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Prior hospital-based infection and risk of eosinophilic esophagitis in a Swedish nationwide case-control study

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Abstract

Background and Aims: Eosinophilic esophagitis (EoE) is an increasingly common, largely food allergen-driven disease characterized by dysphagia. Prior infections are known to associate with other loss of tolerance diseases such as autoimmunity. We aimed to determine if antecedent infection was associated with later EoE development.

Methods: We performed a case-control study of all patients with biopsy-verified EoE diagnosed between 2000 and 2017 in Sweden ($n = 1587$) and matched to 5 general population controls ($n = 7660$). Cases were identified using histopathology codes from the Epidemiology Strengthened by histopathology Reports in Sweden study, a validated cohort of gastrointestinal pathology reports from all 28 pathology centers in Sweden. We used logistic regression to estimate odds ratios (ORs) and 95% confidence intervals for antecedent infections from patients seen at hospital-based outpatient clinics or inpatients. In secondary analyses, we compared EoE patients with their full siblings to further reduce residual confounding.

Results: 564 (35.7%) EoE patients and 1793 (23.4%) matched controls had an earlier record of infection. This corresponded to a 2-fold increased risk of infections in EoE patients (OR 2.01; 95%CI: 1.78–2.27). ORs for earlier gastrointestinal or respiratory infection were 2.73 ($n = 128$ EoE, 268 control; 95%CI: 2.17–3.41) and 1.89 ($n = 305$ EoE, 960 control; 95%CI: 1.63–2.20), respectively. Having an EoE diagnosis was linked to a 3.39-fold increased odds of sepsis ($n = 14$ EoE, 21 control; 95%CI: 1.68–6.65). Individuals with EoE were also more likely to have had an infection compared to their non-EoE siblings ($n = 427$ EoE, 593 control; OR = 1.57; 95%CI = 1.30–1.89).

Conclusion: In this nationwide cohort study, prior infection, was associated with subsequent EoE. Risks were particularly high after sepsis, and gastrointestinal or respiratory infections.

KEYWORDS
allergy, antibiotics, environment, epidemiology, infection, microbiome, pathogens, risk factor

Amiko M. Uchida and Gabrielle Ro co-first authorship.

INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic, allergic inflammatory disease of the esophagus that affects all ages and sexes and is commonly associated with other allergic diseases. It is defined histologically by the presence of ≥15 intraepithelial eosinophils per high powered field on esophageal biopsies along with esophageal symptoms such as dysphagia.[1] Like many allergic diseases, EoE is increasing for unclear reasons.[2–8] Though its pathophysiology remains incompletely understood, EoE appears to be a non-IgE food allergy-driven disease,[9] where loss of oral tolerance may contribute to the de novo development of sensitization to common dietary components such as wheat and dairy. Although the mechanisms of this process are not clear, infections, as well as antibiotic exposure and subsequent microbiome changes, have been shown to disrupt the establishment and maintenance of oral tolerance and have been associated with development of gastrointestinal and other diseases of immune dysregulation.[10–16]

Additionally, it is well-established in other atopic diseases such as asthma, allergic rhinitis, and atopic dermatitis that preceding viral respiratory infection and/or early life antibiotic exposure are associated with later development of disease.[17–20] These associations are underexplored in EoE with just two studies describing potential relationships between risk of EoE and environmental factors such as Cesarean delivery and antibiotic use in the first year of life.[16,21] The first was a study of 31 patients with EoE who underwent a phone-based questionnaire and were compared to patients with gastroesophageal reflux and siblings of nonsyndromic cleft palate patients. In this study, early life antibiotic exposure was associated with 6-fold increased odds of developing pediatric onset EoE.[21] The second study included 25 patients with EoE and 60 controls from well-child visits, and parents of patients completed questionnaires at clinic visits or via e-mail. The investigators found patients with EoE were more frequently born via Cesarean section compared to controls and had a higher rate of antibiotics in the first year of life, although delivery mode was no longer significant when the findings were adjusted for history of atopy.

Using a nationwide database of biopsy-verified patients with EoE, we examined the risk of developing EoE after being diagnosed with infection. Given the strong environmental and genetic overlaps between EoE and other atopic diseases where prior infections have been implicated in disease development, we hypothesized that having an infection would predispose to later EoE.

