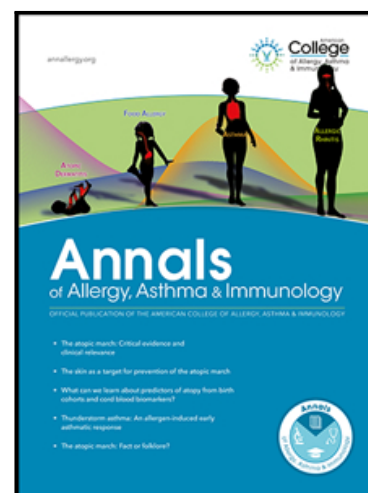


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Title: Comparison of comorbid diagnoses in children with and without eosinophilic esophagitis in a large population

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Abbreviations/Acronyms: ARC, allergic rhinoconjunctivitis; AD, atopic dermatitis; ASD, Autism Spectrum Disorder; CD, Crohn's disease; EMR, electronic medical records; EoE, eosinophilic esophagitis; GI, gastrointestinal; IBD, inflammatory bowel disease; ICD, International Classification of Diseases; TSLP, thymic stromal lymphopoietin; UC, ulcerative colitis.

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Introduction

Eosinophilic esophagitis (EoE) is a chronic immune-mediated inflammatory condition characterized by esophageal dysfunction with associated eosinophilic infiltration of the

esophageal mucosa, occurring in 1/2000 individuals.^{1,2} Since the 1990s, EoE has been recognized as a clinically distinct condition, being seen with increasing incidence and prevalence over time, and currently accounting for the most common cause of chronic dysphagia in pediatric patients in the developed world.³⁻⁶ The pathophysiology is frequently recognized as a food allergy-driven process, characterized by a T_H2-type immune response, with a high rate of concomitant IgE-mediated food allergy observed in patients.⁷⁻⁹ Notably, esophageal inflammation is often reversible with dietary elimination of known food allergens or with adherence to elemental formulas (though not in all patients), further supporting the impact of food protein in disease manifestation.¹⁰⁻¹²

The association between EoE and other atopic diseases is also well established, with rates of allergic rhinoconjunctivitis (ARC), atopic dermatitis (AD) and asthma all described in higher frequency in those with EoE compared to healthy individuals.¹³⁻¹⁶ Interestingly, seasonal exacerbations of EoE have also been reported in children with specific aeroallergen sensitization, suggesting that food may not be the only trigger involved.¹⁷ Consequently, these associations have called into question EoE as an integral member of the atopic march.^{18,19}

Several other reports have suggested that EoE may be more frequently associated with some non-allergic disorders, including gastrointestinal (GI) and autoimmune conditions. The association between celiac disease and EoE, for instance, was first described as a case series in pediatric patients by Shah et al. in 2006.²⁰ More recently, a large population study in 2016 by Peterson et al. reported that patients with EoE were 8.7 times more likely to be diagnosed with celiac disease compared to controls.²¹ Similarly, subjects with Inflammatory Bowel Disease (IBD), both Crohn's Disease (CD) and Ulcerative Colitis (UC), were nearly 4 times more likely to be diagnosed with EoE compared to unaffected controls. This same group reported higher

rates of other autoimmune conditions in patients with EoE, including multiple sclerosis, systemic sclerosis and Hashimoto's thyroiditis. Finally, there appears to be an increased prevalence of EoE in children with connective tissue diseases, including Marfan syndrome and Ehlers-Danlos syndrome, as well as in children with Autism Spectrum Disorder (ASD), though to date, only few reports exist describing these relationships.²²⁻²⁴

Altogether, these studies identify an ongoing need to better characterize the risk and rates of comorbid medical conditions associated with EoE, particularly in children. Thus, we sought to define differences in prevalence rates of comorbid diseases in children with and without EoE using a single large pediatric primary care population with the hypothesis that comorbid disease would be found at a higher rate in children with EoE compared to unaffected controls.

