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ORIGINAL ARTICLE

A Comprehensive Global Population-Based Analysis on the Coexistence of Eosinophilic Esophagitis and Inflammatory Bowel Disease

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Abstract

Background We explored inflammatory bowel disease (IBD) and eosinophilic esophagitis (EoE) coexistence using a global dataset. Investigating their epidemiology, risks, and impact, we aimed to enhance the understanding of concurrent diagnoses and patient outcomes.

Methods A retrospective population-based cohort study was conducted using deidentified patient data from the TriNetX database (2011–2022). We estimated the incidence and prevalence of EoE in patients with IBD, including both Crohn's disease (CD) and ulcerative colitis (UC), and vice versa. Risks of select immune-mediated conditions and disease complications were compared among patients with EoE, IBD, or concurrent diagnoses.

Results Our results included 174,755 patients with CD; 150,774 patients with UC; and 44,714 patients with EoE. The risk of EoE was significantly higher among patients with CD (prevalence ratio [PR] 11.2) or UC (PR 8.7) compared with individuals without IBD. The risk of IBD was higher in patients with EoE (CD: PR 11.6; UC: PR 9.1) versus those without EoE. A propensity-matched analysis of IBD patients revealed that, when comparing patients with and without EoE, the relative risk of immune-mediated comorbidities was significantly greater for celiac disease, IBD-related inflammatory conditions, eczema and asthma (CD: $n=1896$; UC: $n=1231$; $p<0.001$). Patients with a concurrent diagnosis of EoE and IBD had a higher composite risk of IBD-related complications (CD: adjusted HR (aHR) 1.14, $p<0.005$; UC: aHR 1.17, $p<0.01$) and lower risk of food bolus impaction (aHR 0.445, $p=0.0011$).

Conclusion Simultaneous EoE and IBD increased IBD-related complications risk, needing more treatment (glucocorticoids, biologic therapy, abdominal surgery), while reducing EoE-related issues like food bolus impaction.

Key Message

• What is already known?: There is a significantly higher prevalence of EoE among IBD patients and vice versa, but existing research has yielded inconsistent findings regarding the development of EoE-related or IBD-related complications among patients with a co-diagnosis of both conditions.
• What is new here?: This study represents the first globally-representative population-based study with inclusion of patients enrolled in government-funded insurance plans that examines the overlapping features of EoE and IBD.
• How can this study help patient care?: This research underscores the need for vigilant monitoring and a meticulous approach to potential complications in patients diagnosed with both conditions as treatment methodologies continue to evolve particularly in the realm of biologic therapies.

Keywords Eosinophilic esophagitis · Inflammatory bowel disease · Prevalence · Epidemiology

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Introduction

Eosinophilic esophagitis (EoE) and inflammatory bowel disease (IBD) are chronic, immune-mediated diseases with significant clinical implications. EoE is conceptually defined as a chronic, immune/antigen-mediated esophageal disease involving clinical symptoms of esophageal dysfunction with histologic evidence of eosinophil-predominant inflammation [1]. On the other hand, IBD encompasses Crohn's disease (CD) and ulcerative colitis (UC), which both involve aberrant immune responses to microbes in the gut with an associated genetic susceptibility in affected individuals [2]. Previous studies have highlighted the significant overlap between characteristics of both EoE and IBD in terms of the pathogenesis (shared cytokine and helper T cell (Th)-mediated mechanisms and epithelial barrier disruption), epidemiology trends (both EoE and IBD demonstrating rising incidence and prevalence), and treatment principles (use of glucocorticoids and biologics) [3–6]. Finally, genome-wide association studies have identified loci linked to both EoE and IBD, supporting a possible genetic predisposition to developing these conditions [7, 8].

