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Epidemiology, risk factors and natural history of eosinophilic esophagitis in patients with inflammatory bowel disease: a population-based cohort study from the United States

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Abstract

Background Eosinophilic esophagitis (EoE) and inflammatory bowel disease (IBD) are immunemediated disorders whose coexistence is incompletely defined.

Methods We conducted a cohort study using the TriNetX database, examining a cohort of patients with IBD and EoE over the period 2013-2022. We stratified the cohort by type of IBD, age, sex and race, to assess the incidence and risk factors for the development of EoE in patients with IBD. Additionally, we evaluated the 5-year risk of EoE-specific outcomes in patients with and without IBD.

Results Among 234,582 IBD patients (mean age 45.4 years; 52.5% female; 74.8% White; 52.8% Crohn's disease [CD]), EoE incidence was 0.60% in ulcerative colitis (UC) and 0.83% in CD, highest in 30-34yearold White males. IBD increased EoE risk vs. matched nonIBD controls (adjusted odds ratio [aOR] 2.88, 95% confidence interval [CI] 2.59-3.19). Risk factors in UC were age <40 years (aOR 1.82, 95%CI 1.53-2.16) and male sex (aOR 1.83, 95%CI 1.56-2.15). In CD, age <40 years (aOR 2.71, 95%CI 2.35-3.13), male sex (aOR 1.81, 95%CI 1.58-2.06), obesity (aOR 1.41, 95%CI 1.13-1.75), and prior intestinal surgery (aOR 1.22, 95%CI 1.10-1.50) were significant. After PSM, concurrent IBD reduced the 5year composite risk of esophageal dilation and/or dupilumab use (aOR 0.39, 95%CI 0.29-0.52) compared with EoE alone.

Conclusions IBD confers roughly 3fold higher odds of EoE. Younger age and male sex are universal risk factors; obesity and surgery are risk factors in CD. EoE complicating IBD is associated with fewer fibrostenotic sequelae than isolated EoE.

Keywords Eosinophilic esophagitis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, risk factors

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Introduction

Eosinophilic esophagitis (EoE) is a chronic immune-mediated esophageal disorder characterized by eosinophilic infiltration in the esophagus. EoE has been shown to have an increasing prevalence, particularly in western countries, due to environmental and dietary factors, improved diagnostics and heightened awareness [1-6]. EoE affects approximately 1 in 2000 individuals in the United States (US), with regional prevalence as high as 57 per 100,000 [3-5]. It is commonly seen in males, and often associated with atopic conditions [2,7]. Inflammatory bowel disease (IBD), encompassing Crohn's disease (CD) and ulcerative colitis (UC), has a global prevalence of approximately 0.3% and is characterized by chronic gut inflammation due to a dysregulated immune response to intestinal microbiota in genetically predisposed individuals [8-10].

Although EoE and IBD primarily affect distinct regions of the gastrointestinal tract, with potential esophageal involvement in CD, they exhibit notable pathophysiological

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and clinical commonalities. Both diseases are driven by aberrant immune responses to environmental and dietary antigens and are associated with significant morbidity and impaired quality of life [11]. Moreover, the presence of a family history of autoimmune or allergic diseases in patients with either condition indicates common genetic antecedents [10-12]. Recent evidence suggests a potential overlap between EoE and IBD, with several studies reporting a higher prevalence of EoE in patients with IBD compared to the general population [12]. In a study by Malik *et al* comprising 131,953,725 patients, authors found that the prevalence of EoE in IBD was nearly 3 times higher than in those without IBD [13]. Another retrospective cohort study by Fan *et al*, involving 5435 patients from 2008-2016, reported that approximately 1% of patients with IBD had concurrent EoE, which was significantly higher than the prevalence of EoE in the general population [11]. At the current time, the exact nature and implications of this association remain unclear. Some studies have proposed that the co-occurrence of EoE and IBD may represent a shared pathophysiological mechanism, such as a dysregulated immune response involving the Th1 and Th2 pathways [5]. Other hypotheses suggest that the overlap may in fact be coincidental, given the increasing prevalence of both conditions in similar demographics [6,7]. Despite these hypotheses, conflicting results in the literature pose a challenge to understanding the relationship between EoE and IBD.