Methods

Patient cohort and data extraction

We performed a retrospective cross-sectional study of children with and without EoE using a large pediatric primary care database from the Children's Hospital of Philadelphia (CHOP) primary care network. CHOP is one of the largest providers of both primary care and sub-specialty services for children within the eastern Pennsylvania, New Jersey and Delaware regions. The Division of Allergy and Immunology at CHOP includes five outpatient clinic locations including the international referral center for EoE through the Center for Pediatric Eosinophilic Disease, which provides comprehensive collaborative medical services by combined Allergy, GI, and Nutrition specialists.

To assess prevalence rates of comorbid diagnoses, we extracted data from CHOP's electronic medical records (EMR) (Epic Systems, Verona, WI), which totaled 456,148 children

who obtained primary care services from one of 31 CHOP primary care sites between January 1st, 2007 to December 31st, 2016. An honest broker removed direct patient identifiers (e.g. medical record number and patient name, etc.) to create a dataset including all comorbid diagnoses on the patient's problem list, as well as limited identifiers such as date of birth, gender, race, insurance provider and ethnicity. All problem list diagnoses were coupled with International Classification of Diseases, Ninth and/or Tenth Revision, Clinical Modification (ICD9 or 10-CM) diagnostic codes. Patients were separated into two cohorts based on presence or absence of EoE diagnosis based on ICD code. A manual review of 100 randomly selected charts (50 patient with and 50 patients without EoE) was performed to confirm the validity of ICD diagnosis codes. Definite confirmation of presence or absence of EoE diagnosis was made in 94 of the 100 cases, comparing similarly to the true positive EoE diagnosis rate of 92% found by Hill et al., 2017 using a similar study design.⁹ We found an 86% accuracy rate for comorbidity diagnosis, with most discrepancies secondary to absence of diagnosis codes for clinically present atopic diseases in both patients with and without EoE. The study was reviewed and approved by the CHOP Institutional Review Board.

Selection of comorbid conditions

Prior to our primary analysis, we performed a preliminary review of our internal EoE database of patients seen within the Center for Pediatric Eosinophilic Disease at CHOP from 1/1/2007 to 12/31/2016. Patients in this database were those who had been seen for at least one visit with a primary Allergy or GI attending, and with an encounter diagnosis of EoE. Comorbid Problem list diagnoses were obtained totaling 12,907 diagnoses for 1,494 patients. A ranking by rate of comorbid diagnosis was performed with exclusion of infections and symptom-based diagnoses.

From this ranking, we selected the following comorbidities to evaluate in our primary care population for our chief analysis: ARC, asthma, AD, adrenal insufficiency, ASD, celiac disease, connective tissue diseases, cystic fibrosis, hypothyroidism, IBD, and type I diabetes mellitus. In addition to infectious and symptom-based diagnoses, the diagnosis of “food allergy” was also excluded given that patients with EoE frequently hold this problem list diagnosis despite absent clinical history of IgE-mediated food sensitivity. Moreover, the association between IgE-mediated food allergy and EoE has been recently discerned within the CHOP care network.⁹

Definition of conditions

All children included within the EoE cohort held problem list diagnoses corresponding to ICD9 code 530.13 and/or ICD10 code K20.0. The following specific base ICD9/10 codes and appropriate derivatives were used to identify patient’s comorbidities: ARC (477.9,372.14; J30.0, J31.0, H10.1,H10.45), asthma (493;J45), AD(691;L20), adrenal insufficiency (E27; 255), ASD (299; F87), celiac disease (579; K90), connective tissue diseases (756.83, 759.82, 759.89; Q87.4, Q79.6) cystic fibrosis (277, E84), hypothyroidism (244.9; E03), IBD (555.9,556.9; K50, K51), type I diabetes mellitus (250; E10). Of note, ICD codes utilized for connective tissue diseases were consistent with those used in previous reports for the purpose of direct comparability.²²

Statistical Analysis

To compare prevalence rates for comorbid conditions in our patient population, we created 2x2 contingency tables for each comorbidity and then used Fisher’s exact test for dichotomous variables to evaluate for significant differences in rates between those with EoE and those without EoE. Differences in asthma severity were also evaluated between our two cohorts. A

unilateral and multivariable logistic regression model was then used to assess for differences in the odds of comorbidity rates in those with EoE and those without EoE taking age and gender into consideration as covariables. Finally, we performed a subset multivariate analysis in patients with asthma to evaluate for differences in rates of adrenal insufficiency in those with asthma and EoE vs those with asthma but without EoE. Fisher's exact test was used to determine differences in patient demographics, including gender, race, birth year, and insurance provider. A P value <0.05 was considered statistically significant. Data analysis was completed using R version 3.1.2 (Wien, Austria), GraphPad Version 7 (Prism Software, San Diego, CA) and Stata v15 (StataCorp LP, College Station, Tex).