While previous literature has demonstrated that the incidence and prevalence of both EoE and IBD are rising, robust data evaluating the relationship of IBD and EoE co-diagnosis is not yet available. To date, few studies have examined this relationship and its implications on the likelihood of complications related to either disease. Furthermore, existing research has yielded inconsistent findings regarding the development of EoE-related or IBD-related complications among patients with a co-diagnosis of both conditions [5, 9, 10]. For example, in 2019, Lemketkai et al., seeking to investigate the epidemiology of concurrent EoE and IBD, reported a 3–5 times higher incidence of EoE in IBD patients compared to those without IBD in a large population-based prospective cohort study [5]. However, in 2021, aiming to confirm the positive association between EoE and IBD, Sonnenberg et al. published a case-control study using a national electronic database of 302,061 patients who underwent same day bidirectional endoscopy from 2009 to 2016. They demonstrated that EoE was less common among patients with IBD, CD, and microscopic colitis compared to a control group without any type of IBD, microscopic colitis, or GERD diagnosis (adjusted odds ratio [aOR] IBD: 0.64 (95% CI 0.51–0.78), aOR CD: 0.41(95% CI 0.27–0.60), aOR microscopic colitis: 0.68 (95% CI 0.45–0.98)) [10]. The discrepancy in conclusions between Lemketkai and Sonnenberg may be the result of certain underrepresented populations in the analyzed datasets. Considering these inconsistencies, our study intends to illuminate the relationship between the incidence and prevalence of EoE and IBD. Employing an extensive, up-to-date, and global patient dataset, we aim to provide a more accurate and comprehensive perspective on the coexistence of these conditions and its implications on patient outcomes.

Methods

Study Design and Database

A retrospective population-based cohort study was conducted using deidentified patient data from the TriNetX database (2011–2022). The TriNetX database encompasses a global network of 102 healthcare organizations (HCOs) across 14 different countries, including 126,569,535 patients covered by government-sponsored insurance plans such as Medicare and Medicaid. TriNetX treats all counts between one and ten to be equivalent [11]. The MetroHealth institutional review board has deemed studies that use the TriNetX database are exempt from IRB approval due to the aggregated and de-identified nature of the data in the database at the standard defined in Section § 164.514(a) of the HIPAA Privacy Rule. The results reported here follow the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for cohort studies [12].

Patient Selection

All patients in the database from 2011 to 2022 were included in the study. This time interval represents the timeframe from three years after the EoE diagnostic code was first made available through the latest year of available data. To identify patients, the International Classification of Disease (ICD)-10 diagnostic codes were used to identify patients with EoE (K20.0), CD (K50.x) and UC (K51.x) between 2011 and 2022. To reduce the risk of misclassification of EoE or IBD, identification required that the code recurred on at least two occasions separated by at least 30 days.

Evaluation of Immune-Mediated Conditions and Complications

In this study, the risks of developing select Th1 and Th2 associated immune-mediated conditions were evaluated for patients with EoE, IBD, and EoE and IBD co-diagnosis. Selected Th1-mediated diseases included in the analysis were celiac disease (K90.0), IBD-associated rheumatologic diseases (spondyloarthropathies (M45-M49), rheumatoid arthritis (M05-M06), enteropathic arthropathies (M07), juvenile arthritis (M08)), and psoriasis (L40). Selected Th2-mediated diseases included in the analysis were eczema/atopic dermatitis (L20) and asthma (J45). Selected disease related complications were also evaluated for patients

with EoE, IBD, and EoE and IBD co-diagnosis using the appropriate ICD-10 and Common Procedural Terminology (CPT) codes. Selected EoE-related complications included need for esophageal stricture dilation (CPT: 43,195, 43,214, 43,233, 43,249, 43,450 and 43,453) and occurrence of food bolus obstruction (T18.12). IBD-related complications were defined as the need for use of systemic glucocorticoids (injected or orally administered), initiation of IBD-indicated biologic agents (certolizumab pegol, golimumab, infliximab, natalizumab, ustekinumab, vedolizumab), and surgical intestinal resection. Intestinal resection was identified by CPT codes: 44,120, 44,121, 44,160, 44,202, 44,205, 44,140–44,160, and 44,204–44,212.

Statistical Analysis

Descriptive analytics were used to characterize the patient cohorts and estimate the incidence and prevalence of EoE in patients with IBD (including both CD and UC) and vice versa. The incidence of EoE and IBD was defined as the number of new cases over the total follow-up time in person-days. Patients with less than six months of follow-up time prior to the diagnosis of EoE or IBD were considered prevalent cases. Risks of select immune-mediated conditions were compared among patients with EoE, IBD, or concurrent diagnoses. We utilized the TriNetX platform which itself utilizes R 4.0.2. for calculations and statistical analyses. For the purposes of cox-regression analyses, the packages Hmisc 1–1 and Survival 3.2-3 were used. Kaplan-Meier methods were used to determine the risk of EoE-related or IBD-related complications among patients with coexisting conditions. Categorical variables were assessed using a chi-squared test, while continuous variables were assessed using a two-sided t test with P-value < 0.05. Propensity score matching (PSM) was used to adjust for confounding factors such as age, sex, race, and ethnicity. We performed a univariate Cox-regression analysis on propensity matched cohorts. Cohorts were matched one-to-one on relevant covariates using greedy nearest neighbor algorithms with a caliper width of 0.1 pooled standard deviations. Covariate characteristics showing a standardized mean difference lower than 0.1 between cohorts were considered well-matched as per Haukoos et al. [13]. Using the aforementioned statistical packages, a univariate Cox-proportional Hazards model was executed, and the proportional hazards assumption was validated using Schoenfeld residuals.

