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## Phenotypic Characterization of Eosinophilic Esophagitis in a Large Multi-Center Patient Population from the Consortium for Food Allergy Research

Mirna Chehade, MD, MPH<sup>1</sup>, Stacie M. Jones, MD<sup>2</sup>, Robbie D. Pesek, MD<sup>2</sup>, A. Wesley Burks, MD<sup>3</sup>, Brian P. Vickery, MD<sup>3</sup>, Robert A. Wood, MD<sup>4</sup>, Donald Y.M. Leung, MD, PhD<sup>5</sup>, Glenn T. Furuta, MD<sup>6</sup>, David M. Fleischer, MD<sup>6</sup>, Alice K. Henning, MS<sup>7</sup>, Peter Dawson, PhD<sup>7</sup>, Robert W. Lindblad, MD<sup>7</sup>, Scott H. Sicherer, MD<sup>1</sup>, J. Pablo Abonia, MD<sup>8</sup>, Joseph D. Sherrill, PhD<sup>8</sup>, Hugh A. Sampson, MD<sup>1</sup>, and Marc E. Rothenberg, MD, PhD<sup>8</sup>

**Correspondence:** Mirna Chehade, MD, MPH, Mount Sinai Center for Eosinophilic Disorders, Jaffe Food Allergy Institute, Icahn School of Medicine of Mount Sinai, One Gustave L. Levy Place, Box 1198, New York, NY 10029, USA, Phone: (212) 241-4880, Fax: (212) 426-1902, mirna.chehade@mssm.edu.

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<sup>1</sup>Icahn School of Medicine at Mount Sinai, New York, NY

<sup>2</sup>University of Arkansas for Medical Sciences and Arkansas Children's Hospital, Little Rock, AR

<sup>3</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC

<sup>4</sup>Johns Hopkins University Medical Center, Baltimore, MD

<sup>5</sup>National Jewish Health, Denver, CO

<sup>6</sup>Children's Hospital Colorado, University of Colorado School of Medicine, Aurora CO

<sup>7</sup>The EMMES Corporation

<sup>8</sup>Division of Allergy and Immunology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

## Abstract

**Background**—Eosinophilic esophagitis (EoE) is increasingly common, but data on phenotypic aspects are still incomplete.

**Objectives**—To describe the clinical, endoscopic and histopathological features of a large number of children and adults with EoE across the US.

**Methods**—This was a multi-site single visit registry enrolling subjects aged 6 months–65 years with EoE. Participants provided responses regarding their medical history, with verification of the diagnosis and history by the study teams.

**Results**—705 subjects were analyzed (median [IQR] age at enrollment 11.2 [6.7–17.7] years, 68.2% male, 87.9% whites). 67 subjects had concurrent gastrointestinal eosinophilia, with gastric mucosa most common. An age and race-dependent time gap was present between symptom onset and time of diagnosis (adults and whites with longer gap). Food allergy and atopic dermatitis were associated with a decrease in this gap. Symptoms varied with age (more dysphagia and food impaction in adults) and with race (more vomiting in non-whites). Esophageal rings and strictures at diagnosis were more common in adults, although esophageal eosinophilia was comparable among age groups. Concomitant allergic disease (91%), infectious/immunological disorders (44%), neurodevelopmental disorders (30%) and failure to thrive (21%) were common. Depression/anxiety increased with age. EoE was reported in 3% of parents and 4.5% of siblings.

**Conclusions**—Gastrointestinal eosinophilia is present in ~10% of EoE patients; the symptom-diagnosis time gap is influenced by age, race, food allergy and atopic dermatitis; symptoms vary with race; concurrent infectious/immunological disorders and mental health disorders are common; and the level of esophageal eosinophils is comparable in patients with and without fibrostenotic features.

## Keywords

Eosinophilic esophagitis; atopy; autoimmune disease; registry; multi-site; eosinophilic gastritis; eosinophilic gastroenteritis; eosinophilic colitis; food allergy; proton pump inhibitor; race

## Introduction

Eosinophilic esophagitis (EoE) is a chronic immune-mediated disease of the esophagus characterized by symptoms related to esophageal dysfunction, and by an eosinophil-predominant esophageal inflammation.<sup>1</sup> Symptoms vary by patient age, and include abdominal pain, emesis, gastroesophageal reflux (GER) symptoms, dysphagia, esophageal food impactions, and failure to thrive.<sup>1</sup> EoE is triggered by foods and possibly environmental allergens.<sup>2, 3</sup> Prevalence of EoE in the United States (US) has been steadily increasing, with estimates currently at 0.5–1 case/1000 persons.<sup>4</sup> Data on phenotypic aspects of this disease are lacking or incomplete because most reports are derived from single centers<sup>5, 6</sup> where data are limited by the small size of the population studied, biases in which the data is recorded and/or interpreted, and local referral biases at specific institutions or clinical sites, which collectively lead to uncertainty about generalizability.

In this study, we describe the clinical, endoscopic and histopathological features of a large number of children and adults with EoE across the US using a multi-site registry established by the Consortium for Food Allergy Research (CoFAR). The advantages of this cohort compared with prior studies on EoE include the following: (1) large cohort evaluated at 5 US sites, (2) regulatory supervision with independent site monitoring to ensure accuracy of data; (3) inclusion of children and adults in the same study population; and (4) a detailed medical and family history. These unique features allowed a more accurate definition of EoE phenotypes across age groups, as well as discovery of potential disease associations that would not be possible otherwise. In addition, the multi-site study allowed us to capture subjects with a wide range of ages, racial backgrounds, geographical locations and socioeconomic conditions. This heterogeneity allowed us to make several important observations.

## Methods

This was a multi-site, single visit registry of subjects 6 months to 65 years of age of any race, gender or ethnicity, with documented EoE, diagnosis based on histology demonstrating peak intraepithelial esophageal eosinophils  $\geq 15$ / high power field (HPF) and symptoms of esophageal dysfunction. Subjects were recruited from the 5 US sites forming CoFAR: Icahn School of Medicine at Mount Sinai, New York, New York; Duke University Medical Center, Durham, North Carolina (with the investigative team having relocated as of March 2012 to the University of North Carolina, Chapel Hill, North Carolina); National Jewish Health, Denver, Colorado; University of Arkansas for Medical Sciences and Arkansas Children's Hospital, Little Rock, Arkansas; and Johns Hopkins University School of Medicine, Baltimore, Maryland.