Results

Demographics

A total of 456,148 children were extracted to the primary care database for statistical analysis, 428 of which held a diagnosis of EoE. Patients ranged from 0.1-21.5 years of age, with a mean age of 8.6 years. Patients with EoE were more likely to be male and to identify as white, consistent with previous data.^{2,6} Further analysis and significant differences for additional patient demographics including birth year, ethnicity and insurance payer are outlined in Table 1.

Differences in Comorbid Diagnoses

Significant differences in rates of both atopic and non-atopic diseases were appreciated in our cohort. For atopic diseases, there was a higher rate of ARC (60.0% of EoE cohort vs. 17.4% of non-EoE cohort, $P<0.0001$), asthma (59.8% of EoE, 21.4% of non-EoE, $P<0.0001$), and AD (17.8% of EoE, 6.6% of non-EoE, $P<0.0001$) in children with EoE (Fig. 1).

For non-atopic disease, children with EoE had higher rates of the following comorbid medical conditions: adrenal insufficiency (2.6% of EoE, 0.4% of non-EoE, $P<0.0001$), ASD (7.5% of EoE, 1.9% of non-EoE, $P<0.0001$), celiac disease (5.6% of EoE, 0.9% of non-EoE, $P<0.0001$), connective tissue diseases (1.4% of EoE, 0.1% of non-EoE, $P<0.0001$), cystic fibrosis (0.9% of EoE, 0.05% of non-EoE, $P<0.0001$), IBD (0.7% of EoE, 0.2% of non-EoE, $P=0.03$), and type 1 diabetes mellitus (1.2% of EoE, 0.3% of non-EoE, $P=0.0069$). Comorbid hypothyroidism was not significantly different between groups (0.5% of EoE, 0.4% of non-EoE, $P=0.67$). (Fig.2). For both atopic and non-atopic comorbid diseases, the relative risk and confidence intervals are displayed in Table 2.

Using a unilateral and multivariate logistic regression model with age and gender as covariables, the odds for both atopic and non-atopic diseases including ARC, asthma, AD, adrenal insufficiency, ASD, celiac disease, connective tissue diseases, cystic fibrosis, IBD and type 1 diabetes mellitus, were found to be higher in the EoE group compared to the non-EoE group (Table 2). No statistically significant increase in the odds of comorbid hypothyroidism was seen in children with EoE in the logistic regression model.

Differences in Asthma Severity

In children with EoE, the majority of asthma was noted to be either intermittent or mild persistent (72.6%). Persistent asthma was more prevalent in the EoE population, however, including mild persistent (31.6% in EoE, 23.7% in non-EoE, $P=0.004$), moderate persistent (14.5% in EoE, 7.3% in non-EoE, $P<0.0001$), and severe persistent (3.5% in EoE, 0.65% in non-EoE, $P<0.0001$). Compared to children without EoE, those with EoE had a lower rate of intermittent asthma (41.0% in EoE, 51.9% in non-EoE, $P=0.0005$) (Fig. 3). Unspecified asthma

severity accounted for 9.4% compared to 16.5% ($P=0.0013$) in those with EoE vs. those without EoE, respectively (data not graphically depicted).

In the subset analysis of patients with asthma using a multivariate logistic regression model with age, gender, and asthma severity as covariates, the odds of adrenal insufficiency were found to be significantly higher in asthma patients with EoE compared to asthma patients without EoE (OR, 5.5; 95% CI, 2.8-10.8; $p<0.0001$).