Results

Overall, the database contained 131,953,725 patients for primary analysis. The mean age of the patient cohort without EoE or IBD was 43.2 years (SD 23.9) with 54% female composition. The average HCO on the TriNetX network provides at least seven years of follow-up (Table 1).

EoE in Patients with IBD

Among the 174,755 patients with CD, the incidence rate of EoE was 1.460 per 1,000 person-years and the prevalence of EoE was 1.059% (Table 2). The population of patients concurrently diagnosed with CD and EoE presented a higher proportion of males (60% vs. 40%) and exhibited a younger average age (33.8 vs. 48.9 years, $p < 0.0001$) when compared to those diagnosed solely with CD. Similarly, among the 150,774 patients with UC, the incidence rate of EoE was 1.095 per 1,000 person-years and the prevalence of EoE was 0.817%. In this population, those diagnosed with both UC and EoE also trended towards a greater percentage of males (60% vs. 40%) and were younger (mean age 38.3 vs. 53.5 years, $p < 0.0001$) when juxtaposed with patients suffering from UC without an EoE diagnosis.

The prevalence of EoE was higher among patients with CD (prevalence ratio [PR] $1.059/0.094 = 11.2$) or UC (PR $0.817/0.094 = 8.7$) compared with patients without IBD (Table 3). The incidence rate of EoE was significantly higher in male IBD patients when stratified by gender (CD: 2.19 per 1,000 person-years; UC: 1.46 per 1,000 person-years) compared to their female counterparts (CD: 1.095 per 1,000 person-years; UC: 0.73 per 1,000 person-years). Furthermore, EoE prevalence was consistently higher in males when compared to females, regardless of IBD diagnosis

Table 1 – Follow up rate stratified by disease

Primary Diagnosis	Subsequent Diagnosis	Follow up at 6 months	Follow up at 1 year	Follow up at 3 years	Follow up at 5 years	Follow up at 10 years
CD	EoE	82.53%	72.54%	40.30%	18.93%	2.60%
UC	EoE	81.42%	71.82%	41.78%	20.18%	2.40%
EoE	CD	79.40%	70.47%	37.22%	18.13%	1.42%
EoE	UC	82.74%	72.20%	41.82%	21.86%	2.02%
No IBD	EoE	79.37%	69.80%	43.27%	25.22%	4.42%
No EoE	CD	81.27%	73.73	51.70%	34.96%	9.42%
No EoE	UC	81.25%	73.30%	50.26%	33.10%	8.83%

Table 2 – Eosinophilic esophagitis (EoE) in patients with inflammatory bowel disease (IBD) and without IBD