This registry was part of a study conducted by CoFAR, the primary aim of which was to establish the genetic basis of EoE, and was conducted in conjunction with the Cincinnati Children's Hospital Medical Center, which performed the genetic analysis on blood or saliva samples collected from the subjects at the time of enrollment.<sup>7</sup>

Participants provided responses regarding their medical history, with verification of the EoE diagnosis and history by the study teams. Participants with concurrent eosinophilia at gastrointestinal sites in addition to the esophagus were permitted entry into the study, since these patients were thought to have EoE as their primary gastrointestinal disease. This was recorded based on the investigator's judgment at each participating site based on history and local review of the pathology reports. It could be argued that these patients have eosinophilic gastroenteritis or colitis with esophageal involvement rather than EoE, but the patients presented with esophageal symptoms and were clinically diagnosed with EoE. Furthermore, we decided that new and potentially interesting findings would be discovered by allowing more broad inclusion criteria into the study. In addition, resistance to proton pump inhibitor (PPI) therapy was recorded but not required for enrollment. Patients with possible PPI-responsive esophageal eosinophilia (PPI-REE) were not excluded for the following reasons: 1) Since our study allowed recruiting patients at any time after their EoE diagnosis was made, we did not want to exclude subjects diagnosed before 2007 (when the consensus recommendations specified requiring PPI-responsiveness testing or pH probe testing for the diagnosis of EoE)<sup>8</sup> who were historically proven to have EoE by demonstrating histological response to dietary interventions alone; 2) Since this analysis was part of a larger genetic study, we did not want to exclude these patients because we had interest in determining whether these patients had any genotypic similarities/differences from the remainder of the population. More recently, preliminary data demonstrated that patients with PPIREE are similar to those with classic EoE (resistant to PPI therapy) given their favorable response to EoE-specific therapies, as well as evidence of a similar esophageal gene expression profile. 9–11

Exclusion criteria included known causes of esophageal eosinophilia other than EoE, and hypereosinophilic syndrome. Data were obtained using questionnaires with predominantly closed-ended questions that were uniformly used at all sites. De-identified data were then transferred by study staff to a password-protected web-based data entry system managed by the Statistical and Clinical Coordinating Center (The Emmes Corporation, Rockville, MD), which allowed enrollment at all participating sites in a uniform manner. As data were entered, they were validated through range and within-form consistency checks, and duplicate enrollment was prevented in the event a subject had travelled among sites for medical care.

The following information was collected: demographics, medical and surgical history (including review of systems, history of extra-esophageal gastrointestinal eosinophilia, symptoms, self-reported food allergies), and family history. Information was provided by the patients. In addition, histopathological data were collected at each site, as well as endoscopic findings on the corresponding procedure when available.

The study was approved by the institutional review board of each participating center. Written consent and, when applicable assent, were obtained from all participants. The questionnaires employed can be found in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org).

## Statistical analysis

The primary purpose of this study was to establish a genetic basis for EoE and clinical/demographic information were collected as part of that study. As such, there were no pre-specified analyses for phenotypic data. Rather, analysis was primarily descriptive, with continuous variables assessed as medians and interquartile ranges [IQR] and categorical variables described as proportions. Factors were described by age categories at enrollment, and formal hypothesis testing evaluated differences between those age groups using Kruskal-Wallis tests (Wilcoxon Rank sum for pairwise group comparisons) for continuous variables or Fisher's Exact test for categorical variables. Similar analyses were performed comparing whites to non-whites, study sites, and those with and without a greater than 6-week course of high dose PPI. Age groups were defined prior to any analysis as <11 years old, 11 to 17 years old, and adults ≥ 18 years old. Esophageal eosinophil counts per HPF were truncated at 100 per data collection procedures. Participants reporting counts that were not a specific number but were indicated only as being greater than a number less than 100 were excluded from the eosinophil count analysis. This was done to allow comparability of values through 100. Comparison of eosinophil counts between endoscopic findings was performed via Wilcoxon Rank-Sum test. As the analysis was primarily descriptive, significance was assessed at the 0.05 level. Analysis was performed in SAS v9.3.

## Results

### Demographics

708 subjects were enrolled between May 2011 and March 2016, and 705 subjects were analyzed, as 3 were determined to be ineligible. The highest number of participants was enrolled from New York (226 subjects, 32.1%), followed by 142 from Arkansas (20.1%), 127 from North Carolina (18.0%), 110 from Maryland (15.6%) and 100 from Colorado (14.2%). Age at enrollment ranged from 0.9 to 56.2 years, with a median [IQR] of 11.2 [6.7–17.7] years. The majority of the subjects were male (68.2%) and predominantly Whites (87.9%), with 7.1% Black and 2.8% Asian. Household income covered the entire spectrum but the largest group was < \$100,000 (276 subjects), though 235 subjects declined to give a response. A large number reported having private medical insurance (601/703=85.5%). More detailed site-specific demographic characteristics are listed in table E1 available in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org).

### Diagnosis

54.8% had confirmed receiving PPI therapy for more than 6 weeks or a normal pH probe as part of their diagnostic work-up for EoE. No significant differences in age at enrollment and age at diagnosis were found between patients who were treated with PPI and those who did not receive PPI as a diagnostic confirmation therapy or were unsure (median [IQR] age at enrollment 10.7 [6.9–16.9] versus 11.9 [6.5–18.8] years,  $p=0.26$  respectively; median [IQR] age at diagnosis 8.0 [3.0–15.0] versus 8.0 [3.0–16.0] years,  $p=0.69$  respectively). Furthermore, no significant difference was found between the two groups with respect to gender, symptoms and co-morbidities (table E2, available in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). A notable exception was concurrent gastroesophageal reflux disease (GERD). The group that did not have PPI confirmation had significantly fewer

reported diagnoses of GERD than the PPI-confirmed EoE group (47.6% no PPI versus 59.6% PPI,  $p=0.002$ ), suggesting that exclusively GERD patients with esophageal eosinophilia are not overly influencing our non-confirmed group.