The aim of our study was to examine the incidence and risk factors for EoE in patients with IBD, using a large, multi-institutional database. The secondary aim involved analyzing the impact of EoE on the clinical course of IBD, including the need for advanced therapies and surgery and the impact of IBD on outcomes of EoE.

Materials and methods

Database

A retrospective cohort study was performed using the US Collaborative Network within TriNetX (Cambridge, MA, USA), a multi-institutional database. TriNetX is an international federated research network that offers real-time access to de-identified electronic health records for over 105 million patients from more than 60 healthcare organizations across the US. De-identification of data is managed at the network level and is certified through a formal assessment by a qualified expert, as stipulated by the HIPAA Privacy Rule. To maintain patient confidentiality, TriNetX conceals patient counts of fewer than 10. Clinical data are obtained directly from the electronic health records of the participating organizations and supplemented by a built-in natural language processing system that extracts information from clinical documents. Comprehensive quality assurance is conducted at the point of extraction from the electronic health records, ensuring data are included in a systematic and standardized format. The database encompasses both inpatient and outpatient records, as well as prescription claims. The platform only displays aggregate data and statistical summaries to safeguard patient health information, ensuring that data remain de-identified throughout all levels of access and dissemination.

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Study participants and cohorts

We performed a real-time search and analysis of the US Collaborative Network in the TriNetX platform. We identified adults aged ≥18 years old who were diagnosed with IBD between January 1, 2013, and December 31, 2022, using at least 2 International Classification of Disease, Tenth Revision, Clinical Modification (ICD-10-CM) codes for UC (K51*) and CD (K50*), and were taking at least 1 IBD-related medication: mesalamine, sulfasalazine, balsalazide, olsalazine, azathioprine, 6-mercaptopurine, methotrexate, infliximab, adalimumab, golimumab, certolizumab, vedolizumab, ustekinumab, tofacitinib, risankizumab, Upadacitinib, or ozanimod. Complex case definitions for the identification of IBD cohorts, which include ≥1 ICD-10-CM code plus a relevant IBD-related prescription from administrative and claims databases, have been shown to have ≥80% positive predictive value (PPV) and ≥85% specificity [14]. The TriNetX database has been used previously in published studies of patients with IBD [15,16]. Patients with EoE were identified using ICD-10-CM and ICD-9 codes for eosinophilic esophagitis (K20). Validation studies show that a single ICD code for EoE yields 99% specificity and 70% PPV [17,18]. The nonIBD comparison cohort was comprised of adults with no IBD ICD-10-CM codes or prescriptions in their records during 20132022.

Ethical considerations

The study used only de-identified data certified as such by TriNetX; therefore, institutional review board approval and informed consent were not required under 45 CFR §46.102(f).

Study aims

Primary aim

The primary aim of this study was to evaluate the incidence and risk factors of developing EoE among patients with IBD, including both UC and CD, compared to a non-IBD cohort. Incidence of EoE was stratified based on type of IBD, age, sex and race. Patients with UC and CD within the IBD cohort were stratified based on age (<40 vs. ≥40 years), sex, race, smoking

status, obesity (defined by ICD-10-CM codes and/or body mass index [BMI] ≥30 kg/m^2), primary sclerosing cholangitis (PSC), IBD medications (5-aminosalicylic acid, tumor necrosis factor inhibitor [TNFi], non-TNFi advanced therapies and immunomodulators azathioprine, 6-mercaptopurine, methotrexate), and IBD-related surgery.