	Crohn's Disease			Ulcerative Colitis			General population		
	EoE	No EoE	p value	EoE	No EoE	p value	EoE	No EoE	p value
N	1763	172,992	NA	1138	149,546	NA	88,037	131,953,725	NA
Incidence Rate of EOE (cases/ person-year) from 2011–2022	0.00146	NA	NA	0.001095	NA	NA	NA	NA	NA
EoE prevalence from 2011–2022	1.06%	NA	NA	0.82%	NA	NA	0.094%	NA	NA
Age									
pediatric, n (%)	351 (18.5)	6077 (26.3)	NA	187 (15.2)	3462 (2.3%)	NA	11,016 (25.3)	21,250,559 (16.1)	NA
adult, n (%)	1545 (81.5)	170,745 (73.7)	NA	1045 (84.8)	146,084 (97.7)	NA	32,570 (74.7%)	110,703,166 (83.9)	NA
Overall, years (SD)	33.8 ± 18.4	48.9 ± 19.4	< 0.0001	38.3 ± 19.3	53.5 ± 19.7	< 0.0001	34.4 ± 19.7	43.2 ± 23.9	< 0.0001
Sex, n (%)									
Male	1134 (60%)	76,324 (44%)	< 0.0001	742 (60%)	68,380 (47%)	< 0.0001	27,352 (63%)	56,203,402 (46%)	< 0.0001
Female	762 (40%)	95,747 (56%)	< 0.0001	488 (40%)	77,124 (53%)	< 0.0001	16,225 (37%)	65,768,258 (54%)	< 0.0001
Race, n (%)									
White	1544 (81%)	125,965 (73%)	< 0.0001	1004 (82%)	105,364 (72%)	< 0.0001	35,131 (81%)	50,171,363(41%)	< 0.0001
Unknown	190 (10%)	28,699 (17%)	< 0.0001	127 (10%)	27,184 (19%)	< 0.0001	4808 (11%)	57,191,178(47%)	< 0.0001
Black or African American	127 (7%)	14,465 (8%)	0.0077	73 (6%)	9,276 (6%)	0.5254	2899 (7%)	11,468,417 (10%)	< 0.0001
Asian	33 (2%)	2534 (1%)	0.3356	24 (2%)	3,287 (2%)	0.4671	596 (1%)	2,898,820 (2%)	< 0.0001
Native Indian or Alaska Native	10 (1%)	353 (0%)	0.0022	10 (1%)	326 (0%)	< 0.0001	121 (0%)	357,830 (0%)	< 0.0001
Immune-mediated comorbidities, n (Risk %)	($n = 1896$)*			($n = 1231$)*			($n = 43,586$)	($n = 122,512,880$)	
Celiac disease	158 (8.33%)	55 (2.90%)	< 0.0001	137 (11.13%)	35 (2.84%)	< 0.0001	786 (1.80%)	133,348 (0.11%)	< 0.0001
IBD-associated rheumatologic condition	333 (17.56%)	251 (13.24%)	0.0002	218 (17.71%)	146 (11.86%)	< 0.0001	2982 (6.84%)	3,751,010 (3.068%)	< 0.0001
Eczema	69 (3.64%)	34 (1.79%)	0.0005	40 (3.25%)	19 (1.54%)	0.0057	2254 (5.17%)	858,594 (0.702%)	< 0.0001
Asthma	459 (24.21%)	214 (11.29%)	< 0.0001	299 (24.29%)	127 (10.32%)	< 0.0001	10,563(24.24%)	4,217,502 (3.45%)	< 0.0001

*Propensity matched data

(CD: 1.391% vs. 0.701%; UC: 1.081% vs. 0.603%); even among non-IBD patients, males exhibited a higher EoE prevalence (0.099% vs. 0.057%).

Among the 47,615 patients with EoE, the incidence of CD and UC were 4.015 and 3.285 per 1,000 person-years, respectively. The prevalence of CD and UC were 3.041% and 2.240%, respectively. There was 11.6-fold (3.041/0.262) higher prevalence of CD and 9.1-fold (2.24/0.247) higher prevalence of UC among patients with versus without EoE (Table 3). Men and women with EoE had similar incidence rates of CD and UC, but there was a trend toward a higher incidence rate of IBD among men with EoE (CD: 4.38 vs. 4.015; UC: 3.285 vs. 2.92 per 1,000 person-years). The prevalence of IBD among patients with EoE was greater in women versus men (CD: 3.097% vs. 3.008%; UC: 2.393% vs. 2.163%). The prevalence of CD among patients without EoE was greater in women versus men (0.271% vs. 0.252%). The prevalence of UC among patients without EoE was very similar among sexes with a slight trend towards greater prevalence in men vs. women (0.248% vs. 0.247%).

Table 3 – Risk of eosinophilic esophagitis (EoE) in patient with inflammatory bowel disease (IBD) and risk of IBD in patients with EoE

Primary DX	Subsequent DX	Overall		Ped		Adult		Male		Female	
Incidence Proportion		Rate (%)	Total # of indecent cases	Rate (%)	Total # of indecent cases	Rate (%)	Total # of indecent cases	Rate (%)	Total # of indecent cases	Rate (%)	Total # of indecent cases
CD	EoE	1.00	1697	5.30	340	0.89	1486	1.38	1044	0.69	653
UC	EoE	0.81	1186	4.92	179	0.72	1007	1.07	716	0.62	469
EoE	CD	2.92	1300	2.48	272	3.06	1028	2.90	803	2.95	497
EoE	UC	2.18	971	1.49	164	2.40	807	2.11	583	2.29	387
Incidence Rate (case/person-year)											
CD	EoE	0.00146	NA	0.008395	NA	0.001095	NA	0.00219	NA	0.001095	NA
UC	EoE	0.001095	NA	0.00803	NA	0.001095	NA	0.00146	NA	0.0073	NA
EoE	CD	0.004015	NA	0.004015	NA	0.00438	NA	0.00438	NA	0.004015	NA
EoE	UC	0.003285	NA	0.00219	NA	0.003285	NA	0.003285	NA	0.00292	NA
Prevalence (%)		Rate (%)	Total # of prevalent cases	Rate (%)	Total # of prevalent cases	Rate (%)	Total # of prevalent cases	Rate (%)	Total # of prevalent cases	Rate (%)	Total # of prevalent cases
CD	EoE	1.01	1712	5.31	341	0.90	1500	1.39	1051	0.70	661
UC	EoE	0.82	1200	4.97	181	0.73	1019	1.08	725	0.60	469
no IBD	EoE	0.08	80,772	0.10	17,187	0.07	63,585	0.10	47,966	0.06	32,787
EoE	CD	3.04	1356	2.48	272	3.23	1084	3.01	833	3.10	523
EoE	UC	2.24	999	1.50	165	2.48	834	2.16	599	2.39	399
no EoE	CD	0.26	278,786	0.07	12,855	0.30	265,931	0.25	122,718	0.27	155,989
no EoE	UC	0.25	263,311	0.04	6891	0.29	256,420	0.25	120,968	0.25	142,269