Extra-esophageal eosinophilia was most commonly reported in the gastric mucosa; 37/705 (5.2%) had concurrent eosinophilic gastritis versus 4/705 (0.6%) with eosinophilic enteritis and 12/705 (1.7%) with eosinophilic colitis. Eosinophilic infiltration of more than one gastrointestinal site besides the esophagus was rare, with 14/705 (2.0%) of subjects having this diagnosis (table 1). In total, 67 patients (9.5%) had eosinophilia at other sites, such as the gastric, duodenal, or colonic mucosae, including 14 with eosinophilia at more than one gastrointestinal site (table 1). This percentage was comparable when subjects were compared with respect to race (table 1).

Median [IQR] age at diagnosis for the entire cohort was 8.0 [3.0–15.0] years and 5.0 [1.0–12.0] at symptom onset. Among children <11 years of age, median [IQR] age at diagnosis was 3.0 [1.9–6.0] years and 1.1 [0.4–3.0] years at symptom onset. Patients 11–17 years of age had a median [IQR] age at diagnosis of 12.0 [9.0–13.0] years and 10.0 [4.0–12.0] years at symptom onset. Adults (≥ 18 years) had a median [IQR] age at diagnosis of 29.0 [18.0–39.0] years and 19.0 [12.0–30.0] years at symptom onset. These large time gaps between symptoms and diagnosis were more pronounced with increasing age at enrollment; median [IQR] time from symptom onset to diagnosis was 4.0 [1.0–12.0] years in adults, compared to 2.0 [1.0–4.0] years in patients 11–17 years of age and 1.0 [0.5–2.3] in children <11 years of age ( $p<0.0001$ ). This delay was also racedependent, as whites had longer time from symptom onset to diagnosis; median [IQR] time gap 1.8 [0.7–4.0] years compared to 1.0 [0.5–2.0] years in non-whites,  $p=0.005$ .

The time gap between onset of symptoms and diagnosis was independent of concurrent eosinophilia at other gastrointestinal sites, as we found no difference between those with EoE alone (90.5% of subjects) and those with EoE and concomitant eosinophilia at other sites of the gastrointestinal tract (9.5% of subjects) ( $p=0.26$  for age at diagnosis, and  $p=0.54$  for age at EoE symptom onset, and  $p=0.48$  for time from symptom onset to diagnosis; table 1). We further evaluated whether various patient characteristics such as gender, atopic history, or family history of EoE can influence this significant diagnostic delay (table 2). We found that history of food allergy or atopic dermatitis was associated with a significantly shorter time gap between symptom onset and diagnosis. However, no differences were observed with respect to gender (median time gap 1.4 [IQR 0.6–4.0] years in males versus 1.9 [IQR 1.0–5.0] years in females), personal history of other atopic diseases, or even family history of EoE (table 2). History of suspected drug-induced anaphylaxis was associated with a significantly longer diagnostic delay of EoE (table 2).

## Symptoms

Subjects reported a variety of symptoms experienced within the previous 12 months prior to enrollment (table 3). These included abdominal pain (53.6%), dysphagia (50.5%), nausea (40%), emesis (40%), esophageal food impaction (38.1%), heartburn (37.2%), diarrhea (32.1%), chest pain (21.1%), and bloody stools (7.5%), with most subjects reporting multiple symptoms. Abdominal pain, emesis, heartburn and chest pain, as well as dysphagia



and food impaction differed significantly among age groups (table 3). Abdominal pain and emesis were observed to be higher in children <11 years of age and 11–17 years of age than adults; whereas heartburn, chest pain, dysphagia and food impactions were observed to be lowest in children <11 years of age and appeared to increase with age. Nausea, diarrhea and bloody stools were comparable among the 3 age groups. Bloody stools were not limited to subjects with EoE with concurrent gastrointestinal eosinophilia, but were also reported in subjects with EoE alone (6.6% of subjects with EoE alone versus 16.4% of subjects with EoE and eosinophilia at other gastrointestinal sites,  $p=0.01$ ). Of the 42 subjects that had EoE alone without concurrent gastrointestinal eosinophilia and had bloody stools, only one patient had Crohn's disease. We further compared symptoms between subjects with EoE alone to those with EoE and eosinophilia at other gastrointestinal sites and found those with EoE alone had significantly less abdominal pain (51.3% EoE alone versus 74.6% EoE with GI eosinophilia,  $p=0.0003$ ) and significantly more esophageal food impactions (39.6% EoE alone versus 23.9% EoE with GI eosinophilia,  $p=0.01$ ); no differences were found in nausea, emesis, heartburn, chest pain, gastroesophageal reflux, dysphagia, or diarrhea. When symptoms were compared with respect to race, dysphagia, esophageal food impactions and heartburn were significantly more common in whites, while emesis was significantly more common in non-whites (table 3).

Food impactions requiring urgent endoscopic removal were reported in 6.1% of subjects; median [IQR] age of these patients was 26.0 [15.2–41.1] years. Esophageal stricture was seen on endoscopy in 10.1% of subjects; median [IQR] age was 33.2 [19.9–42.4] years. Esophageal dilation was reported in 9.9% of subjects; median [IQR] age was 35.0 [22.1–44.3] years.

When the diagnostic endoscopy was analyzed, esophageal white plaques and furrows were the most common features reported (table 3). Esophageal rings and strictures at diagnosis were significantly different between age groups and were observed to be more common in adults than in patients <11 years of age and 11–17 years of age, while all other features, including inflammatory features (furrows, white plaques and loss of vascular pattern) were comparable (table 3). Consistent with the latter endoscopic finding, esophageal eosinophilia was comparable among the age groups; median peak esophageal eosinophil counts (from the distal, mid, and proximal esophagus) were 50/HPF [IQR 33–84] in children and 55/HPF [IQR 40–90] in adults,  $p=0.30$ . Peak eosinophil counts in those with endoscopic inflammatory features (furrows, white plaques, or loss of vascular pattern) were higher than those without these features (median 60/HPF [IQR 40–100] versus 40/HPF [IQR 29–70],  $p<0.0001$ ). However, peak eosinophil counts in patients with and without fibrostenotic features (rings, stricture or shearing) were comparable (median 60/HPF [IQR 40–93] versus 55/HPF [IQR 34–100],  $p=0.25$ ).

