most cases of both esophageal atresia and EoE are found in children and adolescents, with male patients being twice as predominant as females. A high proportion of these patients exhibit evidence of food and/aeroallergen sensitization and peripheral eosinophilia. Chronic dysphagia that persists after esophageal dilation, despite having achieved a normal caliber for the esophageal lumen, was found to be common among these patients. In addition, long-term untreated EoE may lead to recurrent strictures, due to transmural esophageal inflammation, necessitating repeated dilatations.

The origin of EoE in esophageal atresia has been associated with chronic exposure to acid gastro-esophageal reflux and its complex relationship with EoE [145] and esophageal dysmotility, which prolongs contact between food antigens and esophageal mucosa, and thereby predisposes these patients to EoE [146]. In addition, specific genetic similarities between esophageal atresia and EoE have also been proposed, including microdeletions encompassing the Forkhead box (FOX) transcription factor gene cluster, specifically the *FOXF1* gene, which have been shown to be associated with both conditions [147,148]. Binding sites for the gene's encoded protein, FOXF1, include the promoter region of genes for eotaxins [149].

To summarize, EoE results from the interaction of genetic predisposition with molecular, cellular, and environmental factors [150–153], which have just started to be unveiled.

## 5. What does increasing EoE epidemiology imply for clinical practice?

The incidence and prevalence of EoE continue to increase and it will be a few more years before the frequency of the disease stabilizes. EoE will also grow in geographical areas beyond Europe and North America, as other countries and continents adapt to a more westernized way of life. As a consequence, the health costs associated with EoE will increase dramatically. EoE related costs are mainly due to delayed diagnosis, the need for endoscopy with biopsies to monitor the disease, pharmacological treatments, and an increased use of medical resources compared to healthy individuals [154–156]. The average annual cost attributable to EoE in the United States is estimated at 2,300 USD a year per patient [157] and up to 4,001 USD a year in pediatric patients, far exceeding the cost of Crohn's disease ($ 985) and celiac disease ($ 856) [158]. The annual medical cost for EoE in the United States was estimated at 1.4 USD billion [159] in 2015, similar to that for IBD [160]. However, the prevalence figure of 56.7 cases per 100,000 inhabitants used for this estimation, would now be double, using current prevalence figures. The management of EoE patients involves a number of health professionals – predominantly gastroenterologists, pediatricians, nutritionists, allergists, ENT specialists and pathologists- and other resources in the form of endoscopies, repeated testing and maintaining waiting lists. Therefore, establishing strategies for early diagnosis and effective treatment, both initial and maintaining remission, must be primary goals in EoE. Any treatment must also be capable of preventing complications, especially those derived from structures and perforation [161], and thus reducing the need for repeated endoscopies.

Unequivocally identifying the risk factors associated with the development of EoE should be a priority in future research with the aim of implementing possible preventive actions, elucidating and optimizing cost-effectiveness in diagnostic workup and treatment strategies, and contributing to maximize the limited resources available. Research being developed currently is aiming to define the best strategies to implement into clinical practice [162,163].

## 6. Expert commentary

Understanding the reasons underlying the emergence of EoE and its marked increase over a short period of time to become one of the most prevalent causes of chronic dysphagia in children and adults, represents a challenge for researchers. Since the initial descriptions of the disease in the early 1990s [2,3], EoE has been recognized as a particular form of food allergy [61]. An abnormal response was developed against common diet antigens, mostly milk, wheat, eggs and legumes, which were no longer tolerated to become reactive among these patients. The changes in the methods of cultivation and production of food, in the ways of processing and conservation have been far more wide reaching in recent decades than in any other period of history, and include the use of antibiotics, hormones and pesticides in agriculture and cattle raising, as well as genetic modification of crops. The first genetically modified plants were created in the 1980s and were being sold by 1994. Their use has increased to the point that in 2015, in the United States, 94% of soybeans and 89% of corn plantations were from transgenic varieties [164,165]. Although no study has analyzed this relationship to date, it is tempting to speculate on the parallel growth of EoE and the expansion of all the practices described above. The management of EoE through food restriction, however, has had variable effectiveness depending on the intervention performed [166,167]. In parallel, a wide range of other options to treat EoE patients have been used, from endoscopic dilatations to enlarging the esophageal caliber [168,169], from different drugs, which primarily include topical steroids [170], to inhibitors of the gastric acid secretion [171], anti-allergic agents [172,173], and even monoclonal antibodies [174,175]. In recent years, high quality clinical research, including randomized clinical trials and quasi-experimental prospective studies, have evaluated the effectiveness of the various treatment options available to achieve and maintaining remission in patients with EoE. These have recently been summarized in systematic reviews and meta-analysis and use to inform evidence-based guidelines [1,176] to help doctors in their decision making on how to adequately manage the disorder.