CD: Crohn's disease; UC: Ulcerative colitis

Risk of Other Immune-Mediated Comorbidities

In a PSM analysis of IBD patients with versus without EoE, the risk of predominantly Th1-mediated conditions was greater for celiac disease (CD: 8.333% vs. 2.901%, $n=1896$, $p<0.0001$; UC: 11.129% vs. 2.843%, $n=1231$, $p<0.0001$) and IBD-associated rheumatologic conditions (CD: 17.563% vs. 13.238%, $n=1896$, $p=0.002$; UC: 17.709% vs. 11.86%, $n=1231$, $p<0.0001$) (Table 2). In an analysis of patients without IBD with versus without EoE, the risk was greater for celiac disease (1.803% vs. 0.109%, $p<0.0001$) and IBD-associated rheumatologic conditions (6.842% vs. 3.068%, $p<0.0001$). In a PSM analysis of IBD patients with versus without EoE, the risk of predominantly Th2-mediated conditions was greater for eczema (CD: 3.639% vs. 1.793%, $n=1896$, $p=0.0005$; UC: 3.249% vs. 1.543%, $n=1231$, $p=0.0057$) and asthma (CD: 24.209% vs. 11.287%, $n=1896$, $p<0.0001$; UC: 24.289% vs. 10.317%, $n=1231$, $p<0.0001$). Likewise, in an analysis of patients without IBD with versus without EoE, the risk was greater for eczema (5.171% vs. 0.702%, $p<0.0001$) and asthma (24.235% vs. 3.45%, $p<0.0001$).

Effect of Concurrent EoE and IBD on IBD-Related Management and Complications

In patients with CD, EoE was associated with an increased composite risk of IBD-related complications (adjusted hazard ratio [aHR] 1.137 (95% CI 1.04 to 1.242), $n=1844$, $p<0.05$). Examining IBD-related complications by type, EoE with concurrent diagnosis of CD was associated with a non-statistically significant trend toward higher risk of glucocorticoid treatment (aHR 1.045 (95% CI 0.943 to 1.159), $n=1844$, $p=0.401$). EoE with concurrent diagnosis of CD was associated with a statistically significant higher risk of biologic therapy (aHR 1.184 (95% CI 1.054 to 1.329), $n=1844$, $p<0.005$). EoE with concurrent diagnosis of CD was associated with a non-statistically significant trend toward lower risk of intestinal resection (aHR 0.948 (95% CI 0.69 to 1.3), $n=1844$, $p=0.74$) (Table 4).

In patients with UC, EoE was associated with an increased composite risk of IBD-related complications (aHR 1.166 (95% CI 1.039 to 1.307), $n=1232$, $p<0.01$).

Examining IBD-related complications by type, EoE with concurrent diagnosis of UC was associated with a non-statistically significant trend toward higher risk of glucocorticoid treatment (aHR 1.107 (95% CI 0.972 to 1.454),

Table 4 Risk of complications related to inflammatory bowel disease (IBD) in patients with eosinophilic esophagitis (EoE) versus without EoE