Discussion

The purpose of this study was to define the prevalence rates of comorbid diagnoses in patients with EoE compared to those without EoE in a single large pediatric population. To date, and to the best of our knowledge, this is the first comprehensive report to evaluate both atopic and non-atopic comorbid diseases in a single large population of exclusively pediatric patients. We initially performed a preliminary search of children seen in our combined Allergy and GI clinic (Center for Pediatric Eosinophilic Disease) at CHOP to determine the most frequently associated comorbidities in children with EoE. Based on these findings and considering previously described associations, we selected eleven disease processes and sought to determine the prevalence rate of these conditions in our larger pediatric primary care population. We found that almost all comorbid diseases were more common in children with EoE compared to those without EoE. The rate of comorbid hypothyroidism was the only diagnosis found not to be significantly different in this population. Interestingly, Peterson et al. reported a higher prevalence of Hashimoto's thyroiditis in those with EoE compared to control.²¹ While in their study, adult patients were included in analysis, we limited our review to only children and

adolescents, and so differences in age may account for these findings, with EoE being a potential risk factors for development of hypothyroid as an adult, but not in childhood.

Consistent with our original hypothesis, the rates of all atopic diseases were found to be higher in children with EoE compared to those without EoE, accounting for the most common comorbid diagnoses overall. These data are similar to previous studies showing that roughly 25-50% of those with EoE have concurrent asthma, 30-90% have ARC, and 10-25% have AD.^{15,25-27}

We additionally sought to characterized asthma severity between our two cohorts and found persistent asthma to be more common in children with EoE. Notably, the rate of severe persistent asthma was over 5 times greater in those with EoE compared to those without. These results are not entirely unexpected. It is possible that asthma in EoE may, to some extent, also be eosinophil-driven, which often portends a more severe and difficult to control phenotype. Previous research may very well support this hypothesis. Studies with animal models have shown that mice treated with an anti-IL-5 antibody (mepolizumab) had both reduced eosinophilic airway inflammation and esophageal eosinophilia.^{28,29} Esophageal eosinophilia was not similarly reduced with anti-IgE antibody (omalizumab) therapy,³⁰ which, in conjunction with our findings, suggest that anti-IL5 therapies may be a better target for future investigations of asthma control in patients with EoE. As a more practical comparison, future research might also evaluate asthma severity in patients with EoE compared to those with significant atopy but absence of EoE. Overall, these data advocate for clinical awareness of the potential for more severe and difficult to manage asthma in children with EoE. These patients may require more frequent follow up visits, close evaluation of adherence and potential escalation to biologic therapy if treatment with inhaled corticosteroids has been unsuccessful. Further, research regarding steroid sparing treatments for asthma in EoE is especially necessary, considering the high rate of adrenal

insufficiency seen on our EoE cohort and especially in our subset analysis of patients with asthma. While these findings may reflect use of inhaled or swallowed steroids individually, as previously reported,^{31,32} they also may be indicative of a potential greater risk for adrenal suppression in the subgroup of patients being treated concurrently with swallowed steroids for esophagitis and inhaled steroids for comorbid asthma. Thus, determining which biologic therapies may be best for comprehensive EoE care remains paramount.

We demonstrated that children with EoE also had higher rates of co-existing GI-related diseases, including IBD and celiac disease as well as a higher rate of comorbid ASD. The association between atopic disease, GI disorders and ASD, which has been previously described, might suggest a mechanistic connection between these processes and EoE.^{23,33-37} Thymic stromal lymphopoietin (TSLP) has been one proinflammatory cytokine studied in both atopic diseases and IBD, and is thought to play an important role in inducing both T_H2 innate and adaptive immune responses.³⁸⁻⁴¹ In atopic disease, TSLP appears to be promoted through a positive feedback mechanism leading to chronic T_H2 inflammation involving dendritic cell regulation and production of T_H2 cytokines as well as through basophil activation.^{38,40, 42-44} Notably, TSLP has been found to be overexpressed in esophageal biopsies in individuals with EoE, with basophil-driven inflammation independent of IgE.^{38,41,44,45} This may further account for poor response to anti-IgE antibody therapy in EoE.³⁰ In association of GI diseases such as IBD, dysregulation of TSLP, leading to overexpression and subsequent T_H2 response has been associated with the inflammatory process underlying UC, with absence of TSLP associated with development of CD.^{38,46} Other theories suggest that increased gut permeability with an associated immune-mediated response to luminal antigens is a potential connecting mechanism between EoE, IBD and ASD.⁴⁷⁻⁵⁰