However, despite this mounting evidence, the clinical management of EoE remains complex and varies more than any other aspect of the disease [177], involving individual aspects of each particular patient and the healthcare resources available in their settings [41,178]. The lack of drugs specifically approved for EoE, absence of solid data on the origin of the disorder, factors that determine prognosis, diverging outcomes with topical corticosteroids and diets, and personal and social costs involved all present additional obstacles for a homogeneous therapeutic strategy in clinical practice.

All these reasons make EoE a health and social challenge, affecting a considerable number of young patients in Europe and worldwide, and requiring the collaboration of multiple specialists for its complex management. However, simultaneously, EoE is an extraordinary opportunity for research in the field of diseases with an immuno-allergic basis, which are in continuous expansion worldwide.

Although the etiology of EoE is unknown, epidemiological, clinical and recent preliminary genetic analysis indicate that EoE, like other immuno-allergic based diseases, is the result of an interaction between environmental factors and genetic susceptibility in predisposed individuals [150,179]. Important, but still limited effort, has been made to date to identify the specific environmental factors that influence the onset and course of the disease [100,101]. Proposed as potential triggers, among others, are some early life factors such as Cesarean delivery, avoidance of breastfeeding and antibiotic use. However, how they act to promote EoE is currently unknown. As a particular form of food allergy, the relationship between EoE and diet is evident; the identification of milk, wheat or egg (three foods present in the Western diet from the Neolithic age) as the major triggers of EoE [167] implies that the

tolerance of gut mucosa-associated immunity to some components of the diet has changed dramatically in the last few decades. Modifications in nutritional and eating patterns, industrial food processing and food preservation methods and the effects these have on the microbiome, emerge as potential aspects that deserve to be investigated. So too do the use of genetically modified foods for animal feeding, introduced in 1994, and the role that additional environmental issues play in our interaction with dietary antigens.

In addition to dietary antigens, seasonal, geographic, and climate-based differences effecting EoE prevalence have been reported [179]. The extent to which aeroallergens, a particular type of exposure to antigens which varies over time and from place to place, and the exact mediators by which they exert their influence on the EoE process remains elusive. Their accurate identification and mechanistic description could aid the development of future preventive strategies.

Genetic factors still play a role in the pathogenesis of immune system diseases, including EoE. Indirect evidence comes from the stark differences in the incidence of EoE between genders (up to 4 times more common in males) [4], ethnic groups (more common in Caucasians) [180], frequent familial aggregation [95], and greater concordance in monozygotic regarding dizygotic twins [96]. Due to the relative youth of the disease, characterization of the genetic factors that contribute to EoE has only just started to be developed, however it is undoubtedly one of the most important aspects in understanding the origin and evolving patterns of this disease. The lack of either large multinational registries of EoE patients or large multinational banks of biological samples have restricted significantly the amount of knowledge on the origin of EoE [181]. Recent descriptive studies have detailed associations between EoE and an increasing number of diseases, some also characterized by tissue infiltration [116], an aspect which requires further assessment.

The identification of the environmental, clinical, molecular and genetic risk factors conferring susceptibility for EoE, and their interplay in determining the clinical features and development of the disease, will undoubtedly help for the first time in designing preventive strategies. Applied early after a diagnosis is given, they will help reduce the impact of the disease on patient outcomes and quality of life. However, the greatest ambition and challenge is to achieve a reduction in the appearance of the incidence rate of EoE in the future by avoiding exposure or by controlling the effect of the various risk determinants for this disease.

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