Secondary aims

The secondary aims of the study were as follows:

- Compare the natural history of UC and CD in patients with and without EoE prior to the diagnosis of IBD. We assessed the risk of intravenous steroid use, oral steroid use, initiation of advanced therapy, risk of new-onset PSC, and IBD-related surgery within a 5-year period. A 5-year follow up was chosen to allow for adequate sample size and follow up. Patients were required to have a diagnosis of IBD prior to 2020 to allow for an adequate follow-up period. We also assessed the risk of stricturing and/or fistulizing disease in patients with CD. Each outcome was identified by the appropriate ICD-10-CM, Current Procedural Terminology, or ICD-10 Procedure Coding System codes, which can be found in Supplementary Table 1.
- Compare the natural history of EoE in patients with and without IBD prior to the diagnosis of EoE. We assessed the risk of esophageal stricture requiring dilation, food impaction, and use of dupilumab within 5 years.

Statistical analysis

Statistical analysis was performed using the TriNetX platform, specifically leveraging the browser-based real-time analytics tool TriNetX Live (TriNetX LLC, Cambridge, MA). Baseline characteristics of the study cohorts were summarized using means, standard deviations and proportions for continuous and categorical variables. Relevant covariates, including demographics, comorbidities, laboratory values and prior use of IBD medications, were identified for analysis. To adjust for potential confounders, 1-to-1 propensity score matching (1:1) was conducted between the 2 sub-cohorts of interest, ensuring balance across key variables such as age, sex, race, proton pump inhibitor use, topical budesonide or fluticasone use, obesity and nicotine dependence. The TriNetX platform employs logistic regression models to calculate propensity scores based on the user-specified covariates for each individual in the dataset. These scores are subsequently used to match patients in a 1:1 ratio using a greedy nearest-neighbor algorithm, with a maximum caliper width of 0.1 pooled standard deviations, to minimize selection bias. The platform also randomizes the order of the rows to mitigate bias from the matching process. Standardized mean difference after propensity-score matching indicates the success of matching a covariate between the 2 cohorts. A standardized mean difference <0.1 indicates that the difference between the cohorts for the covariate is small. After matching, the risk of each outcome was evaluated and reported as an adjusted odds ratio (aOR) with 95% confidence interval (CI).

Results

Incidence of EoE in IBD patients

We identified 234,582 patients with IBD, of whom 108,095 had UC and 123,945 had CD. The overall incidence of EoE was 0.60% in the IBD cohort and 0.20% in the non-IBD cohort. After PSM, there was a higher risk of EoE in the IBD cohort compared to the non-IBD cohort (aOR 2.88, 95%CI 2.59-3.19; P<0.001). There was a higher risk of EoE in both the UC cohort (aOR 2.9, 95%CI 2.49-3.39; P<0.001) and the CD cohort (aOR 3.53, 95%CI 3.09-4.02; P<0.001) compared to the non-IBD cohort (Table 1).

Among age groups, the highest incidence of EoE in the overall IBD cohort was observed in patients aged 30-34 years, with a rate of 0.60%. This pattern was consistent in both UC (0.69%) and CD (0.66%) cohorts. As age increased, the incidence of EoE progressively declined across all cohorts, with the lowest incidence seen in those aged 70-74 years (0.17% in the IBD cohort, 0.23% in the UC cohort and 0.29% in the CD cohort) (Fig. 1). In the overall IBD cohort, the incidence in males was 0.85%, compared to 0.44% in females. This trend persisted in both UC (0.83% in males vs. 0.43% in females) and CD (1.16% in males vs. 0.55% in females) cohorts. White patients had the highest incidence rates across all cohorts: 0.67% in the overall IBD cohort, 0.66% in the UC cohort and 0.88% in the CD cohort. In contrast, African American patients exhibited lower incidence rates, with 0.38% in the IBD cohort, 0.34% in the UC cohort and 0.49% in the CD cohort. Hispanic or Latino patients also showed a lower incidence compared to White patients, with rates of 0.56% in the IBD cohort, 0.42% in the UC cohort and 0.58% in the CD cohort (Table 2).