Endoscopic features were evaluated in relation to the subjects' race. Esophageal rings, but not strictures, were significantly more often reported in whites. However, endoscopic inflammatory features were comparable among race (table 3) as were peak esophageal eosinophils/HPF (median 50/HPF [IQR 35–85] in whites versus 50/HPF [IQR 35–75] in non-whites,  $p=0.50$ ).

## Medical history

Concomitant medical and surgical histories were obtained and are summarized in table 4. As expected,<sup>8</sup> concurrent GERD was very commonly reported (54.2%). While other gastrointestinal diseases were present including lower gastrointestinal disorders, they were similar in prevalence to that of the general population except for celiac disease reported in 2.0% of subjects, which appeared slightly higher than expected for the general population (0.3–1%).<sup>12</sup> Notably, concurrent inflammatory bowel disease (Crohn's and ulcerative colitis) was found in a total of 11 subjects with median [IQR] age of 19.8 [14.5–26.0] years; these subjects did not have eosinophilia in any other GI site besides the esophagus. Irritable bowel syndrome was significantly more common in adults.

Allergic disorders were reported in the majority of subjects (90.6%), both in adults and children (table 4). Food allergy was most commonly reported (67.0%) followed by allergic rhinitis (60.3%), atopic dermatitis (46.4%), asthma (45.4%), allergic conjunctivitis (31.2%), urticaria (26.2%), food anaphylaxis (27.1%) and angioedema (13.2%). Food allergies, food anaphylaxis, asthma and allergic skin disorders (atopic dermatitis and urticaria) had significant differences among age groups and were observed to be higher in children <11 years of age and 11–17 years of age compared to adults, while allergic rhinitis and conjunctivitis did not differ between age groups. Nonwhites had significantly higher rates of food allergy and atopic dermatitis (table 4), both of which were associated with a shorter gap between symptom onset and diagnosis in the overall population (table 2).

Subjects in this study also reported a high prevalence of infections (44.4%), such as sinusitis (28.5%) and pneumonia (24.5%). Surgeries related to these disorders were also common, including tympanostomy tube placement (19.6%). Autoimmune disease was also reported in 4.7% of subjects, which appeared comparable to what is reported in the general population (3.2%).<sup>13</sup> Interestingly, autoimmune disease was only reported in white subjects (table 4). Depression/anxiety was more prevalent than what is known for the general population,<sup>14</sup> and was significantly more often reported with increasing age (24.0% in adults compared to 9.3% in children <11 years of age, and 19.0% in those 11–17 years of age,  $p < 0.0001$ ). Failure to thrive was also common (21.3% of subjects), and was significantly different among age groups with it being more frequently reported in the younger population ( $p < 0.0001$ ). 5.8% of subjects underwent gastrostomy tube placement, mostly children (table 4). 29.6% had history of neurological/developmental disorders. Specifically, 6.8% of the EoE patients had a history of prematurity, significantly higher in non-white individuals (12.9% non-white vs. 6.0% white,  $p = 0.03$ ) (table 4); there was also a high rate of other comorbidities such as developmental delay (11.2%).

While subjects reported IgE-mediated allergy to multiple foods known as common allergens such as milk, egg, wheat, soy, peanut, tree nuts, fish, and shellfish (table E3, available in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)), high rates of allergy were also reported to less common allergens such as beef, poultry and corn. Interestingly, these allergies were not limited to young children as would be expected for less common allergies,<sup>15</sup> but were also present in older children and adults.



## Family History

Parents and siblings of subjects with EoE had a high prevalence of atopic diseases including asthma, allergic rhinitis, atopic dermatitis and urticaria, as well as food allergy (table E4, available in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). Family history of EoE was also more common than that expected for the general population (0.5–1/1000):<sup>4</sup> 3.0% of subjects had 1 parent with a history of EoE, 4.5% had 1 sibling with a history of EoE, and 6.2% had 1 parent and/or sibling with a history of EoE. In addition, 8.1% reported having 1 parent with food impaction and 5.2% having 1 parent who had esophageal dilation. This difference in the prevalence of EoE versus the symptoms of food impaction and esophageal dilations was not found in siblings. GERD was also more prevalent in parents than in siblings of subjects with EoE. In addition to EoE, eosinophilic gastrointestinal disorders (EGID) besides EoE were surprisingly prevalent in family members, given that EGIDs are even less prevalent than EoE in the general population, with 2.9% having 1 parent with EGID, 2.9% having 1 sibling with EGID, and 4.8% having 1 parent and/or sibling with EGID. An increased rate of other immune diseases was noted in parents of subjects with EoE (7.9% had 1 parent with inflammatory bowel disease, 6.9% had 1 parent with autoimmune disease, and 1.4% had 1 parent with celiac disease), all these being higher than expected for the general population.<sup>12, 13, 16</sup> (table E4, available in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org))

## Discussion

In this multi-center registry of subjects with EoE that included an extensively detailed medical history, we were able to capture subjects with a wide range of ages, racial backgrounds, geographical locations and socioeconomic conditions. This heterogeneity allowed us to make several important observations. Amongst these, the following findings have been described for the first time or have been solidified in this study: (1) gastrointestinal eosinophilia at the site contiguous to the esophagus occurs in ~5% of patients; (2) a large time gap (1.5 years) between symptom onset and disease diagnosis exists, and this gap is influenced by age (adults had a longer time from symptom onset to diagnosis than children), race (whites had a longer time from symptom onset to diagnosis) and history of food allergy or atopic dermatitis (both associated with a decrease in the time gap); (3) symptoms vary with age (non-specific gastrointestinal symptoms were more common in children, and esophageal symptoms such as heartburn, chest pain and dysphagia were common in adults); (4) symptoms vary with race (dysphagia, esophageal food impactions and heartburn were significantly more common in whites, while emesis was significantly more common in non-whites); (5) failure to thrive was common (21.3% of subjects) especially in the younger population; (6) infectious/immunological disorders including celiac disease were prevalent in EoE subjects and their family members; (7) depression and anxiety had significant differences between age groups of EoE patients and were observed to increase with age (for example, 24.0% in subjects 18 years of age compared to 9.3% in children <11 years of age); (8) there was a high prevalence of neurodevelopmental disorders including prematurity in the EoE population; (9) peak esophageal eosinophil counts in patients with and without fibrostenotic features (rings, stricture or shearing) were comparable, suggesting that fibrostenotic complications are not

necessarily an end-stage component of the disease, and pointing towards the importance of concurrently treating the underlying esophageal inflammation when performing esophageal dilation in patients with fibrostenosis; and (10) family history of EoE and EGID is present in a relatively large fraction of EoE patients (6.2% and 4.8% with 1 parent and/or sibling respectively), consistent with a strong hereditary component as now observed in this multi-site large cohort.