	HR (95% CI)	p values	aHR* (95% CI) (after matching)	p values
Crohn's Disease			(*n* = 1844)	
Glucocorticoid	1.344 (1.249, 1.446)	< 0.0001	1.045 (0.943, 1.159)	0.4007
Biologic therapy	1.764 (1.627, 1.911)	< 0.0001	1.184 (1.054, 1.329)	0.0042
Abdominal surgery	0.957 (0.759, 1.207)	0.7131	0.948 (0.691, 1.3)	0.7381
Composite	1.478 (1.389, 1.572)	< 0.0001	1.137 (1.04, 1.242)	0.0046
Ulcerative Colitis			(*n* = 1152)	
Glucocorticoid	1.403 (1.282, 1.535)	< 0.0001	1.107 (0.972, 1.26)	0.123
Biologic therapy	1.929 (1.723, 2.16)	< 0.0001	1.132 (0.962, 1.333)	0.1345
Abdominal surgery	1.014 (0.716, 1.436)	0.9369	0.846 (0.528, 1.355)	0.4854
			NA	
Composite	1.54 (1.423, 1.667)	< 0.0001	1.166 (1.039, 1.307)	0.0086

*Propensity matched data

CI: confidence interval; HR: hazard ratio; aHR: adjusted hazard ratio

Table 5 Risk of complications related to eosinophilic esophagitis (EoE) in patients with inflammatory bowel disease (IBD) versus without IBD

	HR (95% CI)	p values	aHR* (95% CI)	p values
Food bolus impaction	0.53 (0.35,0.79)	0.0015	0.45 (0.27,0.73)	0.0011
Esophageal stricture dilation	1.04 (0.83,1.29)	0.7509	0.99 (0.73,1.33)	0.9236
Composite	1.04 (0.83,1.29)	0.7509	0.99 (0.73,1.33)	0.9236

*Propensity matched data, *n* = 1879

CI: confidence interval; HR: hazard ratio; aHR: adjusted hazard ratio

n = 1232, *p* = 0.123). EoE with concurrent diagnosis of UC was associated with a non-statistically significant trend toward higher risk of biologic therapy (aHR 1.132 (95% CI 0.962 to 1.333), *n* = 1232, *p* = 0.1345). EoE with concurrent diagnosis of UC was associated with a non-statistically significant trend toward lower risk of intestinal resection (aHR 0.846 (95% CI 0.528 to 1.1355), *n* = 1232, *p* = 0.4854) (Table 4).

Effect of Concurrent EoE and IBD on EoE-related Complications

In patients with EoE, concurrent diagnosis of IBD was associated with a statistically significant lower risk of food bolus impaction (aHR 0.445 (95% CI 0.269 to 0.734), *n* = 1879, *p* = 0.0011) and a non-statistically significant trend toward lower risk of requiring esophageal stricture dilation (aHR 0.985 (95% CI 0.73 to 1.331), *n* = 1879, *p* = 0.9236) (Table 5).

Discussion

EoE and IBD are chronic immune-mediated diseases with overlapping pathologies whose complexities are yet to be fully delineated. Historically, investigations into the intersection of EoE and IBD were largely confined to case reports. However, within the past half-decade, our understanding of the epidemiology and treatment implications of these diseases occurring simultaneously has significantly improved.

Fan et al. found a five-fold increase in EoE prevalence among IBD patients, using a sample from a single tertiary center [9]. However, this study lacked a population-based control group. Furthermore, Lemketkai et al. highlighted an upward trend in concurrent IBD and EoE, through a cohort analysis spanning 2009–2016 [5], excluding patients on government health insurance plans (Medicare, Medicaid, and Children's Health Insurance Programs). The study noted that EoE incidence in IBD patients was 3–5 times higher, and IBD incidence in EoE patients was 3–6 times higher than in non-affected counterparts. While acknowledging that the exact mechanisms of overlapping pathogenesis of each disease is not well defined, the authors discuss the similarities of both conditions involving environmental factors, abnormal host immune responses, and likely genetic predispositions [5]. Limketkai et al. also found that patients with both CD and EoE had lower rates of biologic initiation, surgical resection, and higher corticosteroid treatment rates; EoE patients with IBD had fewer EoE-related complications. Interestingly, in 2021, Sonnenberg et al., leveraging a national electronic database comprising 302,061 patients, posited a significantly divergent relationship between IBD and EoE compared to the earlier two studies. This investigation found a lesser prevalence of EoE in patients diagnosed with CD or microscopic colitis, relative to a control group of patients with no IBD, microscopic colitis, or GERD diagnosis. This discrepancy highlights the complex relationship between these immune-mediated conditions, emphasizing the need for further exploration.