Table 1 Risk of EoE in patients with IBD

Risk of EoE	N (%)	aOR	95%CI	P-value
IBD total (UC and CD)	1407 (0.60%)	2.88	2.59-2.19	<0.001
Non-IBD total	491 (0.20%)			
UC total	634 (0.60%)	2.9	2.49-3.39	<0.001
Non-IBD total	219 (0.20%)			
CD total	1003 (0.83%)	3.53	3.09-4.02	<0.001
Non-IBD total	286 (0.23%)			

Non-IBD cohorts were used as the reference group for comparison

Significant associations (P<0.001) indicate an elevated risk of EoE in IBD, UC and CD cohorts compared to non-IBD controls

EoE, eosinophilic esophagitis; IBD, inflammatory bowel disease; aOR, adjusted odds ratio; CI, confidence interval; UC, ulcerative colitis; CD, Crohn's disease

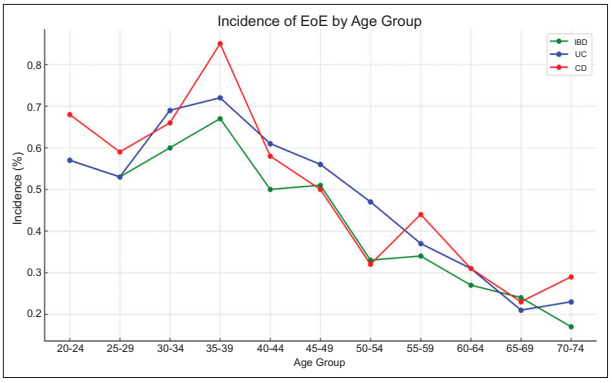

Figure 1 Incidence of EoE by age groups in IBD, UC and CD population
EoE, eosinophilic esophagitis; IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease

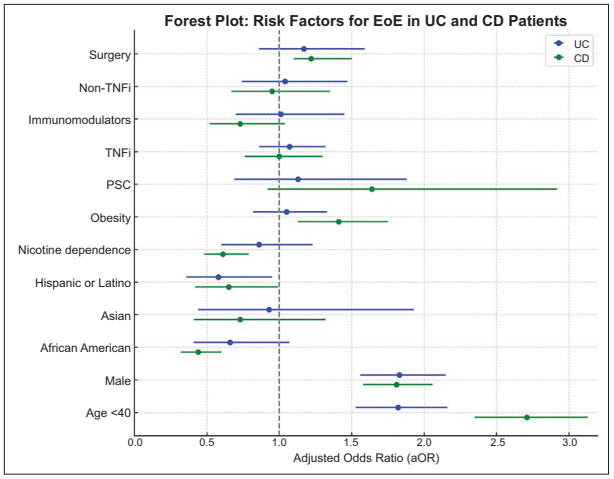

Figure 2 Forest plot of adjusted odds ratios for risk factors of EoE in patients with UC and CD
EoE, eosinophilic esophagitis; IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; PSC, primary sclerosing cholangitis; TNFi, tumor necrosis factor inhibitors

Risk factors for EoE in IBD

In the UC cohort, younger age (<40 years old) was associated with a significantly higher risk of EoE (aOR 1.82, 95%CI 1.53-2.16; P<0.001). Male sex was also associated with a higher risk of EoE (aOR 1.83, 95%CI 1.56-2.15; P<0.001) compared to female sex. Hispanic or Latino race was associated with a lower risk of EoE (aOR 0.58, 95%CI 0.36-0.95; P=0.03) compared to White race. Nicotine dependence, obesity, PSC, IBD medications and history of colectomy were not associated with a higher risk of EoE (Fig. 2, Table 3).

In the CD cohort, younger age (<40 years old) was associated with a significantly higher risk of EoE (aOR 2.71, 95%CI 2.35-3.13; P<0.001). Similarly, male sex was also associated with a higher risk of EoE (aOR 1.81, 95%CI 1.58-2.06; P<0.001) compared to female sex. African American (aOR 0.44, 95%CI 0.32-0.60; P<0.001) and Hispanic or Latino (aOR 0.65, 95%CI 0.42-0.99; P=0.04) patients with IBD had a lower risk of EoE compared to White race. Obesity (aOR 1.41, 95%CI 1.13-1.75; P=0.002), nicotine dependence (aOR 0.61, 95%CI 0.48-0.79; P<0.001), and history of prior surgery (aOR 1.22, 95%CI 1.10-1.50; P=0.04) were associated with a higher risk of EoE. PSC and IBD medications were not associated with a higher risk of EoE (Fig. 2, Table 3).