Relevant to our findings, there may also be a genetic overlap between these disease and type 1 diabetes mellitus, which has previously been associated with both celiac disease and IBD.^{51,52} Finally, the hygiene hypothesis has been implicated as a potential link between atopic disease and ASD.⁵³ We acknowledge a possible selection bias in these findings, namely that patients undergoing more frequent endoscopic evaluation for known GI disorders or for evaluation of feeding dysregulation associated with ASD might be more likely to be diagnosed with EoE. That said, our data would promote efforts to determine potential biomarkers or other clinical indicators that can be utilized to define EoE screening recommendations in patients with associated comorbid conditions.

As previously reported in a case series by Goralski and colleagues,⁵⁵ we also found an increase prevalence of cystic fibrosis in our EoE cohort, which may be due to widespread occurrence of atopic disease. Similar to IBD and ASD, the increased association between EoE and cystic fibrosis may also be prone to selection bias given the increased propensity for these patients to develop GI-related comorbidity and to potentially undergo endoscopy at higher rates. Finally, our data are consistent with the previously described association between EoE and inherited connective tissue diseases.²² In this previous study, the rate of connective tissue diseases in those with EoE was 0.8%, compared to 1.4% in our population, strongly supporting the need for future exploration of this seemingly dissimilar relationship.

To our knowledge, this is the largest study to date to use an entirely pediatric population in the evaluation of both atopic and non-atopic diseases and thus provides insight into comorbid conditions that specifically impact children affected by EoE. Strengths of our study include use of the CHOP primary care network, which encompasses a large, demographically diverse population of all children and adolescents cared for in single network pediatric outpatient setting.

Comparison of both study groups from a single primary care network reduced potential selection bias more likely to result in the evaluation of a specialized or referral-based population. Care should be taken, however, in consideration of the generalizability of our results, as our population demographics were not fully representative of regional demographics and may not be representative of other populations or geographic areas. Generalizability may also be limited given differences in dietary and environmental exposures in other countries or regions which might impact manifestation of atopic diseases including EoE. Other limitations include use of the EMR's problem list to define patient comorbid diagnoses. Similarly, use of ICD9 and 10 codes may lead to a potential misclassification bias, though the diagnostic codes for EoE have been studied for validity in the past.⁵⁴ In terms of misclassification of problem list diagnoses, we specifically selected a primary care population with the assumption that primary care physicians would best maintain an updated, comprehensive and accurate problem list for patients, compared to using a patient database from a specialty care clinic where patients may be seen for targeted consultation and thus might not have the problem list comprehensively updated. Finally, with a cross-sectional analysis, it is difficult to determine a time course relationship between EoE and specific comorbidities, which limits our ability to define screening recommendations. Selection bias, as discussed earlier, should also be considered in interpretation of our results.

In summary, in a large pediatric primary care population, we show that children with EoE have markedly higher rates of both atopic and non-atopic diseases compared to children without EoE. Several comorbid conditions found to be significantly different between our EoE and non-EoE cohorts support previously described associations, which suggests that these associations should be considered in both comprehensive clinical care and in future research initiatives. We particularly note differences in asthma severity with higher rates of persistent and severe asthma

seen in patients with EoE compared to those without. Thus, careful attention to asthma management in patients with EoE should be integral to routine EoE management. Overall, we strongly suggest a complete review of patients' medical history with attention to symptoms that may indicate potential comorbid conditions among the diagnoses presented herein. Further, in patients holding diagnoses such as ASD, connective tissue diseases, or other GI-related diseases, symptoms consistent with EoE including feeding difficulties or failure to thrive should prompt EoE screening and referral to a qualified Allergy or GI specialist. Similarly, future work might also consider screening implications for select comorbid diseases in those diagnosed with EoE. Given the high rate of adrenal insufficiency in the EoE population, efforts are needed to determine steroid sparing options for both EoE and asthma management in EoE, which may prevent long term morbidity, given the chronicity of these diseases. Most importantly, continued investigation into the underlying mechanisms of EoE and associated conditions may enlighten our understanding, options for treatment and prevention measures in the future.

