

Prevalence of atopic disease in patients with eosinophilic esophagitis

Michael S. Benninger, MD¹, Madeleine Strohl, BA², Chantal E. Holy, PhD³, Andrea L. Hanick, BS¹ and Paul C. Bryson, MD¹

Background: The objective of this work was to evaluate prevalence of eosinophilic esophagitis (EoE) in the United States, and analyze prevalence of atopic disease in patients with EoE. The study design was a retrospective administrative database analysis in U.S.-based outpatient settings.

Methods: A retrospective claims analysis in the inpatient and outpatient setting (using MarketScan) was conducted to analyze prevalence of atopic disease diagnoses in patients with EoE in 2012, and timing of those diagnoses vs EoE.

Results: From published evidence, prevalence of EoE was estimated at 1 to 5 patients per 10,000 and prevalence of asthma, allergic rhinitis (AR), and atopic dermatitis (AD) concurrent to EoE ranged from 20% to 50%, 50% to 75%, and 2% to 19% cases, respectively. From 2009 and 2013, the estimated prevalence of EoE in MarketScan increased from 2.7 to 5.6 per 10,000 enrollees age 34.5 ± 18.43 years (mean $\pm$ standard deviation). Age followed a bimodal distribution with peaks at 12 and 41 years. Women accounted

for 35.6% cases. Prevalence of asthma, AR, AD, and food allergies up to 12 months post-EoE diagnosis reached 44.7%, 27.1%, 25.2%, and 16.9%, respectively, with 63.5% of all patients suffering from at least 1 of these 4 diseases and 3.0% suffering from all 4.

Conclusion: The diagnosis of EoE is associated with the diagnoses of asthma, AR, AD, and food allergies. The high prevalence of these conditions in EoE patients further strengthens the hypothesis of a common pathogenesis.
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Key Words:

eosinophilic esophagitis; prevalence; atopic disease; allergen asthma; AD; AR

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Eosinophilic esophagitis (EoE) is a relatively new diagnosis describing an inflammatory disease of the esophagus characterized by eosinophil predominant inflammation in the esophagus and clinical symptoms related to esophageal dysfunction.¹ The disease was once believed to be relatively rare, yet has been shown to affect as many 0.7% of the general population.² However, accurate estimates of prevalence and incidence for EoE are still unknown because published data vary significantly across

studies.³ EoE has nevertheless seen a surge in interest due to a suspected increase in its overall prevalence.

EoE is often observed in patients with dysphagia, and to some lesser extent, proton pump inhibitor (PPI)-resistant gastroesophageal reflux disease (GERD).^{4,5} Most studies also report associations between EoE and atopic disorders, suggesting a potential common pathogenesis. Specifically, it has been hypothesized that eosinophils migrate to the esophagus in response to various ingested and/or inhaled allergens, thus associating EoE to allergy-induced diseases.⁶ As a result, high prevalence of atopic diseases (eg, asthma, allergic rhinitis [AR] and atopic dermatitis [AD]) and sensitization to food and environment allergens is seen in pediatric and adult EoE populations.^{7,8} However, most studies describe concomitant disease as self-reported by the patients and thus are prone to bias and underrepresentation or overrepresentation of comorbidities.³

Due to the relative novelty of the diagnosis and the significant uncertainty on the etiology of the disease, little is known on the clinical pathway leading to an EoE diagnosis and the treatments provided to date to patients with EoE. More research is needed to better understand the clinical

¹The Cleveland Clinic, Cleveland, OH; ²Case Western Medical School, Cleveland, OH; ³Acclarent, part of the Johnson & Johnson Family of Companies, New Brunswick, NJ

Correspondence to: Michael S. Benninger, MD, Head and Neck Institute, Lerner College of Medicine, The Cleveland Clinic, 9500 Euclid Avenue, A-71, Cleveland, OH 44195; e-mail: benninm@ccf.org

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journey of patients before and after they are diagnosed with EoE. In the present study, we used the MarketScan™ Commercial Claims and Encounters database to evaluate the prevalence of EoE in the United States and to analyze the incidence of coexisting atopic conditions in patients with EoE.