We were able to confirm the predominance of males among those with EoE, and the fact that EoE affects patients of all races.<sup>1, 17</sup> We observed for the first time that concurrent eosinophilic gastritis is not uncommon in patients with esophageal eosinophilia and its related symptoms, with 5.2% of our subjects diagnosed with eosinophilic gastritis. Previous studies have examined the reverse association, i.e. the prevalence of esophageal eosinophilia in patients with eosinophilic gastritis. In a study by Jensen et al examining children and adults,<sup>18</sup> 10.6% of the EG patients had concurrent EoE, although these data were derived from a large insurance database and therefore could not be verified. In a single-center pediatric study by Ko et al,<sup>19</sup> where all data were verified and biopsies were re-evaluated by the investigators, 43% of the patients with EG had concurrent EoE. In addition, Caldwell et al found that ~90% of EG patients had extra-gastric involvement with the esophagus being the most commonly involved secondary organ.<sup>20</sup> This association of esophageal and gastric eosinophilia is important to emphasize, since it highlights that the vast majority of EoE patients with extra-esophageal eosinophilia have only gastric involvement and rarely hypereosinophilic syndrome and/or other extra-esophageal disease. Nevertheless, it is important for clinicians to be aware of the association, necessitating the consideration of endoscopic biopsies of the stomach and duodenum in EoE patients at the time of diagnosis, and possibly at follow-up,<sup>21</sup> as finding gastrointestinal eosinophilia beyond the esophagus may influence management decisions.

We found a large time gap between symptom onset and the diagnosis of EoE. This gap was independent of concurrent gastrointestinal eosinophilia at other sites. The time gap was age-dependent, however, as it increased with increasing patient age at diagnosis. We also found that food allergy and atopic dermatitis were associated with a more prompt diagnosis. Food allergy and atopic dermatitis were more common in the younger population, therefore potentially influencing the variability of the diagnostic time gap with age. We also found that the time gap was race-dependent, with whites having a longer gap between symptom onset and diagnosis. But again here, non-white subjects had significantly more food allergy and atopic dermatitis, which could have also influenced this finding. One potential explanation for food allergy and atopic dermatitis influencing the time gap from symptoms to diagnosis may be that clinicians are aware of EoE being associated with allergic disease,<sup>1</sup> and are including it in their differential diagnosis when gastrointestinal complaints are noted. Interestingly, family history of EoE was not associated with a shorter time gap to diagnosis, likely because parents of EoE subjects often have their EoE diagnosis made after, not before, their children get diagnosed; as they discover through their children's medical visits that their chronic esophageal symptoms are also suggestive of EoE. This observation stresses the importance of increasing knowledge about the disease, particularly focusing on the strong heritability of EoE. Furthermore, a large percentage of our subjects had private health insurance, which tends to be linked to easier access to care. Therefore, it is possible that the

time gap between symptom onset and diagnosis of EoE is even longer in the general population.

Adult subjects predominantly presented with dysphagia and esophageal food impactions rather than abdominal pain, nausea and emesis. Dysphagia in EoE is known to be a slowly progressive symptom, often with behavioral feeding modifications made by patients to prevent worsening of dysphagia and esophageal food impactions.<sup>22</sup> Due to the progressive nature of the disease, patients may develop compensatory eating behaviors, potentially leading to a delay in seeking medical attention and proper diagnosis. Similar findings were obtained in a study of Swiss EoE adult patients, where the median diagnostic delay in adults was twice that in children, with characteristics such as EoE family history and atopic diseases/allergies not found to be risk factors for the increased length of diagnostic delay.<sup>23</sup>

Abdominal pain, emesis and dysphagia were some of the most common symptoms reported in our study. Dysphagia and esophageal food impactions, in addition to gastroesophageal symptoms including heartburn, were more common in whites, and non-whites reported more emesis. Our findings validate a large retrospective multicenter study<sup>17</sup> in which whites had more dysphagia, food impactions and classic features such as esophageal rings than non-whites, although heartburn was less common in whites in that study. It is notable that genetic analysis of EoE has been limited to whites,<sup>7</sup> calling attention to the importance of examining the genetic basis of non-whites as sample sizes grow. In addition, we confirmed previous reports<sup>5, 24</sup> of a high prevalence of failure to thrive in EoE, especially in the younger population, which necessitates future in-depth evaluation.

Interestingly, lower gastrointestinal symptoms including diarrhea and bloody stools were commonly reported by our subjects. While the accuracy of these reports was limited by the absence of strict definitions for each symptom in the questionnaire, these observations warrant further investigation. Diarrhea has been reported previously in children with EoE,<sup>24</sup> and intestinal permeability has been reported to be increased in patients with EoE.<sup>25</sup>

Around 15% of subjects in this study reported depression/anxiety, which increased in prevalence with age. Depression/anxiety and decreased quality of life have been reported previously in EoE.<sup>26, 27, 28</sup> Our data suggest that a more comprehensive approach that includes mental health support should be considered in the management of patients with EoE. Furthermore, neurodevelopmental disorders were reported in our subjects and deserve particular attention. EoE and developmental disorders have been described previously,<sup>29</sup> and pediatric phenome-wide associated studies point to a potential link between EoE and these disorders.<sup>30</sup>