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Figure Legends

Figure 1. Prevalence rates of atopic comorbidities. Prevalence rates of comorbid atopic diseases in patients with history of EoE compared to those without EoE. A p values <0.05 was considered statistically significant. Abbreviations: EoE, eosinophilic esophagitis.

Figure 2: Prevalence rates of non-atopic comorbidities. Prevalence rates of comorbid non-atopic diseases in patients with history of EoE compared to those without EoE. A p values <0.05 was considered statistically significant. Abbreviations: EoE, eosinophilic esophagitis; DM, diabetes mellitus.

Figure 3: Rates of asthma severity: Differences in asthma severity prevalence rates in children with and without EoE. A p value <0.05 was considered statistically significant. ** for $P \leq 0.01$; *** for $P \leq 0.001$; **** for $P \leq 0.0001$. Abbreviations: EoE, Eosinophilic esophagitis.

Figure 1.

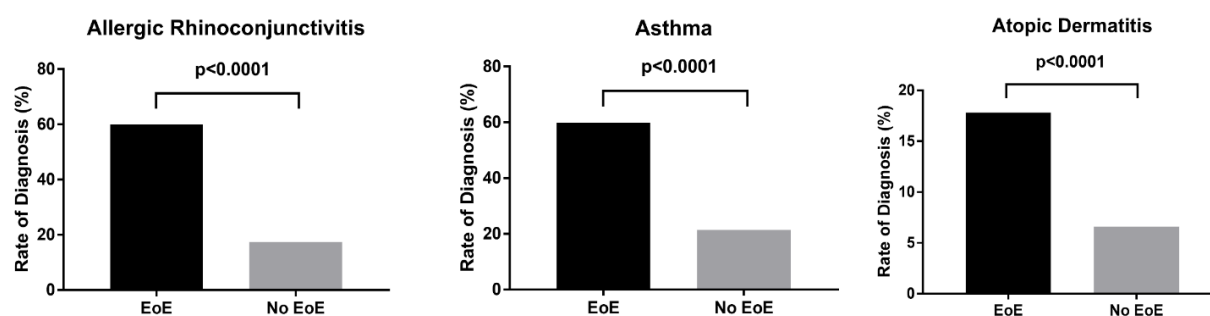


Figure 2.