METHODS

Study cohort

Ascertainment of eosinophilic esophagitis cases

The Epidemiology Strengthened by histoPathology Reports in Sweden (ESPRESSO) cohort contains all biopsies obtained from the gastrointestinal tract during 1965–2017 at 28 pathology

Key summary

What is known?
- Eosinophilic esophagitis (EoE) is increasingly common and costly.
- The impact of prior infection on EoE is poorly understood.

What is new here?
- In a nationwide-case control cohort study, prior infection was associated with subsequent EoE diagnosis.
- Risk for EoE was highest after sepsis, and gastrointestinal or respiratory infection.

departments in Sweden.[22] The Personal Identity Number is a unique number assigned to each resident in Sweden and allows for large-scale linkages and epidemiological research.[23] We linked data on all EoE cases in the ESPRESSO cohort (Topography T62, Morphology M47150) to the nationwide Swedish healthcare registers including the Patient Register.[22,24–26] The diagnosis of EoE was histological and based on the detection of ≥15 eosinophils/high power field. Our EoE cohort was recently validated and found to have a positive predictive value of 89%.[22] We examined cases diagnosed between 1 January 2000 and 31 December 2017 because (a) there was significant heterogeneity in diagnostic criteria and generally low awareness of EoE in Sweden, and elsewhere, prior to 2000, and (b) to allow three years with International classification of diseases (ICD) codes prior to EoE diagnosis (ICD was introduced in Sweden in 1997).[26]

Individuals were excluded if they had a known prior history of tissue or organ transplantation, or a diagnosis of cancer (before EoE onset) other than non-melanoma skin cancer. Lastly, individuals were excluded administratively if they formally emigrated from Sweden at the time of biopsy.

Controls

Each individual with EoE was matched with up to five age, sex, county of residence, and birth year controls from the Swedish Total Population Register.[27] County of residence was used to better reflect healthcare access and balance the risk of surveillance bias between cases and controls. These were biopsy-naïve controls, meaning they were not required to have prior unremarkable endoscopy with biopsy. Controls had to be free from EoE at the time of matching but could still be included in the study if they developed EoE later, after matching.

Sibling comparators

We identified siblings of the EoE patients through the Swedish Multigeneration Register, a sub-section of the Total Population

Register. Sibling data were available on all individuals born after 1932 and who were registered as residents of Sweden in 1961 or later. To minimize intrafamilial confounders (shared genetic and early environmental factors) that could potentially influence both the risk of infections and EoE, sibling comparators were examined.

Ascertainment of exposure information (infections)

Our exposure was infection requiring medical care through the Swedish Patient Register. This register includes individual-level data on inpatient and outpatient encounters at a nationwide level since 1987 (with some counties reporting sine 1964).[27] Information on infections before study entry (among cases or matched controls) were collected from the register using International Classification of Diseases codes (Supplementary Table 1). The accuracy of ICD coding for ascertainment of diagnoses for the inpatient component of Swedish Patient Register has been previously validated with a positive predictive value of 85%–95%.[26] Exposures were defined as in Supplementary Table 2.

We ascertained infections up until 3 months before the index endoscopy diagnosing EoE. The 3 months prior to EoE diagnosis were excluded to rule out infection related changes from being misinterpreted as EoE or trigger EoE investigations. Comorbidities were defined until biopsy/matching date. Patients were stratified based on country of birth, education, or other autoimmune disease.

Alternative exposures

We examined individuals who experienced infections only while inpatient, and therefore presumed to be more severe cases of infection with associated thorough examinations, as well as patients with multiple infections. The latter was defined as two infections or three or more infections as different exposures prior to EoE diagnosis. Additionally, we examined antibiotics administered three or more months prior to endoscopic biopsy for EoE as a risk factor. This analysis was used on individuals diagnosed 1 January 2006 or later to allow earlier exposure time for antibiotics.

Statistical analyses

For the general population case-control study, we used a logistic regression, adjusting for matching factors and education at index date. Odds ratios (ORs) were presented with 95% CIs. Clinical covariates were modeled up to and excluded the index biopsy date. Odds ratios for infections between 3 months and less than 1 year or between 1 and 5 years before EoE diagnosis and ≥5 years before EoE diagnoses were analyzed in stratified analyses. Statistical analyses were carried out using R statistical software (version 4.1.0, R

Foundation for Statistical Computing, Vienna, Austria) and the survival package (version 3.2–11, Therneau, T (2015), https://CRAN.R-project.org/package=survival).

For sibling analyses, a conditional logistic regression was used, taking the same covariates into consideration.