Comparative outcomes of EoE in patients with and without IBD

We identified 488 patients in the EoE-IBD cohort and 26,433 patients in the EoE control cohort. The EoE-IBD cohort had a mean age of 34±18 years; 81.8% had White race, and 38.1% had female sex. The risk of a composite outcome of esophageal dilation and food impaction was significantly lower in the EoE-IBD cohort compared to the EoE-only cohort (aOR 0.39, 95%CI 0.29-0.52; P<0.001) within 5 years. Similarly, the incidence of esophageal dilation (aOR 0.51, 95%CI 0.37-0.71; P<0.001), and food impaction alone (aOR 0.20, 95%CI 0.11-0.36; P<0.001) was lower in the EoE-IBD cohort compared to the EoE-only cohort (Table 4). No significant difference was observed in the mean number of esophageal dilations required between the 2 cohorts (P=0.24). The use of dupilumab did not differ significantly between the EoE-IBD cohort and the EoE-only cohort (aOR 1.2, 95%CI 0.51-2.79; P=0.66).

Table 2 Incidence of EoE in IBD by age, sex and race

	IBD*	UC	CD
By age	Incidence	Incidence	Incidence
20-24	0.57%	0.57%	0.68%
25-29	0.53%	0.53%	0.59%
30-34	0.60%	0.69%	0.66%
35-39	0.67%	0.72%	0.85%
40-44	0.50%	0.61%	0.58%
45-49	0.51%	0.56%	0.50%
50-54	0.33%	0.47%	0.32%
55-59	0.34%	0.37%	0.44%
60-64	0.27%	0.31%	0.31%
65-69	0.24%	0.21%	0.23%
70-74	0.17%	0.23%	0.29%
By sex	Incidence	Incidence	Incidence
Male	0.85%	0.83%	1.16%
Female	0.44%	0.43%	0.55%
By race	Incidence	Incidence	Incidence
White	0.67%	0.66%	0.88%
African American	0.38%	0.34%	0.49%
Asian	0.54%	0.64%	0.90%
Hispanic or Latino	0.56%	0.42%	0.85%

Incidence rates are presented as percentages for each subgroup stratified by age, sex, and race

*IBD includes UC and CD, with comparisons across subgroups

EoE, eosinophilic esophagitis; IBD, inflammatory bowel disease; aOR, adjusted odds ratio; CI, confidence interval; UC, ulcerative colitis; CD, Crohn's disease