Materials and methods

Database analysis

The MarketScan Database is a claims database with, in 2011 and 2012, more than 50 million patients. Designed initially for payment medical care, this database allows longitudinal tracking of patients over multiple years and includes both clinical events as well as prescription history for all patients. Research from this database has been extensively published.⁹ The version available for research has no identification of individual patients and therefore this research was exempt from IRB approval.

Cohort identification and estimate of yearly prevalence of EoE diagnoses

A diagnostic code for EoE was introduced into the MarketScan Database in 2008. Therefore, we identified all patients from the years 2009 to 2013 with at least 1 diagnosis of EoE (International Classification of Diseases, 9th edition [ICD-9] code 530.13) and at least 12 months of continuous enrollment were identified. The volume of patients with at least 1 EoE diagnosis was estimated relative to the total volume of patients in the database for that particular year, to provide an estimate count of patients. For U.S.-wide prevalence analyses, the MarketScan projection methodology was utilized as described.¹⁰ Briefly, each patient was assigned a value reflective of patient demographic and geographic location. This value was mapped against the Medical Expenditure Panel Survey (MEPS) data to identify the frequency of equivalent patients included in that value. The MarketScan methodology was used to project frequency of disease to population with commercial insurance (eg, 158 million non-Medicare and 14 million Medicare patients in 2012). An additional ratio was applied to all patients based on whether they were Medicare-eligible or not, to account for patients without private insurance and provide nationwide prevalence estimates.

Comorbidities

To evaluate patient comorbid conditions and procedures, a subcohort of patients was identified with EoE between January 1, 2011, and December 31, 2012, and complete medical and prescription history at least 24 months pre-EoE diagnosis and 12 months post-EoE diagnosis ("Index"). This cohort of patients was analyzed for occurrence and timing of the following diagnoses: asthma (ICD-9 493 [all subcategories]); AD (ICD-9: 691.8 Other AD and related conditions; 692.9 Contact dermatitis and other eczema, unspecified cause); food allergies (ICD-9: V15.01

Personal history of allergy to peanuts; V15.02 Personal history of allergy to milk products; V15.03 Personal history of allergy to eggs; V15.04 Personal history of allergy to seafood; V15.05 Personal history of allergy to other foods; 692.5 Contact dermatitis and other eczema due to food in contact with skin; 693.1 Dermatitis due to food taken internally; 995.60 Anaphylactic reaction due to unspecified food; 995.66 Anaphylactic reaction due to food additives; 995.69 Anaphylactic reaction due to other specified food); and AR (ICD-9: 477 [all subcategories]). The timing of those diagnoses relative to that of EoE was calculated for all patients.

Statistical analyses

This study was purely observational, and therefore no comparative statistics were performed. Descriptive statistics to describe cohort demographics include means, standard deviations, and confidence intervals (CIs). Frequencies and percentages are shown for categorical variables. CIs were calculated for $\alpha = 0.05$. All statistical analyses were performed using SAS EG 4.3 (SAS Institute, Inc., Cary, NC).

Results

From 2009 to 2013, the prevalence of patients diagnosed with EoE increased from 2.7 to 5.2 per 10,000 enrollees, as shown in Figure 1. Patients were predominantly male (73.9% across all years) and the average age was relatively constant across all years, ranging from 32.6 ± 18.6 to 35.2 ± 18.7 years. However, as shown in Figure 2, the age histogram indicates a bimodal age distribution with 2 peaks at 12 years and 41 years.

From January 1, 2009, to December 31, 2013, a total of 10.6 million⁸ patients had continuous medical history in the database. Of these, 7722 patients were diagnosed with EoE between January 1, 2011, and December 31, 2012. This cohort was comparable to the overall EoE population, with, however, slightly more females (63.9% males vs 73.9% across the entire 5 years) and slightly older (average age of 37.7 ± 19.0). Pediatric patients represented 23.7% of the entire cohort. The cohort did, however, demonstrate the bimodal age distribution characteristic of that seen in the general EoE population.