Secondary analyses

We performed stratified analyses according to age (<18, ≥18), sex (female, male), calendar year period (2000–2010, 2011–2017), country of birth (Nordic vs. Non-Nordic), education (≤9 years, 10–12 years, ≥13 years), and presence of autoimmune disease (Supplemental Table 2).

Ethics

This study was approved by the Stockholm Ethics board. Informed consent was waived since the study was strictly register-based.[28]

RESULTS

Study cohort

Between 2000 and 2017, we identified 1587 patients with histologically verified EoE and 7660 matched general population controls (Table 1). The mean age of diagnosis was 37 years for EoE and 36 for controls, and 25% of EoE cases were female. Most individuals were diagnosed in adulthood (≥18 years; 77%) and diagnosed between 2011 and 2017. EoE patients were more likely to be born in a Nordic country compared to general population controls (95% vs. 84%). Sibling and EoE case baseline characteristics are also shown in Table 1.

Infectious exposure

We found that 564 (35.7%) patients with EoE and 1793 (23.4%) matched controls had an earlier record of any infection (inpatient care or hospital-based outpatient care). Hence, patients with EoE had more often suffered from an infection requiring medical care than the general population (OR = 2.01; 95%CI = 1.78–2.27) (Table 2). Additionally, the ORs for antecedent gastrointestinal infection was 2.73 (95%CI = 2.17–3.41) and respiratory infection was 1.89 (95%CI = 1.63–2.20). An EoE diagnosis was associated with a 3.39-fold increased odds of prior sepsis (1.68–6.65). Other forms of infection including urinary or skin were found to have significant odds of preceding exposure in EoE cases compared to the general population.

Prior infection was a risk factor for EoE both in females (OR = 2.25; 95%CI = 1.78–2.83), and males (OR = 1.94; 95%

CI = 1.67–2.24). Children with EoE had a 2.76-fold increased odds of antecedent infection, whereas the OR for EoE diagnosed in adulthood was lower (OR = 1.78) (Table 2). We found the highest ORs for infections within the year before an EoE diagnosis (OR = 2.28; 95%

CI = 1.43–3.57). Exposure to infection ≥5 years prior to diagnosis had 2.05-fold increased odds (95%CI = 1.78–2.37).

We also examined if a diagnosis of autoimmunity at the time of infection was associated with increased odds of later EoE

TABLE 1 Summary statistics for general population controls, Eosinophilic esophagitis (EoE) patients and their siblings

	Controls[a] n (%)	EoE n (%)	Sibling n (%)	EoE n (%)
Total	7660 (100.00)	1587 (100.00)	2045 (100.00)	1214 (100.00)
Male	5744 (74.99)	1189 (74.92)	1049 (51.30)	914 (75.29)
Female	1916 (25.01)	398 (25.08)	996 (48.70)	300 (24.71)
Age at diagnosis or matching				
Mean [SD] years	36.14 (19.54)	36.95 (19.91)	36.75 (19.40)	35.50 (18.61)
Median [IQR] years	37.00 (18.00–51.00)	38.00 (19.00–52.00)	38.00 (21.00–51.00)	36.00 (19.00–50.00)
<18 years	1810 (23.63)	365 (23.00)	426 (20.83)	285 (23.48)
> = 18 years	5850 (76.37)	1222 (77.00)	1619 (79.17)	929 (76.52)
Year of diagnosis				
2000–2010		305 (19.22)		224 (18.45)
2011–2017		1282 (80.78)		990 (81.55)
Country of birth				
Nordic	6415 (83.75)	1508 (95.02)	1972 (96.43)	1188 (97.86)
Other	1244 (16.24)	79 (4.98)	73 (3.57)	26 (2.14)
NA	1 (0.01)	0 (0.00)	0 (0.00)	0 (0.00)
Education				
Compulsory school, (< = 9 years)	1441 (18.81)	247 (15.56)	297 (14.52)	172 (14.17)
Upper secondary school (10–12 years)	2711 (35.39)	563 (35.48)	735 (35.94)	430 (35.42)
College or university (> = 13 years)	1992 (26.01)	493 (31.06)	633 (30.95)	389 (32.04)
NA	1516 (19.79)	284 (17.90)	380 (18.58)	223 (18.37)
Infectious exposure				
Any	1793 (23.41)	564 (35.54)	593 (29.00)	427 (35.17)
Respiratory	960 (12.53)	305 (19.22)	310 (15.16)	237 (19.52)
Gastrointestinal	268 (3.50)	128 (8.07)	88 (4.30)	95 (7.83)
Urinary	172 (2.25)	68 (4.28)	84 (4.11)	49 (4.04)
Skin	336 (4.39)	117 (7.37)	111 (5.43)	84 (6.92)
Other	600 (7.83)	225 (14.18)	232 (11.34)	175 (14.42)
Opportunistic	27 (0.35)	9 (0.57)	15 (0.73)	7 (0.58)
Sepsis	21 (0.27)	14 (0.88)	5 (0.24)	5 (0.41)
Age at first exposure				
Mean [SD] years		22.89 (21.76)		21.01 (20.35)
Median [IQR] years		18.35 (1.74–38.08)		15.36 (1.66–36.19)
<18 years	917 (51.14)	281 (49.82)	276 (46.54)	224 (52.46)
> = 18 years	876 (48.86)	283 (50.18)	317 (53.46)	203 (47.54)
Number of infections				
1	925 (12.08)	233 (14.68)	263 (12.86)	172 (14.17)
2	309 (4.03)	99 (6.24)	120 (5.87)	82 (6.75)
> = 3	366 (4.78)	180 (11.34)	145 (7.09)	138 (11.37)