Table 3 Risk factors for EoE in patients with UC and CD

UC	N (%)	aOR	95%CI	P-value	*CD*	N (%)	aOR	95%CI	P-value
Age <40	364 (0.89%	1.82	1.53-2.16	<0.001	Age <40	709 (1.34%)	2.71	2.35-3.13	<0.001
Age >40	203 (0.50%)				Age >40	263 (0.5%)			
Male	426 (0.92%	1.83	1.56-2.15	<0.001	Male	627 (1.24%)	1.81	1.58-2.06	<0.001
Female	225 (0.48%)				Female	348 (0.69%)			
Race					Race				
African American	28 (0.38%)	0.66	0.41-1.07	0.09	African American	59 (0.54%)	0.44	0.32-0.60	<0.001
White	42 (0.57%)				White	132 (1.21%)			
Asian	14 (0.57%)	0.93	0.44-1.93	0.85	Asian	20 (1.08%)	0.73	0.41-1.32	0.3
White	15 (0.62%)				White	27 (1.46%)			
Hispanic or Latino	26 (0.48%)	0.58	0.36-0.95	0.03	Hispanic or Latino	36 (0.89%)	0.65	0.42-0.99	0.04
White	44 (0.82%)				White	55 (1.36%)			
Nicotine dependence	56 (0.46%)	0.86	0.60-1.23	0.41	Nicotine dependence	101(0.48%)	0.61	0.48-0.79	<0.001
No Nicotine dependence	65 (0.54%)				No Nicotine dependence	163 (0.77%)			
Obesity	138 (0.64%)	1.05	0.82-1.33	0.66	Obesity	196 (0.82%)	1.41	1.13-1.75	0.001
No obesity	131 (0.60%)				No obesity	139 (0.58%)			
PSC	33 (1.007%)	1.13	0.69-1.88	0.6	PSC	31 (1.92%)	1.64	0.92-2.92	0.08
No PSC	29 (0.88%)				No PSC	19 (1.17%)			
Medications					Medications				
TNFi	177 (0.79%)	1.07	0.86-1.32	0.51	TNFi	108 (0.76%)	1	0.76-1.30	>0.99
5-ASA	165 (0.74%)				5-ASA	108 (0.76%)			
Immunomodulators	60 (0.61%)	1.01	0.70-1.45	0.92	Immunomodulators	57 (0.62%)	0.73	0.52-1.04	0.08
5-ASA	59 (0.60%)				5-ASA	77 (0.84%)			
Non-TNFi	67 (0.61%)	1.04	0.74-1.47	0.79	Non-TNFi	63 (0.80%)	0.95	0.67-1.35	0.79
5-ASA	64 (0.58%)				5-ASA	66 (0.84%)			
Total colectomy	89 (0.78%)	1.17	0.86-1.59	0.3	Surgery	208 (1.01%)	1.22	1.10-1.50	0.04
No colectomy	76 (0.67%)				No Surgery	170 (0.83%)			

EoE, eosinophilic esophagitis; UC, ulcerative colitis; CD, Crohn's disease; aOR, adjusted odds ratio; CI, confidence interval; PSC, primary sclerosing cholangitis; TNFi, tumor necrosis factor inhibitors; 5-ASA, 5-aminosalicylic acid derivatives

Discussion

Utilizing a large multi-institutional database, our study found a significant association between EoE and IBD, demonstrating that patients with IBD have a greater risk of developing EoE compared to the general population. The incidence was highest in the younger cohorts and male sex, and lower in patients of African American or Hispanic race. The analysis revealed that younger age and male sex were significant risk factors for EoE in both UC and CD, while additional risk factors in patients with CD include obesity and a history of CD-related surgery. We also found that patients with IBD and concurrent EoE had a lower risk of esophageal dilation and food impaction, compared to patients with EoE alone.

Our findings align with and expand upon those of previous studies that reported a higher incidence of EoE in patients with IBD. Uchida *et al* reported that individuals with IBD had 15 times the odds of EoE diagnosis compared to the general population (aOR 15.39, 95%CI 7.68-33.59) [19]. A study by Fan *et al* reported that the prevalence of EoE in patients with IBD was approximately 0.1%, which is higher than the estimated 0.05% prevalence in the general population [1,11]. Previously, numerous population-based studies in the US and other industrial countries have reported prevalence rates of EoE in the adult and pediatric population; these ranged from 2.3 to 400 cases per 100,000 in various time frames between 1976 and 2014, suggesting a rising trend in EoE diagnosis [4]. Our study corroborates these findings and provides updated estimates, showing a higher incidence of

Table 4 Esophageal outcomes in patients with EoE and IBD

EoE outcomes in IBD	N	%	aOR	95%CI	P-value
Composite of dilation or food impaction	74	8.30%	0.39	0.29-0.52	<0.001
	166	18.70%			
Esophageal dilation	64	7.20%	0.51	0.37-0.71	<0.001
	116	13.09%			
No. of dilation (mean)	2.8				0.24
	2.08				
Dupilumab use	12	1.35%	1.2	0.51-2.79	0.66
	10	1.12%			
Food impaction	14	1.58%	0.2	0.11-0.36	<0.001
	65	7.33%			

EoE, eosinophilic esophagitis; IBD, inflammatory bowel disease; aOR, adjusted odds ratio; CI, confidence interval