This research aligns with several findings from past investigations while offering new insights. Similarly to Limketkai et al., this analysis demonstrated that among patients with IBD, individuals with the codiagnosis of either CD or UC with EoE were more likely to be male and younger age compared to those without an EoE co-diagnosis. Furthermore, EoE patients were significantly more likely to have a concurrent diagnosis of CD or UC. In terms of gender influences on the epidemiology of EoE and IBD, we echoed findings from Limketkai et al. wherein males and females with EoE had comparable incidence rates of CD and UC, although men displayed a trend toward higher incidence of IBD. Both conditions have ties to multiple genetic loci, potentially influencing their shared pathophysiology and clinical presentations [14, 15]. Further investigation of these genetic connections may shed light on the underlying mechanisms responsible for the observed overlap between EoE and IBD. We found that the prevalence of IBD among EoE patients was higher in females than in males, unlike Limketkai et al.'s findings. This divergence underscores the necessity for more research to explain this difference and identify any biological or environmental factors contributing to the observed gender variances. Although previous epidemiologic research has demonstrated a consistent trend of increased prevalence of EoE among male patients as compared to female patients, to date, the underlying explanation for this relationship is yet to be determined [1, 3, 16]. In a retrospective analysis of 208 patients with confirmed EoE diagnosis, Sperry et al. found that overall, there were few differences in endoscopic features (such as presence of rings, linear furrow, plaques/exudates, or strictures) and histologic features (such as eosinophil count) between sexes [16]. Based on their findings, the authors suggested that future research could evaluate whether the epidemiologic differences between sexes are better explained by the underlying pathophysiology of EoE or social/environmental factors. Once the underlying explanation of the epidemiologic variation in EoE prevalence among sexes has been formulated, it would be pertinent to evaluate whether it extends to patients with overlapping diagnoses of EoE and IBD. Finally, our findings provide further evidence of the overlapping pathophysiology of EoE, IBD, and other immune-mediated conditions given that among patients with IBD, the codiagnosis of EoE had a statistically significant stronger association with Th1-mediated and Th2-mediated conditions when compared to patients without the EoE codiagnosis.

Significant variation in findings relates to IBD and EoE treatment and complications. Unlike Limketkai et al., our study found no significant glucocorticoid use difference among CD patients, irrespective of EoE status. Unlike Limketkai et al. who found that UC patients with EoE had increased glucocorticoid use, our study found no significant glucocorticoid use difference among UC patients, irrespective of EoE status. Our findings suggest that EoE co-diagnosed patients with CD but not UC were more likely to be treated with biologic agents compared to their non-EoE counterparts. The difference could stem from data sources, with Limketkai et al. relying on insurance claims. The trend of increased biologic use among patients with CD and EoE could reflect advancements in biologic agents and early initiation associated with improved outcomes [17, 18].

Our study found a non-statistically significant trend toward reduced intestinal resection in IBD and EoE co-diagnosed patients, diverging from Limketkai et al. who reported a significantly lower likelihood of intestinal resection in IBD patients with EoE compared to those without. There are several potential explanations for the observed trend toward a lower likelihood of intestinal resection in patients with IBD and EoE. One possibility is that the coexistence of EoE and IBD may lead to a distinct immunological environment, characterized by a different balance of Th1, Th2, and Th17 immune responses. The interplay between these immune processes could influence the inflammatory response, as is hypothesized in the pathophysiology of asthma, resulting in a milder disease course and reduced need for surgery [19]. Alternatively, differences in treatment strategies and clinical management for patients with both IBD and EoE could play a role in the observed trend. The presence of EoE in patients with IBD may lead to more aggressive or tailored treatment approaches, targeting both conditions and potentially reducing the need for surgery [20]. Finally, increased surveillance and more frequent follow-up for patients with both IBD and EoE may contribute to earlier identification of disease complications, allowing for timely intervention and potentially reducing the need for surgery.

The presence of EoE resulting in increased surveillance to prevent end-stage complications is further supported by the fact that our study found a statistically significant overall greater composite risk of IBD-associated complications among patients with IBD with versus without EoE. More frequent endoscopic evaluations and closer monitoring of symptoms could increase the likelihood of detecting IBD-associated complications at an earlier stage. However, this increased vigilance may also contribute to the higher reported risk of complications in patients with both conditions. Future studies could investigate whether patients with the codiagnosis of EoE and IBD have greater severity of IBD based on standard endoscopic scoring systems such as the Crohn's Disease Endoscopic Index of Severity (CDEIS) or Simple Endoscopic Score for CD (SES-CD) for CD or the Mayo endoscopic sub-score (MES) and the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) for UC.