The rate of concurrent comorbidities is shown in Table 1. In the year preceding the EoE diagnosis, asthma, AR, AD, and food allergies were prevalent in 22.2%, 32.9%, 15.6%, and 13.2% of patients, respectively. Following the EoE diagnosis, additional patients were diagnosed for atopic disease such that the prevalence of asthma, AR, AD, and food allergies within 12 months post-EoE diagnosis reached 44.7%, 27.1%, 25.2%, and 16.9%, respectively. Asthma and AR together were prevalent within the same patients in 8.3% of cases, and 3.0% of patients suffered from all 4 conditions concurrently. Over the entire study period, a total of 63.5% of all patients suffered of at least 1 of these 4 diseases.

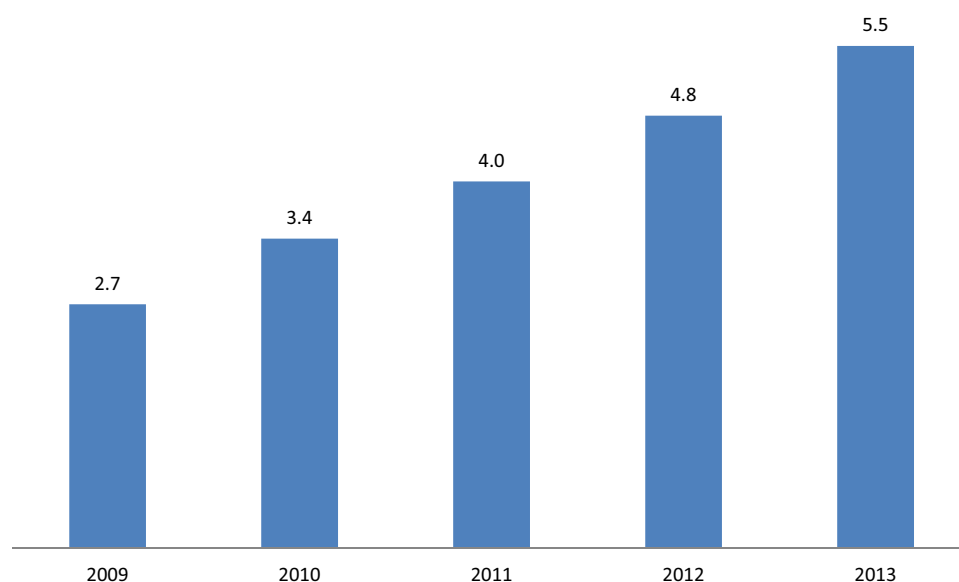


FIGURE 1. Yearly prevalence of patients diagnosed with EoE in the MarketScan database, per 10,000 enrollees. EoE = eosinophilic esophagitis.