EoE in patients with IBD [20]. However, Sonnenberg *et al* reported that EoE was less common in the overall IBD case population than in the control population (aOR 0.64, 95%CI 0.51-0.78) [21]. The inverse relationship seen in the above study can be explained by its case–control study design, and by the use of antisecretory medication in the treatment of gastroesophageal reflux disease and EoE, which may influence the gastrointestinal microbiome and IBD occurrence, as the authors pointed out [21]. On the other hand, patients with IBD are more likely to undergo an upper endoscopy. This practice is likely to increase the surveillance bias for detecting a new EoE diagnosis [19]. The consistently higher odds of EoE in CD than in UC can partly be attributed to surveillance bias: routine esophagogastroduodenoscopy is more common in CD, because up to 60% of patients show macroscopic uppergastrointestinal involvement when systematically scoped, whereas upper endoscopy is not standard in uncomplicated UC. Thus, there is a greater likelihood of EoE detection in CD [22]. The paradox persists, however, that UC and EoE share a type2 cytokine milieu, whereas CD is predominantly type1/Th17; one mechanistic explanation is that suppressing Th1 inflammation in CD, whether spontaneously or through antiTNF and related biologics, may shift the immune balance toward residual Th2 pathways, creating conditions favorable for EoE [23].

In our study, younger age, male sex, and white race were associated with higher odds of developing EoE in patients with IBD. Studies have shown that EoE is up to 3 times more common in males than females in the general population, with a peak incidence in the third decade of life [2,24]. This sex-related disparity may be attributed to differences in gene transcription within mast cells and eosinophils, which are key players in the pathophysiology of EoE [25]. The earlier onset could be due to a higher genetic burden of disease in this subset, leading to a younger age at diagnosis and potentially more severe disease presentations, akin to other immune-mediated conditions such as type 1 diabetes mellitus and systemic lupus erythematosus. [26-30]. Nicotine dependence may protect against EoE in IBD, especially CD. Koutlas *et al* reported that patients with EoE were significantly less likely to have a history of smoking than controls (23% vs. 47%, P<0.001). [31]. Obesity was found to be a significant risk factor for EoE in patients with CD. The relationship between EoE and BMI has been less thoroughly investigated. A prospective cohort study indicated that patients with EoE had lower BMIs compared to controls, while a decreasing BMI was correlated with fibrostenotic features such as esophageal strictures and narrowing [32]. Similarly, Ketchem *et al* found that as BMI increases in patients with EoE, the likelihood of histologic, symptomatic and endoscopic responses to topical corticosteroids diminishes, with obese patients experiencing an approximately 40% decrease in response odds [33].

Our study indicates that the natural history of patients with concurrent EoE and IBD is favorable compared to those with EoE alone. Malik *et al* reported a significantly lower risk of food bolus impaction in the EoE-IBD cohort (adjusted hazard ratio (aHR) 0.445, 95%CI 0.269-0.734; P=0.0011) and a non-significant trend toward a reduced need for esophageal stricture dilation (aHR 0.985, 95%CI 0.73-1.33) [13]. Similarly, Limketkai *et al* found a significantly lower risk of food bolus impaction and esophageal stricture dilation, and a lower overall composite risk of EoE-related complications in patients with both EoE and IBD [34]. One potential explanation for these better outcomes is the frequent use of systemic corticosteroids in patients with IBD, which may also mitigate EoE-related complications [35,36]. Additionally, it has been suggested that patients with IBD, who are accustomed to long-term medication adherence, may exhibit higher compliance with their EoE treatment regimens, thereby reducing the risk of EoE-related complications [34]. Another reason for this finding maybe that EoE is usually diagnosed after IBD—Fan *et al* reported that 92% of dualdiagnosis patients developed esophageal eosinophilia a mean 9.6 years following their IBD diagnosis, suggesting a shorter EoE disease duration that may limit timedependent fibrostenotic complications [11].

Our study has several notable strengths. Utilizing a comprehensive, multi-institutional database significantly enhances the generalizability of our results. The novel contribution of our study lies in the identification of specific risk factors that predispose patients with IBD to the development of EoE. While previous research has suggested a general association, our study is among the first to systematically stratify risk by age, sex and IBD subtype, thereby providing a more detailed risk profile. Furthermore, our use of robust propensity score matching minimizes confounding and selection biases, thereby providing a more reliable estimate of the association between EoE and IBD outcomes. Lastly, stratifying risk factors based on IBD subtypes and demographic characteristics allows for a more nuanced understanding of the relationship between these conditions.