Concerning complications related to EoE, our study's results resembled those of Limketkai et al. While Limketkai et al. found a statistically significant lower risk of food-bolus impaction, esophageal stricture dilation, and overall composite risk of EoE-related complications in patients with EoE and IBD codiagnosis, our study demonstrated only a statistically significant lower likelihood of food bolus impaction. Our findings demonstrated a non-statistically significant trend towards lower likelihood of having an esophageal dilation procedure in those with EoE and IBD codiagnosis. This finding supports the idea that the coexistence of IBD and EoE may lead to a more benign clinical course for EoE patients. Taken together, the present study validates the previous findings that EoE and IBD codiagnosis is predictive of a more benign clinical course of EoE.

Our study possesses several strengths. While the database used by Limketkai et al. was large and inclusive of the entire geographic population of the U.S., the dataset was based on insurance claims-based reports. Thus, the dataset excluded patients who were enrolled in government-sponsored insurance plans, including Medicare, Medicaid, and CHIP. In contrast, the TriNetX database is not a "claims-based" dataset and does not exclude enrollees of Medicare, Medicaid, and CHIP, which as of December 2022 consisted of 65,007,351; 85,280,085; and 7,060,500 individuals, respectively [21, 22]. Second, TriNetX adds the benefit of global representation, as the database contains patient data from a total of 14 different countries across North America, South America, Europe, the Middle East, Africa, and the Asia-Pacific regions. Finally, the TriNetX database offers the opportunity to expand on the timeframe investigated by Limketkai et al. from 2016 as the last included year of data collected to 2022 in the present study. Altogether, by expanding the diversity of patients included in the analysis in terms of geographic location and insurance coverage and by extending the timeframe of data collection, this study tests the external validity of prior published studies.

This study does have limitations which are mostly related to the observational design and being inherently subjected to confounding bias. To reduce the risk of confounding bias, PSM analyses were performed. One significant limitation arises from the nature of the dataset itself, which precluded an assessment of disease severity and did not allow for direct analysis of endoscopy reports. This inability to gauge disease severity could have an impact on our findings, as disease severity often plays a critical role in treatment strategies and outcomes. Further, the dataset did not allow us to ascertain the specific rationale behind the prescription of glucocorticoids. For patients with a dual diagnosis of IBD and EoE, we were unable to confirm whether glucocorticoids were prescribed primarily to manage IBD, EoE, or some other concurrent disease. This limitation hinders our ability to fully understand the therapeutic considerations for these patients. Hence, future studies that can address these limitations are needed to provide a more comprehensive understanding of the interplay between IBD, EoE, and treatment modalities. Although typical HCOs where from data is collected into the TrinetX database are large, academic health institutions with both inpatient and outpatient centers, further details regarding the exact centers, their locations, and whether they cater primarily to urban versus rural patient populations is not available from the database. While the TrinetX database includes data from patients from HCOs in and outside of the United States as well as data from patients with government-sponsored insurance and private insurance, the database does not allow for stratification based on location or insurance status. Thus, sensitivity analyses based on these variables is not possible, representing another study limitation.

Overall, this study represents the first globally-representative population-based study with inclusion of patients enrolled in government-funded insurance plans that examines the overlapping features of EoE and IBD. Our findings align with previous research, demonstrating a significantly higher prevalence of EoE among IBD patients and vice versa. This study not only validates but also extends the understanding of prior findings by providing evidence of their applicability across a more diverse population. However, despite these advancements, our understanding of the common pathophysiological mechanisms underlying EoE and IBD remains incomplete. As such, future studies that focus on these shared mechanisms are paramount for enhancing our comprehension of these interconnected conditions. Furthermore, the field of biologic therapy is rapidly evolving, offering new steroid-sparing agents with indications for both EoE and IBD. We anticipate that the emergence of these novel therapies will likely change the treatment landscape, potentially reducing the reliance on glucocorticoids. This study underscores the importance of ongoing research in this area, as a more nuanced understanding of these conditions and advancements in treatment strategies will ultimately translate into improved patient care.

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Declarations

Transparency statement We adhere to ethical and legal guidelines for data access and protection. Depending on the nature of the data and

any applicable privacy or legal restrictions, we may provide access to the data upon reasonable request. Requests for data access can be directed to the corresponding author.

Conflict of interest The authors have no conflicts of interest to declare.

Summary This study explored links between Eosinophilic Esophagitis (EoE) and Inflammatory Bowel Disease (IBD). Simultaneous EoE and IBD increased IBD-related complications risk, needing more treatment (glucocorticoids, biologic therapy, abdominal surgery), while reducing EoE-related issues like food bolus impaction.

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