Celiac disease was slightly more prevalent in EoE subjects than expected for the general population. Although the association between EoE and celiac disease remains unclear as the two diseases are currently thought to be likely independent,<sup>31</sup> our finding warrants further investigation. Autoimmune diseases were reported in our subjects (4.7%) and their family members. This finding was limited to white subjects, raising the suspicion for a different disease phenotype in this patient subset. Further studies are warranted for this subgroup, since findings from these results may influence future medical therapies for these patients, as

shared immunopathology may be present. A very similar result was found in a single population-based cohort study in Utah, a predominantly white cohort of northern European descent, where a high rate of both personal and family histories of autoimmune disorders was found.<sup>32</sup> In addition to atopic diseases in both subjects and their families, subjects with EoE also reported a high rate of pneumonia and sinusitis, which can possibly be secondary to poorly controlled allergic rhinitis and asthma, and immunodeficiency. These concurrent immune-related/infectious diseases suggest the possibility of a systemic immune dysregulation in EoE beyond its localization to the esophagus, and is worth further investigation since immunodeficiency has been reported previously in patients with significant esophageal eosinophilia.<sup>33, 34</sup>

Lastly, EoE and EGID were common in family members of patients with EoE. Interestingly, the prevalence of food impactions and esophageal dilatations was higher than the reported prevalence of EoE in parents, while this difference was not seen in siblings. This observation in parents is possibly secondary to an increase in EoE awareness over time, leading to a diagnosis of EoE in children more readily than in adults, while siblings, who are younger, may not yet have developed these esophageal complications, or they were adequately treated as therapy options increased with the next generation. In addition, GERD was more prevalent in parents than in siblings of our subjects with EoE, with esophageal food impactions and dilatations in that case being potential complications of GERD rather than EoE in some of the parents.

Our study has several limitations. We decided to include patients who did not have PPI therapy as a requirement for EoE diagnosis. Therefore, patients with PPI-REE were not excluded in this study. Recent research, however, is identifying patients with PPI-REE as having EoE. In fact, the European Society of Eosinophilic Oesophagitis established PPI-REE as EoE in their new guidelines, therefore eliminating the concept of PPI-REE as a separate entity,<sup>35, 36</sup> based on evidence of similar gene expression profiles in EoE and PPI-REE,<sup>10, 11</sup> demonstration of an anti-inflammatory effect of PPI,<sup>37</sup> and reports of patients that interchangeably respond to PPI and dietary eliminations targeted for EoE patients.<sup>9, 38</sup> Based on the above, we do not believe that GERD is the cause of PPI-REE. We believe that patients with GERD accounting for esophageal eosinophilia were not included in this study, since all patients included had their diagnosis confirmed by the investigators, i.e. other causes of esophageal eosinophilia including GERD were ruled-out. In addition, our study is limited by self-report of co-morbidities, although research coordinators verified the information provided by medical record review as available. Lastly, assessment of gastrointestinal eosinophilic disease beyond the esophagus was limited by the fact that no definitions yet exist for eosinophilic gastritis, enteritis and colitis, therefore we had to accept the pathologists' reports at each site.

Despite these limitations, our study has several strengths. We have analyzed a large cohort of pediatric and adult EoE patients derived from the food allergy referral centers associated with CoFAR. The sample size, patient heterogeneity and extensive systematically collected information provided a unique opportunity for disease assessment, which will also be correlated in the future with gene sequencing data to understand how the described disease characteristics vary as a function of genetics. Notable findings from our current analysis

included a persistent gap between symptom onset and diagnosis, influenced not only by age and race but also by presence of food allergy and atopic dermatitis. The interplay of these factors needs to be further investigated. Diagnostic delay after symptom onset was longer in white individuals and adults, findings that illustrate unique presentations dependent upon race and age and thus inform clinical practice and directions for future research. In addition, we found symptom variability with age and race, suggesting the need to elucidate the reasons for these differences. Of equal importance are the high prevalence of failure to thrive and depression/anxiety, which emphasize the need for a more comprehensive multidisciplinary care for patients with EoE. Other notable findings included the co-existence of extraesophageal eosinophilic gastrointestinal inflammation, multiple atopic diatheses and concurrent autoimmune diseases in EoE, as well as enrichment of EoE/EGID in first-degree relatives. Although it is possible that the high prevalence of co-morbid atopic disorders was in part influenced by heavy recruitment from allergy clinics, EoE is a disease that requires co-management by an allergist regardless of allergic comorbidities, and therefore less likely to bias our findings. We also confirmed that esophageal rings and strictures at diagnosis were significantly more common in adults, and underscore the need for early recognition and treatment. Esophageal eosinophilia was still significant in these patients, arguing for the use of medical therapies rather than contending with esophageal dilatations. Finally, analysis of co-morbidities in our cohort reveals the need for educational efforts to be aimed at a wider range of health care providers to consider a work-up for EoE, and to include those patients not only with esophageal symptoms, but also with various gastrointestinal symptoms.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Abbreviations

<b>CoFAR</b>	Consortium for Food Allergy Research
<b>EGID</b>	eosinophilic gastrointestinal disorder
<b>EoE</b>	Eosinophilic esophagitis

<b>HPF</b>	high power field
<b>IQR</b>	Interquartile range
<b>GER</b>	gastroesophageal reflux
<b>GERD</b>	gastroesophageal reflux disease
<b>GI</b>	gastrointestinal
<b>PPI</b>	proton pump inhibitor
<b>PPI-REE</b>	PPI-responsive esophageal eosinophilia
<b>US</b>	United States

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### Highlights box

**What is known about this topic?**

EoE is increasingly common, but data on its phenotypic aspects are still incomplete.

**What does this article add to our knowledge?**

An age and race-dependent variation in endoscopic features, symptoms and time gap to diagnosis is present. Concurrent atopic diseases, failure to thrive and depression/anxiety are prevalent in patients with EoE. Esophageal eosinophilia is present even when the esophagus has fibrostenotic features.

**How does this study impact current management guidelines?**

Physician education is important regarding symptom variability. A multi-disciplinary approach is needed for better care of EoE patients given the co-morbidities.