TABLE 1 (Continued)

	Controls[a] n (%)	EoE n (%)	Sibling n (%)	EoE n (%)
Earlier autoimmunity[b]				
No	7307 (95.39)	1458 (91.87)	1912 (93.50)	1128 (92.92)
Yes	353 (4.61)	129 (8.13)	133 (6.50)	86 (7.08)

[a]Controls = general population control.

[b]Autoimmunity up until EoE diagnosis. Autoimmune disorders included in the concept autoimmunity: diabetes mellitus, psoriasis, SLE, rheumatoid arthritis, thyroiditis, hyperthyroidism, sarcoidosis, primary biliary cirrhosis, ANCA vasculitis and other vasculitis, pelvospondylitis, autoimmune hepatitis, primary sclerosing cholangitis, celiac disease.

TABLE 2 Eosinophilic esophagitis (EoE) odds ratios for Infections versus reference individuals and siblings

	Controls	EoE	OR (95CI)[a]	Sibling	EoE	OR (95CI)
Type of infection						
Any	1793	564	2.01 (1.78–2.27)	593	427	1.57 (1.30–1.89)
Respiratory	960	305	1.89 (1.63–2.20)	310	237	1.51 (1.21–1.90)
Gastrointestinal	268	128	2.73 (2.17–3.41)	88	95	2.37 (1.64–3.42)
Urinary	172	68	2.04 (1.51–2.71)	84	49	1.38 (0.92–2.06)
Skin	336	117	1.79 (1.43–2.22)	111	84	1.37 (0.98–1.90)
Other	600	225	2.09 (1.76–2.47)	232	175	1.56 (1.22–1.99)
Opportunistic	27	9	1.70 (0.75–3.49)	15	7	1.10 (0.41–2.97)
Sepsis	21	14	3.39 (1.68–6.65)	5	5	1.15 (0.31–4.32)
Sex						
Males	1251	386	1.94 (1.67–2.24)	274	291	1.50 (1.14–1.97)
Females	542	178	2.25 (1.78–2.83)	319	136	2.05 (1.30–3.23)
Age at EoE diagnosis or matching date						
<18 years	781	241	2.76 (2.16–3.54)	215	190	2.80 (1.78–4.41)
> = 18 years	1012	323	1.74 (1.51–2.02)	378	237	1.31 (1.05–1.64)
Years exposed to infection prior to EoE						
<1	93	30	2.28 (1.43–3.57)	26	11	1.78 (0.72–4.40)
1 < = 5	541	149	1.61 (1.30–1.97)	143	95	1.65 (1.17–2.34)
> = 5	1159	382	2.05 (1.78–2.37)	424	289	1.57 (1.26–1.95)
Year of end follow up						
2000–2010	284	90	1.98 (1.47–2.66)	93	63	1.40 (0.85–2.32)
2011–2017	1509	474	2.02 (1.77–2.31)	500	364	1.59 (1.30–1.94)
Earlier autoimmunity[b]						
No	1683	503	2.03 (1.78–2.30)	536	385	1.58 (1.29–1.93)
Yes	110	61	1.68 (1.04–2.70)	57	42	1.82 (0.00-N/A)

[a]Analyses adjusted for age, year, gender, county of residence at biopsy, education.