However, there are several limitations to consider. The retrospective nature of the study limits our ability to establish causality. Moreover, reliance on diagnostic codes to identify

cases of EoE and IBD may lead to misclassification bias, as the accuracy of coding can vary between institutions. The lack of data on specific IBD medication regimens, adherence and lifestyle factors, such as diet and smoking, further limits our ability to fully elucidate the relationship between these conditions. Finally, our study did not differentiate between subtypes of EoE (e.g., proton pump inhibitor-responsive vs. non-responsive), which could have implications for treatment outcomes and prognosis. Histology and endoscopy data are also not available from the database, which limits our ability to analyze these as potential predictors and outcomes.

In conclusion, our study provides updated epidemiological data in patients with EoE and IBD in the biologic era. Our findings underscore the importance of comprehensive management strategies that address both conditions to improve outcomes and quality of life for affected patients.

Summary Box

What is already known:

- Eosinophilic esophagitis (EoE) and inflammatory bowel disease (IBD) are immunemediated gastrointestinal diseases with overlapping genetic and environmental influences
- Several singlecenter studies suggest higher EoE prevalence in IBD, but estimates vary
- Data on risk modifiers (age, sex, obesity) and on the clinical course of EoE in IBD are limited

What the new findings are:

- IBD patients had a 3fold incidence of EoE compared with matched nonIBD controls
- Age <40 years and male sex raised EoE risk in both ulcerative colitis and Crohn's disease; obesity and prior surgery were additional predictors in Crohn's disease
- African American and Hispanic patients with IBD exhibited a lower risk of EoE than White patients
- Concurrent IBD was associated with lower 5year rates of esophageal dilation and food impaction than EoE without IBD, indicating a milder fibrostenotic course

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or inhibitors; 5-ASA, 5-aminosalicylic acid derivatives.

Supplementary material

Supplementary Table 1 Before and after propensity score matching for calculating EoE outcomes in EoE in IBD, and EoE without IBD cohorts

Category	Metric	EoE + IBD	EoE without IBD	Std. Diff.
Demographics				
Age at index	Mean ± SD	32.5±17.7 (n=840)	33.9±17.7 (n=27,286)	0.0799
	After matching	32.5±17.7 (n=840)	31.9±17.2 (n=840)	0.033
White	% of cohort	81.19% (n=682)	80.76% (n=22,036)	0.011
	After matching	81.19% (n=682)	82.38% (n=692)	0.0308
Male	% of cohort	63.10% (n=530)	59.51% (n=16,238)	0.0737
	After matching	63.10% (n=530)	64.64% (n=543)	0.0322
Black or African American	% of cohort	4.76% (n=40)	4.24% (n=1,156)	0.0253
	After matching	4.76% (n=40)	4.17% (n=35)	0.0288
Hispanic or Latino	% of cohort	4.29% (n=36)	3.78% (n=1,032)	0.0256
	After matching	4.29% (n=36)	3.69% (n=31)	0.0304
Asian	% of cohort	1.55% (n=13)	1.17% (n=318)	0.033
	After matching	1.55% (n=13)	1.19% (n=10)	0.0307
Medication				
Proton pump inhibitors	% of cohort	62.98% (n=529)	52.11% (n=14,219)	0.2212
	After matching	62.98% (n=529)	62.86% (n=528)	0.0025
Fluticasone	% of cohort	24.05% (n=202)	24.08% (n=6,571)	<0.001
	After matching	24.05% (n=202)	23.57% (n=198)	0.0112
Budesonide	% of cohort	23.45% (n=197)	8.56% (n=2,336)	0.4148
	After matching	23.45% (n=197)	23.33% (n=196)	0.0028

EoE, eosinophilic esophagitis; IBD, inflammatory bowel disease