Age at diagnosis and at symptom onset, and time from symptom onset to diagnosis by involvement of GI sites beyond the esophagus

**Table 1**

	No. subjects (%)	% among whites	% among non-whites	P-value	Age at EoE diagnosis Median [IQR]	Age at EoE symptom onset* Median [IQR]	Time from symptom onset to diagnosis* Median [IQR]
EoE, total cohort	705				8.0 [3.0–15.0]	5.0 [1.0–12.0]	1.5 [0.7 – 4.0]
EoE without other GI site eosinophilia	638 (90.5)	90.5	90.6	1.00	8.0 [3.0–15.0]	5.0 [1.0–12.0]	1.5 [0.7 – 4.0]
EoE with only eosinophilic gastritis	37 (5.2)	5.2	5.9	0.79	5.0 [3.0–15.0]	2.0 [0.8–13.0]	1.2 [0.8 – 3.7]
EoE with only eosinophilic enteritis	4 (0.6)	0.5	1.2	0.40	6.0 [0.7–14.0]	5.5 [0.7–13.0]	0.5 [0.0 – 1.0]
EoE with only eosinophilic colitis	12 (1.7)	1.8	1.2	1.00	6.0 [3.0–11.0]	3.5 [1.5–8.5]	1.3 [1.0 – 3.5]
EoE with eosinophilia at >1 GI site	14 (2.0)	2.1	1.2	1.00	10.5 [4.0–16.0]	5.5 [1.0–12.0]	1.0 [0.0 – 9.0]

\* Twelve subjects are missing age at EoE symptom onset, so their time from symptom onset to diagnosis cannot be calculated and is also missing.

Analysis of time gap between age at symptom onset and age at diagnosis by gender, family history of EoE and personal history of atopy.

**Table 2**

	Time from Symptom Onset to Diagnosis (years)							p-value
	Absent			Present				
	N	Median	IQR	N	Median	IQR		
<b>Family history of EoE</b>								
Any family history of EoE	645	1.4	0.7-4.0	46	2.0	0.8-3.0	0.91	
Parental history of EoE	662	1.4	0.7-4.0	21	2.0	0.8-5.0	0.59	
Sibling history of EoE	525	1.8	0.8-4.0	25	2.0	0.8-3.0	0.55	
<b>Allergic disorders</b>								
Allergic conjunctivitis	474	1.3	0.5-4.0	219	1.5	1.0-4.9	0.16	
Allergic rhinitis	275	1.5	0.8-3.9	418	1.5	0.6-4.9	0.61	
Asthma	378	1.8	0.9-4.0	315	1.3	0.5-4.0	0.31	
Atopic dermatitis	372	2.0	1.0-5.0	321	1.0	0.5-3.0	<b>0.001</b>	
Urticaria	509	1.5	0.7-4.0	184	1.6	0.7-3.9	0.90	
Angioedema	601	1.4	0.7-4.0	92	1.8	0.5-3.7	0.86	
Food allergy	226	2.0	1.0-6.0	466	1.1	0.5-3.5	<b>0.0008</b>	
Food anaphylaxis	497	1.5	0.8-4.0	186	1.3	0.5-3.7	0.19	
Drug anaphylaxis	617	1.3	0.6-4.0	76	2.7	1.0-7.0	<b>0.008</b>	
Latex allergy	645	1.5	0.7-4.0	47	1.9	0.7-5.9	0.35	

**Table 3**

Percentage of subjects who reported various EoE symptoms within 12 months prior to enrollment and who reported various endoscopic findings at diagnosis, categorized by age at enrollment, and compared with respect to race.

	Total (n=705)		Patients <11 years of age		Patients 11-17 years of age		Patients 18 years of age		Age comparison		% among whites (n=620)		% among non-whites (n=85)		Race comparison	
	N Total#	% Cases	N Total#	% Cases	N Total#	% Cases	N Total#	% Cases	P-Value**	N Total#	% Cases	N Total#	% Cases	P-value		
<b>Symptoms</b>																
Abdominal Pain	704	53.6	344	57.6	189	57.1	171	41.5	<b>0.001</b>	619	53.8	85	51.8	0.73		
Nausea	703	40	343	38.8	189	44.4	171	37.4	0.34	618	40.3	85	37.6	0.72		
Emesis	705	40	345	47	189	40.2	171	25.7	< <b>0.0001</b>	620	38.4	85	51.8	<b>0.02</b>		
Heartburn	696	37.2	336	22.9	189	42.9	171	59.1	< <b>0.0001</b>	612	39.5	84	20.2	<b>0.0005</b>		
Chest Pain	703	21.1	343	15.7	189	25.9	171	26.3	<b>0.003</b>	618	21.2	85	20.0	0.89		
Gastroesophageal Reflux	705	51.3	345	43.5	189	52.4	171	66.1	< <b>0.0001</b>	620	52.9	85	40.0	<b>0.03</b>		
Dysphagia	705	50.5	345	38.3	189	52.4	171	73.1	< <b>0.0001</b>	620	52.4	85	36.5	<b>0.008</b>		
Esophageal Food Impactions	704	38.1	344	20.3	189	42.3	171	69	< <b>0.0001</b>	619	40.5	85	20.0	<b>0.0002</b>		
Diarrhea	705	32.1	345	32.2	189	27.5	171	36.8	0.17	620	33.1	85	24.7	0.14		
Bloody Stools	705	7.5	345	7.5	189	6.9	171	8.2	0.90	620	7.3	85	9.4	0.51		
Food impactions requiring urgent endoscopic removal	705	6.1	345	0.9	189	5.8	171	17.0	< <b>0.0001</b>							
Esophageal dilation	700	9.9	342	0.9	187	5.3	171	32.7	< <b>0.0001</b>							
<b>Endoscopic Findings at diagnosis*</b>																
Furrows	487	68.4	219	63.5	127	74	141	70.9	0.10	439	69.7	48	56.3	0.07		
White Plaques	478	55	218	53.7	127	58.3	133	54.1	0.69	433	54.7	45	57.8	0.75		
Loss of Vascular Pattern	334	32.6	148	27.7	85	40	101	33.7	0.15	306	32.7	28	32.1	1.00		
Rings	437	16.5	193	3.1	108	11.1	136	39.7	< <b>0.0001</b>	398	17.8	39	2.6	<b>0.01</b>		
Stricture	434	10.1	192	1.6	114	6.1	128	26.6	< <b>0.0001</b>	394	10.7	40	5.0	0.41		
Shearing	378	8.5	174	9.8	100	10	104	4.8	0.27	342	8.2	36	11.1	0.53		

\*Number of subjects with data available.