[b]Autoimmunity up until EoE diagnosis. Autoimmune disorders included in the concept autoimmunity: diabetes mellitus, psoriasis, SLE, rheumatoid arthritis, thyroiditis, hyperthyroidism, sarcoidosis, primary biliary cirrhosis, ANCA vasculitis and other vasculitis, pelvospondylitis, autoimmune hepatitis, primary sclerosing cholangitis, celiac disease.

diagnosis. We found that among individuals with autoimmunity, infection was linked to 1.68-fold increased odds of later EoE, compared with 2.03 among individuals without autoimmunity (OR = 2.03).

Sibling comparisons

We identified 1214 individuals with EoE and 2045 matched sibling controls, where environmental and genetic factors are assumed to be

similar and thus limit confounding. Of these individuals, 427 (35%) EoE and 593 (29%) siblings had an infectious exposure of any type prior to the diagnosis of EoE (Table 1). Patients with EoE had a 1.51-fold increased odds of prior infection of any type compared to sibling controls (95%CI = 1.30–1.89) (Table 2). Gastrointestinal infection had a notable OR of 2.37 (95%CI = 1.64–3.42), while the risk for preceding respiratory infection was 1.51 (95%CI = 1.21–1.90).

Secondary analyses

When restricting our exposure definition to *inpatient* infections, we found that gastrointestinal infections conferred the highest odds (3.95-fold) of later EoE diagnosis, and this increased OR persisted in sibling analyses (Table 3; OR = 2.78; 95%CI = 1.76–4.39).

In other subgroup analyses, we examined the ORs for multiple (2 or ≥3) infections and found that the odds mildly increased with each subsequent infection from an OR of 2.52 for EoE after 2 infections to 2.72 after ≥3 infections but 95%CIs were wide and overlapping

(Table 4, Table 5). This relationship was also seen when comparing EoE cases to sibling controls, albeit at a lesser magnitude (OR = 1.80 with two infections and 1.89 with ≥3 infections).

Antibiotic exposure

Lastly, we investigated the odds of antibiotic exposure in patients with EoE, independent of any infection, and found that patients with EoE had a significantly increased odds of being exposed to antibiotics compared to the general population (OR = 1.65; 95%CI = 1.46–1.87) as well as in sibling analyses (Table 6; OR = 1.30; 95%CI = 1.08–1.56).

DISCUSSION

We describe for the first time a nationwide case-control study of 1587 biopsy-verified patients with EoE and found that any prior infection which required hospital-based inpatient or outpatient care

TABLE 3 Eosinophilic esophagitis (EoE) odds ratios versus reference individuals and siblings for inpatient only infections

	Controls	EoE	OR (95CI)	Siblings	EoE	OR (95CI)
Type of infection						
Any	584	230	2.24 (1.89–2.64)	191	168	1.89 (1.46–2.43)
Respiratory	289	105	1.96 (1.54–2.47)	82	76	1.78 (1.24–2.55)
Gastrointestinal	106	75	3.95 (2.90–5.36)	44	56	2.78 (1.76–4.39)
Urinary	57	26	2.35 (1.44–3.72)	33	16	1.22 (0.63–2.36)
Skin	84	19	1.16 (0.68–1.88)	24	15	1.21 (0.59–2.51]
Other	125	70	2.96 (2.18–3.98)	49	45	1.45 (0.93–2.26]
Opportunistic	12	1	0.42 (0.02–2.15)	5	1	0.73 (0.08–6.43)
Sepsis	21	13	3.15 (1.53–6.25)	4	5	1.27 (0.32–5.05)

TABLE 4 Eosinophilic esophagitis (EoE) odds ratios versus reference individuals and siblings for two Infections

	Controls	EoE	OR (95CI)	Siblings	EoE	OR (95CI)
Type of infection						
Any	729	331	2.52 (2.16–2.95)	266	228	1.80 (1.39–2.31)

TABLE 5 Eosinophilic esophagitis (EoE) odds ratios versus reference individuals and siblings for three Infections

	Controls	EoE	OR (95CI)	Siblings	EoE	OR (95CI)
Type of infection						
Any	426	230	2.72 (2.26–3.27)	155	139	1.89 (1.38–2.59)

TABLE 6 Eosinophilic esophagitis (EoE) odds ratios versus reference individuals and siblings for antibiotic use

	Controls	EoE	OR (95CI)	Siblings	EoE	OR (95CI)
Antibiotic use	4731	1142	1.65 (1.46–1.87)	1432	878	1.30 (1.08–1.56)

was associated with a two-fold increased risk of EoE. This increased risk persisted even when an infection had occurred ≥5 years earlier. Interestingly, we found that having a prior gastrointestinal infection translated to a nearly a three-fold increased risk of EoE, while prior respiratory infections carried almost a two-fold risk. The strongest risk of EoE development was associated with prior diagnosis of sepsis (over three-fold risk).