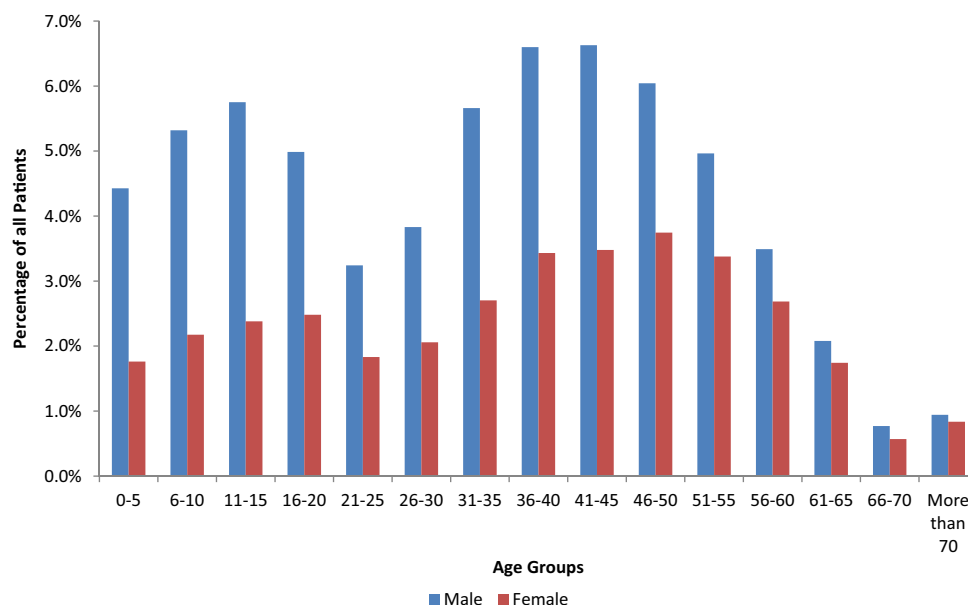


FIGURE 2. Age and gender distribution of all patients presenting with at least 1 diagnosis of EoE between 2009 and 2013. EoE = eosinophilic esophagitis.

There was an inverse relationship between comorbidities and age. Patients with no asthma, AR, AD, or food allergies were significantly older than patients with comorbidities. Patients with all 4 (asthma, AR, AD, and food allergies) had the lowest average age. For comparative purposes, from the entire 10.6 million patients with continuous medical history and no EoE, 20.0% had AR, 12.3% had asthma, 14.8% had AD, and 1.0% had food allergies. Therefore, Crude unadjusted risk ratios (RRs) for those conditions were as follows: RR (AR): 2.24 (95% CI, 2.18 to 2.29); RR (asthma): 2.19 (95% CI, 2.16 to 2.22); RR (AD): 1.53 (95% CI, 1.47 to 1.60); and RR (food allergies): 17.05 (95% CI, 16.2 to 18.0).

On average, all atopic diseases considered herein were diagnosed *prior* to the EoE diagnosis. As shown in Table 2, asthma was diagnosed at least 1 year prior to EoE. Food allergies were the closest to the EoE diagnosis, being diagnosed on average 6 months prior to EoE (169.6 days). The distribution of timing of these diagnoses is shown in Figure 3. For nearly 35% patients with food allergies, these were identified within the year when EoE was diagnosed.

Discussion

This study was designed to better understand EoE patient prevalence and demographics, and further analyze patient

TABLE 1. Rate of atopic disease in a patient cohort with at least 2 years medical history pre-EoE diagnosis and 1 year medical history post-EoE diagnosis

Conditions	Patient count or percentage	Average age of cohort (years) (mean $\pm$ SD [95% CI])
N (100%)	7722	37.6 $\pm$ 19.0 [37.2–38.1]
No atopic conditions	36.5%	43.6 $\pm$ 16.6 [43.0–44.2]
AR, with or without other conditions	44.70%	32.9 $\pm$ 19.0 [32.2–33.5]
AD, with or without other conditions	25.2%	34.6 $\pm$ 21.1 [33.7–35.6]
Asthma, with or without other conditions	27.1%	31.0 $\pm$ 20.0 [30.1–31.8]
With AR	8.3%	35.1 $\pm$ 17.8 [33.6–36.4]
With AR, AD, and food allergies	3.0%	15.2 $\pm$ 15.8 [13.2–17.3]
Food allergies, with or without other conditions	17.70%	22.7 $\pm$ 17.8 [21.7–23.6]

AD = atopic dermatitis; AR = allergic rhinitis; CI = confidence interval; EoE = eosinophilic esophagitis; SD = standard deviation.