Since full endoscopy reports were not a required document for enrollment, and since variability in reporting of endoscopic features was present among endoscopists, some features were not reported on some subjects. In addition, p-values for endoscopic findings were calculated excluding missing values and N/A values in the questionnaires.

\*\* P-value is the result of comparison of all 3 age groups.

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**Table 4**

Percent of subjects with comorbidities, stratified by age at enrollment and by race.

	Total		Patients <11 years of age		Patients 11-17 years of age		Patients 18 years of age		Age comparison		% among whites		% among non-whites		Race comparison P-Value
	N	% Cases	N	% Cases	N	% Cases	N	% Cases	N	% Cases	N	% Cases	N	% Cases	
<b>Gastrointestinal disorders</b>															
GERD	705	54.2	345	55.7	189	49.7	171	56.1	620	36	620	55.0	85	48.2	0.25
Barrett's esophagus	705	0.4	345	0.0	189	0.5	171	1.2	620	0.08	620	0.5	85	0.0	1.00
Celiac disease	705	2.0	345	2.3	189	2.6	171	0.6	620	0.34	620	2.1	85	1.2	1.00
Irritable bowel syndrome	705	6.5	345	3.2	189	3.7	171	16.4	620	< 0.0001	620	7.1	85	2.4	0.11
Crohn's disease	671	0.6	319	0.0	184	1.1	168	1.2	592	0.08	592	0.7	79	0.0	1.00
Ulcerative colitis	671	1.0	319	0.3	184	1.1	168	2.4	592	0.07	592	1.0	79	1.3	0.59
Other gastrointestinal disorders*	671	5.4	319	5.3	184	3.8	168	7.1	592	0.39	592	5.9	79	1.3	0.11
<b>Allergic disorders</b>															
Allergic conjunctivitis	705	31.2	345	29.3	189	30.2	171	36.3	620	0.26	620	30.2	85	38.8	0.13
Allergic rhinitis	705	60.3	345	60.9	189	60.8	171	58.5	620	0.85	620	60.3	85	60.0	1.00
Asthma	705	45.4	345	48.4	189	49.2	171	35.1	620	0.007	620	42.9	85	63.5	0.0004
Atopic dermatitis	705	46.4	345	61.2	189	36.0	171	28.1	620	< 0.0001	620	43.5	85	67.1	< 0.0001
Urticaria	705	26.2	345	32.2	189	22.8	171	18.1	620	0.001	620	26.1	85	27.1	0.90
Angioedema	705	13.2	345	14.8	189	12.7	171	10.5	620	0.41	620	12.6	85	17.6	0.23
Food allergy	704	67.0	345	75.9	188	62.8	171	53.8	620	< 0.0001	620	65.6	84	77.4	0.04
Food anaphylaxis	695	27.1	341	29.3	186	32.8	168	16.1	611	0.0005	611	26.5	84	31.0	0.43
Drug anaphylaxis	705	10.8	345	7.5	189	13.8	171	14.0	620	0.02	620	11.3	85	7.1	0.35
Latex allergy	704	6.8	345	5.5	188	6.9	171	9.4	619	0.27	619	6.1	85	11.8	0.06
<b>Infectious/immunological disorders</b>															
Sinusitis	705	28.5	345	27.5	189	29.1	171	29.8	620	0.84	620	29.4	85	22.4	0.20
Pneumonia	705	24.5	345	22.0	189	27.5	171	26.3	620	0.29	620	24.4	85	25.9	0.79
Immunodeficiency	705	2.6	345	2.3	189	3.7	171	1.8	620	0.50	620	2.9	85	0.0	0.15
Autoimmune disease	705	4.7	345	3.5	189	2.6	171	9.4	620	0.007	620	5.3	85	0.0	0.02

	Total		Patients <11 years of age		Patients 11-17 years of age		Patients 18 years of age		Age comparison		% among whites		% among non-whites		Race comparison	
	N	% Cases	N	% Cases	N	% Cases	N	% Cases	P-Value*	N	% Cases	N	% Cases	N	% Cases	P-Value
<b>Neurological/developmental disorders</b>																
Developmental delay	705	11.2	345	18.0	189	7.9	171	1.2	< 0.0001	620	10.8	85	14.1			0.36
Prematurity	705	6.8	345	9.9	189	3.7	171	4.1	0.008	620	6.0	85	12.9			0.03
Depression/anxiety	705	15.5	345	9.3	189	19.0	171	24.0	< 0.0001	620	16.8	85	5.9			0.006
Autism/behavioral disorder	705	6.2	345	7.8	189	8.5	171	0.6	0.0003	620	6.3	85	5.9			1.00
Mitochondrial disorder	705	0.4	345	0.3	189	1.1	171	0.0	0.32	620	0.5	85	0.0			1.00
<b>Other systemic problems</b>																
Failure to thrive	705	21.3	345	31.9	189	18.0	171	3.5	< 0.0001	620	20.3	85	28.2			0.12
<b>Surgical history</b>																
Typanostomy tube placement	705	19.6	345	24.3	189	20.1	171	9.4	0.0001	620	19.5	85	20.0			0.88
Sinus surgery	705	3.4	345	3.8	189	3.2	171	2.9	0.89	620	3.5	85	2.4			0.76
Fundoplication	705	0.7	345	0.9	189	0.5	171	0.6	1.00	620	0.8	85	0.0			1.00
Gastrostomy tube placement	705	5.8	345	7.8	189	6.3	171	1.2	0.003	620	5.3	85	9.4			0.14

#Number of subjects with data available.

\* The most frequent self-reported gastrointestinal disorders included: Constipation (n=6), gastritis (n=3), ulcer (n=4), gluten intolerance/possible gluten intolerance (n=2), Hirschprung's disease (n=2), and small intestine bacterial overgrowth (n=2).

\* P-value is the result of comparison of all 3 age groups.