We note that patients with an infection requiring hospital-care (as inpatients or outpatients) are generally unwell and undergo increased surveillance, potentially confounding results. It is therefore of particular importance that we were able to compare EoE patients to sibling controls. This is notable as siblings often share a similar healthcare seeking pattern, but also because a sibling comparison will minimize, though not negate, the impact of genetics and shared early environmental exposures. Compared to siblings, prior infection was still associated with a 1.57-fold increased risk of EoE, with a particularly strong link with earlier gastrointestinal infection (OR = 2.37). Our data also revealed that a potential dose-related effect of multiple infections conferred increasing odds of later EoE diagnosis, although we urge caution when interpreting these findings since 95% CI were overlapping.

Interestingly, while it is well described that EoE occurs in a roughly 3:1 ratio of males:females in their 2nd—3rd decades of life, we found in our analyses that females and pediatric patients (children) with infectious exposures associated with a higher odds ratio of EoE development. However, again, the 95%CIs were overlapping so this difference between sexes should be interpreted with caution and is based on smaller numbers.

We also examined the association of antibiotic exposure with development of EoE given that some infections are treated with antibiotics, and antibiotic related perturbations in the microbiome (dysbiosis) have been implicated in the later development of atopy.[29] We found that antibiotic use translated to a 1.65-fold increased odds in development of EoE. These findings could be attributable to antibiotics themselves, or as a surrogate for infection or microbial dysbiosis. Two prior groups have investigated the association of EoE with antibiotics or other early life exposures in pediatric patients at single centers using survey questionnaires.[16,21] Jensen et al found a 6-fold increase in later EoE development when antibiotics were administered in the first year of life when compared to control patients recruited from a pediatric surgery clinic.[21] Interestingly, when the investigators assessed antibiotic association comparing EoE cases to controls with gastroesophageal reflux disease rather than surgical patients, this relationship was lost. A second group also found an increased odds of infant antibiotic use predating EoE development with an adjusted OR of 3.58 (95%CI = 1.27–10.13) compared to well-child visit control individuals.[16] In our current study, we found rather low ORs for the relationship between antibiotic use and later development of EoE, with an upper 95% CI of 1.87. This is comforting as antibiotics are often needed to treat bacterial infections and can be lifesaving.

While the pathophysiology of EoE is not fully understood, our data supports a potential role for antecedent infectious triggers in EoE pathogenesis, of which gastrointestinal and more severe infections in particular carry greater risk.

There are several strengths of this study, which include incorporation of a nationwide population cohort with a validated histopathologic dataset to identify cases. This approach allows for sufficient power to detect associations as described here. The utilization of a validated EoE histopathology dataset increases the specificity and sensitivity of accurate EoE diagnostic cases. Our nationwide cohort approach also minimizes several types of bias such as selection, recall and collection bias and is not limited to a single center, rendering findings somewhat generalizable. Additionally, our dataset provides sibling analyses which allows us to address difficult to control factors such as genetics, environmental and social aspects that could confound risk calculations. While validation studies on Swedish ICD coding for infections are rare, the Swedish Patient Register has a high accuracy for most disorders with positive predictive values for most diagnoses ranging between 85% and 95%.[26]

We also acknowledge limitations in our approach. Our exposures were classified based on diagnostic codes for patients who sought hospital-based healthcare (outpatient and inpatient), and therefore we could have missed infections that did not seek medical attention in both cases and controls or those exclusively met with general practitioners who are not affiliated with a hospital outpatient clinic. Similarly, our EoE cohort may include false-positive cases as our criteria for inclusion was histopathologically based. However, our validation study had a substantial positive predictive value of 89%.[22] Additionally, we had a limited sample size for subgroup analyses and did not have the statistical power to detect which type of gastrointestinal, respiratory, or other infection specifically conferred a greater risk of EoE development. We also cannot rule out that in some patients, undiagnosed EoE may have preceded the infection or that mild cases of yet-to-be diagnosed EoE occurred in controls. Other potential confounders that could be related to EoE development that were not controlled for in this study include dietary and environmental factors such as formula feeding or smoking. Both have been linked to infection risk but neither has been linked to EoE.[30]

In conclusion, in a nationwide biopsy-verified EoE case-control study, we demonstrate that preceding infection is associated with an increased risk of subsequent EoE. The associations were particularly strong for gastrointestinal and sepsis infections. Multiple episodes of previously diagnosed infections also conferred a dose-related increased risk for EoE. Future investigations should be directed at specific types of gastrointestinal infections such as luminal versus non-luminal infections which may have differing effects.