TABLE 2. Timing of atopic disease diagnoses relative to EoE diagnosis

Timing of diagnoses relative to EoE diagnosis	Days prior to EoE (mean $\pm$ SE)	95% CI
Asthma	–373.2 $\pm$ 13.1	–347.4 to –398.9
AR	–294.1 $\pm$ 10.0	–274.5 to –313.7
AD	–169.4 $\pm$ 14.8	–140.2 to –198.5
Food allergy	–169.6 $\pm$ 13.5	–143.1 to –196.0

AD = atopic dermatitis; AR = allergic rhinitis; CI = confidence interval; EoE = eosinophilic esophagitis; SE = standard error.

comorbidities as related to atopic diseases and treatments. The claims database analyses was made possible by the fact that in 2008, a diagnostic code was introduced for EoE (ICD-9: 530.13) and recent studies have shown—at least in the academic centers—excellent specificity for identifying EoE cases based on this code.¹¹ Our study included both academic and community centers, and therefore may have had greater variability in the specificity of this code.

Our study showed a significant linear increase year over year of patients diagnosed with EoE. This growth may be a result of the recent introduction of this diagnosis and greater awareness and understanding of the condition in recent years. It is also possible that the prevalence of EoE actually increased, as shown in recent articles,^{12–14} but due to the novelty of this diagnosis, additional data points over longer periods of time would be required within the claims database to conclusively demonstrate growth in EoE. Our findings, however, are aligned with prior prevalence estimates of 1 to 4 patients per 10,000.^{3,15}

To evaluate comorbidities, a subcohort of 7722 patients was identified. These patients all had at least 3 years of continuous medical history available in the database, 2 years pre-EoE index and 1 year post-EoE index. From a

demographic standpoint, this subcohort had slightly more females and was slightly older than the general EoE population. Therefore, in order to identify presence of comorbidities with some accuracy, a reasonable amount of medical history pre-index and post-index was required, hence justifying the use of this cohort for this particular purpose. In order to maintain a large pool of patients in the subcohort, we also did not attempt to match the subcohort to the general EoE population for age and gender. In our study, 44.7% patients had AR, 27.1% had asthma, 25.2% had AD, and 16.9% had food allergies, which was comparable to rates reported in the published literature.^{16–24} The results from our study are therefore aligned with overall published estimates and confirm a greater-than-average prevalence of asthma, AR, and food allergies in patients with EoE, as the overall U.S. prevalence of these conditions was estimated at 14%, 10%, and 8.9%, respectively.^{25–27}

The association between AD and EoE may, however, still be questionable as U.S.-wide prevalence of AD was estimated at 17%,^{24,25} which is significantly lower than our finding but not very different from that of other EoE studies, in which AD was estimated at rates ranging from 2% to 19%.^{16–19,28} There is an impression that EoE may be due in part to food allergies. A couple of studies from the United States estimated the prevalence of urticarial or anaphylactic reactions to food to be between 10% and 20%,^{29,30} whereas a study from Australia estimated a higher incidence of 24%.³¹ A number of studies have showed that the majority of patients with EoE have evidence of immunoglobulin E (IgE)-mediated sensitization to food based on in vitro specific IgE or skin-prick testing.^{25,29,32,33} One study showed 39% of patients had a positive skin test to egg and pork, 34% to soy, and 29% to cow's milk.²⁹ Another study showed that the overall prevalence of food sensitization in EoE patients was as high as 80% as demonstrated by serum IgE testing.³⁴ In comparison, overall food sensitivity prevalence in the United States is estimated to be 5% to 10%.^{35–37} Studies of EoE patients