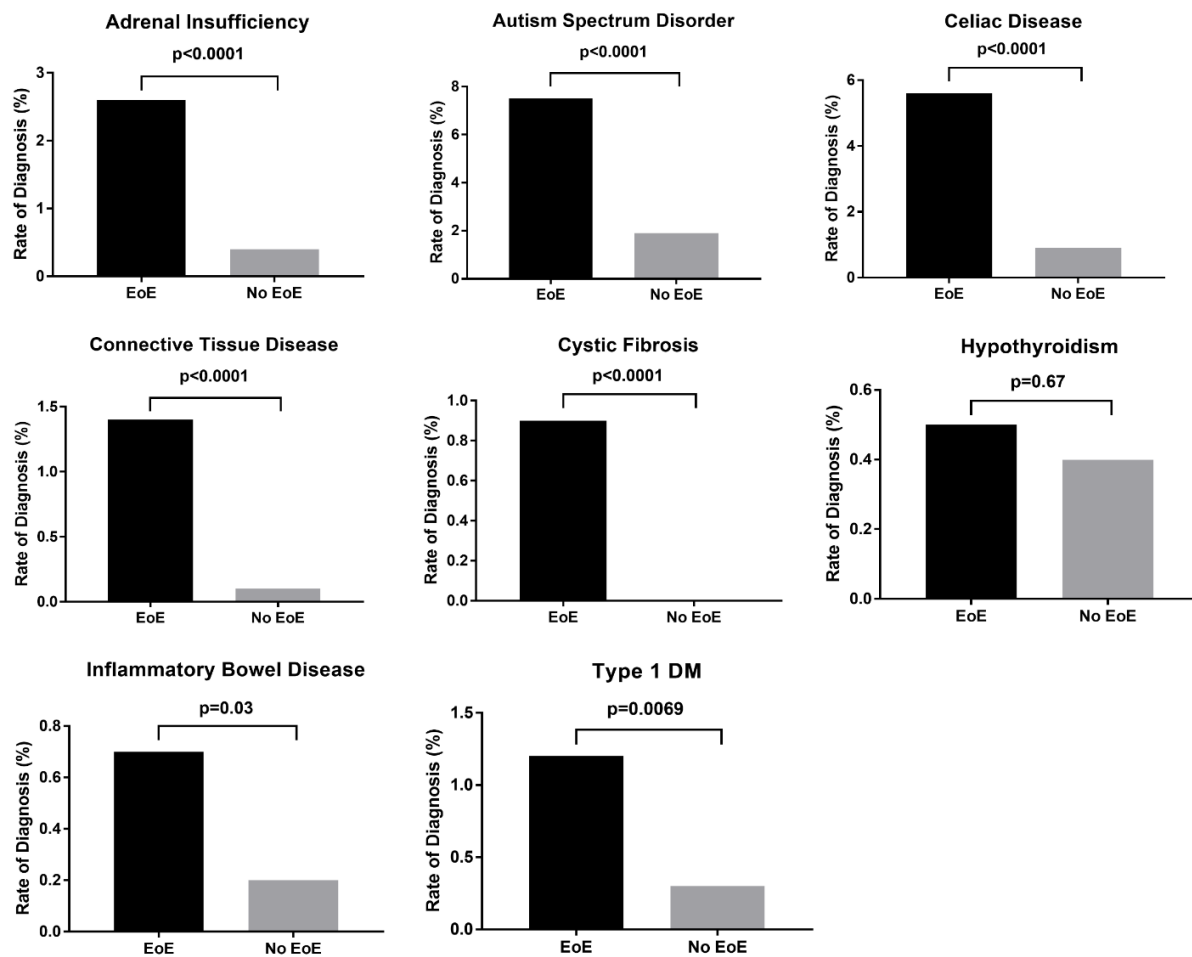


Figure 3.