AUTHOR CONTRIBUTIONS

Amiko M. Uchida and Gabrielle Ro constructed the first draft of the manuscript. Jonas F. Ludvigsson completed the final version of the manuscript and is the guarantor of the article. All authors read, edited, and agreed with the final version of the manuscript.

CONFLICT OF INTEREST

Dr. Uchida is an advisor/consultant for Sanofi-Genzyme, Regeneron (unrelated to this study). Dr. Ludvigsson has coordinated a study on behalf of the Swedish inflammatory bowel disease quality register. That study received funding from Janssen corporation.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ETHICS STATEMENT

The study was approved by the Regional Ethics Committee, Stockholm, Sweden (Protocol no 2014/1287-31/4) 27 August 2014.

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REFERENCES

1. Dellon ES, Liacouras CA, Molina-Infante J, Furuta GT, Spergel JM, Zevit N, et al. Updated international consensus diagnostic criteria for eosinophilic esophagitis: proceedings of the AGREE conference. Gastroenterology. 2018;155:1022–33.e10.
2. Dellon ES, Jensen ET, Martin CF, Shaheen NJ, Kappelman MD. Prevalence of eosinophilic esophagitis in the United States. Clin Gastroenterol Hepatol. 2014;12(4):589–96.e1. https://doi.org/10.1016/j.cgh.2013.09.008
3. Nwaru BI, Hickstein L, Panesar SS, Muraro A, Werfel T, Cardona V, et al. The epidemiology of food allergy in Europe: a systematic review and meta-analysis. Allergy. 2014;69(1):62–75. https://doi.org/10.1111/all.12305
4. Koplin JJ, Mills EN, Allen KJ. Epidemiology of food allergy and food-induced anaphylaxis: is there really a Western world epidemic? Curr Opin Allergy Clin Immunol. 2015;15(5):409–16. https://doi.org/10.1097/aci.0000000000000196
5. Gupta RS, Springston EE, Warrier MR, Smith B, Kumar R, Pongracic J, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. Pediatrics. 2011;128(1):e9–17. https://doi.org/10.1542/peds.2011-0204
6. Soller L, Ben-Shoshan M, Harrington DW, Fragapane J, Joseph L, St. Pierre Y, et al. Overall prevalence of self-reported food allergy in Canada. J Allergy Clin Immunol. 2012;130(4):986–8. https://doi.org/10.1016/j.jaci.2012.06.029
7. Dunlop JH, Keet CA. Epidemiology of food allergy. Immunol Allergy Clin North Am. 2018;38(1):13–25. https://doi.org/10.1016/j.iac.2017.09.002
8. Garber JJ, Lochhead PJ, Uchida AM, Roelstraete B, Bergman D, Clements MS, et al. Increasing incidence of eosinophilic esophagitis in Sweden: a nationwide population study. Esophagus. 2022;19(4):535–41. https://doi.org/10.1007/s10388-022-00926-5
9. Clayton F, Fang JC, Gleich GJ, Lucendo AJ, Olalla JM, Vinson LA, et al. Eosinophilic esophagitis in adults is associated with IgG4 and not mediated by IgE. Gastroenterology. 2014;147(3):602–9. https://doi.org/10.1053/j.gastro.2014.05.036
10. Hand TW, Dos Santos LM, Bouladoux N, Molloy MJ, Pagan AJ, Pepper M, et al. Acute gastrointestinal infection induces long-lived microbiota-specific T cell responses. Science. 2012;337(6101):1553–6. https://doi.org/10.1126/science.1220961
11. Wucherpfennig KW. Mechanisms for the induction of autoimmunity by infectious agents. J Clin Invest. 2001;108(8):1097–104. https://doi.org/10.1172/jci200114235
12. Chakravarty EF. Viral infection and reactivation in autoimmune disease. Arthritis Rheum. 2008;58(10):2949–57. https://doi.org/10.1002/art.23883
13. Bjornevik K, Cortese M, Healy BC, Kuhle J, Mina MJ, Leng Y, et al. Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis. Science. 2022;375(6578):296–301. https://doi.org/10.1126/science.abj8222
14. Axelrad JE, Olen O, Askling J, Lebwohl B, Khalili H, Sachs MC, et al. Gastrointestinal infection increases odds of inflammatory bowel disease in a nationwide case-control study. Clin Gastroenterol Hepatol. 2019;17(7):1311–22.e7. https://doi.org/10.1016/j.cgh.2018.09.034
15. Khalili H, Axelrad JE, Roelstraete B, Olen O, D'Amato M, Ludvigsson JF. Gastrointestinal infection and risk of microscopic colitis: a nationwide case-control study in Sweden. Gastroenterology. 2021;160(5):1599–607.e5. https://doi.org/10.1053/j.gastro.2021.01.004
16. Radano MC, Yuan Q, Katz A, Fleming JT, Kubala S, Shreffler W, et al. Cesarean section and antibiotic use found to be associated with eosinophilic esophagitis. J Allergy Clin Immunol Pract. 2014;2(4):475–7.e1. https://doi.org/10.1016/j.jaip.2014.02.018
17. Schwarze J, Gelfand EW. Respiratory viral infections as promoters of allergic sensitization and asthma in animal models. Eur Respir J. 2002;19(2):341–9. https://doi.org/10.1183/09031936.02.00254302
18. Ni J, Friedman H, Boyd BC, McGurn A, Babinski P, Markossian T, et al. Early antibiotic exposure and development of asthma and allergic rhinitis in childhood. BMC Pediatr. 2019;19(1):225. https://doi.org/10.1186/s12887-019-1594-4
19. Toivonen L, Schuez-Havupalo L, Karppinen S, Waris M, Hoffman KL, Camargo CA, et al. Antibiotic treatments during infancy, changes in Nasal microbiota, and asthma development: population-based cohort study. Clin Infect Dis. 2021;72(9):1546–54. https://doi.org/10.1093/cid/ciaa262
20. Ortqvist AK, Lundholm C, Kieler H, Ludvigsson JF, Fall T, Ye W, et al. Antibiotics in fetal and early life and subsequent childhood asthma: nationwide population based study with sibling analysis. BMJ. 2014;349:g6979. https://doi.org/10.1136/bmj.g6979
21. Jensen ET, Kappelman MD, Kim HP, Ringel-Kulka T, Dellon ES. Early life exposures as risk factors for pediatric eosinophilic esophagitis. J Pediatr Gastroenterol Nutr. 2013;57(1):67–71. https://doi.org/10.1097/mpg.0b013e318290d15a
22. Rojler L, Glimberg I, Walker MM, Garber JJ, Ludvigsson JF. Validation of the diagnosis of eosinophilic esophagitis based on histopathology reports in Sweden. Ups J Med Sci. 2021:126.
23. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in