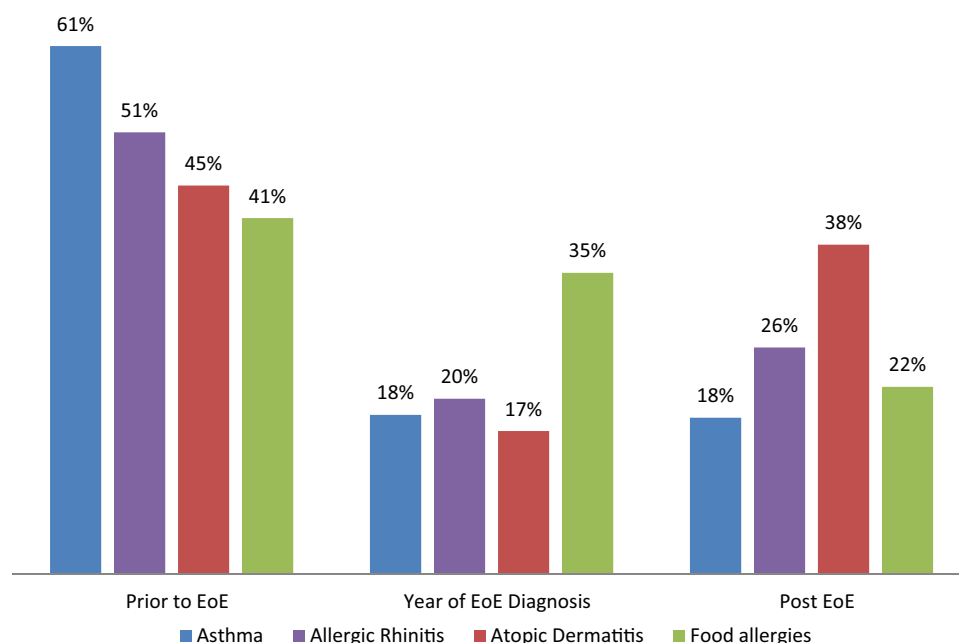


FIGURE 3. Timing of asthma, AR, AD and food allergy diagnoses vs EoE. (For all conditions, 100% = all patients that received at least 1 diagnosis). AD = atopic dermatitis; AR = allergic rhinitis; EoE = eosinophilic esophagitis.

who are placed on restricted or elemental diets provide the strongest evidence that food allergies may be 1 potential cause of EoE. In a number of different studies, the success of dietary avoidance in children with EoE in improving symptoms ranged from 75% to 100%, and a decrease in the number of eosinophils by 74% to 100%.^{30,38–44} Relapse is common upon food reintroduction.^{28,45} Therefore, except for AD, our findings reinforce the concept that there may be an association between EoE and atopic diseases, thus a common pathogenesis. This theory has also been recently demonstrated in murine models, in which food allergens and aeroallergens have been implicated as factors in inducing and maintaining eosinophilic inflammation in the esophagus.^{34,46}

There are inherent limitations in any study using claims-based data. These include the accuracy of diagnosis, the potential to overdiagnose or underdiagnose, or treatment based on an empiric diagnosis. The diagnosis may also be dependent on whether it is made by a primary care provider or a specialist. The diagnosis of EoE is usually based on clinical evaluation and often with a biopsy, which would suggest some accuracy in diagnosis, although PPI-responsive esophageal eosinophilia may be grouped under an EoE code. A stronger correlation might have been made if it was confirmed by both esophagogastroduodenoscopy (EGD) and biopsy, although sometimes the diagnosis is also made with transnasal esophagoscopy (TNE). We did not look at the frequency of either EGD or TNE in potentially confirming the diagnosis and relied on the coded diagnosis of EoE.

It is not clear why the initial diagnosis of other atopic diseases tended to precede that of EoE, as noted in Table 2. There is a possibility that other atopic disorders may play a role in the development of EoE; it has been hypothesized that eosinophils migrate to the esophagus in response to various ingested and/or inhaled allergens, thus associating EoE to allergy-induced diseases.⁶ However, there is growing evidence that EoE is based on both environmental and genetic or familial factors.⁴⁷ The timing of diagnosis may therefore be coincident to the timing of the development of symptoms in a similar way to the diagnosis of asthma occurring after the diagnosis of AR.

Conclusion

EoE is an inflammatory esophageal disease that would appear to be growing either in prevalence or increasing diagnosis. There is a strong association between allergic diseases including asthma, AR, AD, and food allergies, with these diagnoses typically being made prior to the diagnosis of EoE. Because patients with EoE are at increased risk of asthma, AR, AD, and food allergies, the high prevalence of these conditions in EoE patients further strengthens the hypothesis of a common pathogenesis. 🌐

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