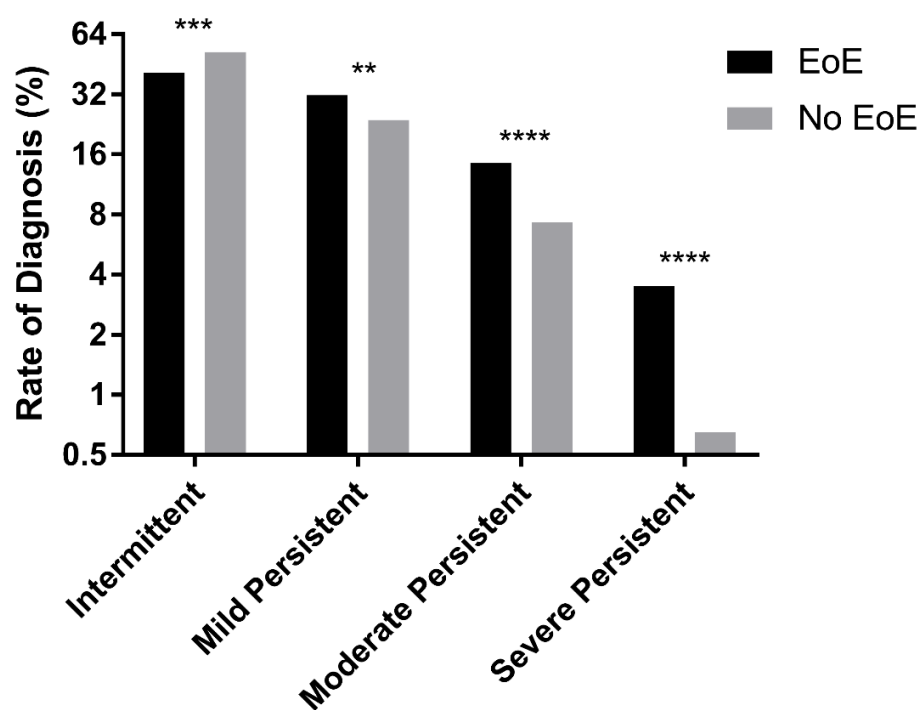


Table 1. Demographics

	EoE N (%)	No EoE N (%)	P value
N Total	428	455,720	
Birth Year			
Before 2000	122 (28.5)	137,481 (30.2)	0.49
2000-2004	113 (31.1)	94,625 (20.8)	0.005*
2005-2009	130 (30.4)	104,601 (23.0)	0.004*
2010-2016	63 (14.7)	119,013 (26.1)	<0.001*
Race			
White	311 (72.7)	238,368 (52.3)	<0.001*
Black	68 (15.9)	134,037 (29.4)	<0.001*
Asian/Pacific Islander	15 (3.5)	15,979 (3.5)	>0.99
Other	5 (1.2)	5,571 (1.2)	>0.99
Unknown	29 (6.8)	61,765 (13.6)	<0.001*
Ethnicity			
Non-Hispanic	405 (94.6)	430,611 (94.5)	>0.99
Hispanic	23 (5.4)	25,109 (5.5)	>0.99
Gender			
Male	307 (71.7)	231,264 (50.7)	<0.001*
Female	121 (28.3)	224,456 (49.3)	<0.001*
Payer			
Non-Medicaid	330 (77.1)	323,772 (71.0)	0.006*
Medicaid	98 (22.9)	131,948 (29.0)	0.0002*

*Statistically significant differences between patients with and without EoE.

Abbreviations: EoE, Eosinophilic esophagitis.

Table 2. Differences in comorbidity prevalence rates, EoE vs. No EoE

Comorbidity	Fisher's*		Unilateral†		Multivariate‡	
	P value	RR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)
ARC	<0.0001	3.4 (3.2-3.7)	<0.0001	7.1 (5.9-8.6)	<0.0001	7.1 (5.8-8.6)
Asthma	<0.0001	2.8 (2.6-3.0)	<0.0001	5.5 (4.5-6.6)	<0.0001	5.2 (4.3-6.3)
AD	<0.0001	2.7 (2.2-3.3)	<0.0001	3.1 (2.4-3.9)	<0.0001	3.1 (2.4-4.0)
Adrenal Insuff	<0.0001	6.7 (3.8-11.9)	<0.0001	6.9 (3.8-12.6)	<0.0001	8.4 (4.6-15.4)
ASD	<0.0001	4.0 (2.8-5.5)	<0.0001	4.2 (2.9-6.0)	<0.0001	3.4 (2.4-4.9)
Celiac Disease	<0.0001	6.6 (4.5-9.6)	<0.0001	6.9 (4.6-10.5)	<0.0001	8.0 (5.3-12.2)
CTD	<0.0001	10.4 (4.7-22.5)	<0.0001	10.5 (4.7-23.6)	<0.0001	11.0 (4.9-24.8)
CF	<0.0001	19.9 (7.7-51.0)	<0.0001	20.1 (7.4-54.2)	<0.0001	19.3 (7.1-52.3)
Hypothyroidism	0.67	1.3 (0.4-4.7)	0.71	1.3 (0.3-5.2)	0.63	1.4 (0.3-5.6)
IBD	0.03	4.5 (1.5-13.2)	0.009	4.5 (1.5-14.2)	0.006	4.9 (1.6-15.4)
Type 1 DM	0.0069	4.3 (1.8-9.9)	0.001	4.3 (1.8-10.4)	0.001	4.5 (1.9-11.0)

* Fisher's exact test.

† Unadjusted results of unilateral logistic regression.

‡ Multivariate analysis considering age and gender as covariates.

Abbreviations: ARC, allergic rhinoconjunctivitis; AD, atopic dermatitis; ASD, Autism Spectrum Disorder; CF, cystic fibrosis; CI, confidence interval; CTD, Connective tissue disease; DM, diabetes mellitus; EoE, eosinophilic esophagitis; IBD, Inflammatory bowel disease; Insuff, insufficiency; OR, odds ratio; RR, relative risk.