healthcare and medical research. Eur J Epidemiol. 2009;24(11): 659–67. https://doi.org/10.1007/s10654-009-9350-y

24. Brooke HL, Talback M, Hornblad J, Johansson LA, Ludvigsson JF, Druid H, et al. The Swedish cause of death register. Eur J Epidemiol. 2017;32(9):765–73. https://doi.org/10.1007/s10654-017-0316-1

25. Cnattingius S, Ericson A, Gunnarskog J, Kallen B. A quality study of a medical birth registry. Scand J Soc Med. 1990;18(2):143–8. https://doi.org/10.1177/140349489001800209

26. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC Publ Health. 2011;11(1):450. https://doi.org/10.1186/1471-2458-11-450

27. Ludvigsson JF, Almqvist C, Bonamy AK, Ljung R, Michaelsson K, Neovius M, et al. Registers of the Swedish total population and their use in medical research. Eur J Epidemiol. 2016;31(2):125–36. https://doi.org/10.1007/s10654-016-0117-y

28. Ludvigsson JF, Haberg SE, Knudsen GP, LaFolie P, Zoega H, Sarkkola C, et al. Ethical aspects of registry-based research in the Nordic countries. Clin Epidemiol. 2015;7:491–508. https://doi.org/10.2147/clep.s90589

29. Mubanga M, Lundholm C, D'Onofrio BM, Stratmann M, Hedman A, Almqvist C. Association of early life exposure to antibiotics with risk of atopic dermatitis in Sweden. JAMA Netw Open. 2021;4:e215245. https://doi.org/10.1001/jamanetworkopen.2021.5245

30. Stuebe A. The risks of not breastfeeding for mothers and infants. Rev Obstet Gynecol. 2009;2:222–31.

SUPPORTING INFORMATION

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