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Gastroenterology: Eosinophilic Gastrointestinal Disorders

Proton pump inhibitors, antibiotics, and atopy increase the risk of eosinophilic esophagitis in children with esophageal atresia

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Abstract

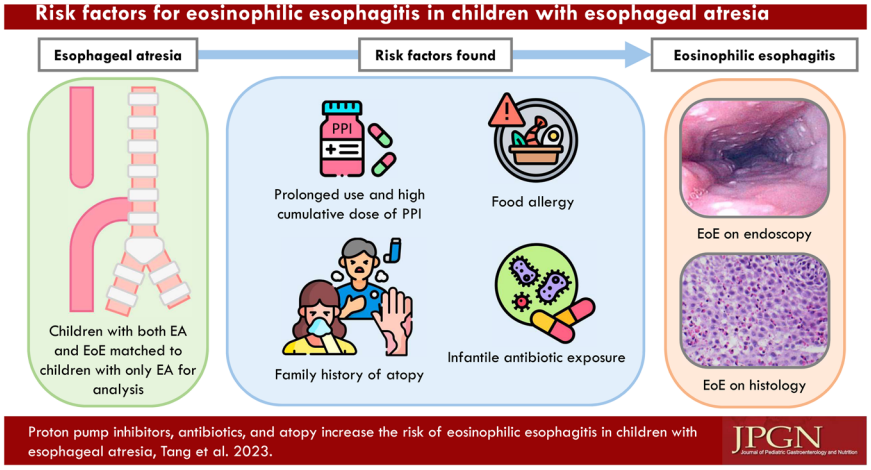
Objective: To determine whether proton pump inhibitor (PPI) exposure is associated with an increased risk of developing eosinophilic esophagitis (EoE) in children with esophageal atresia (EA).

Study Design: A retrospective chart review of children with EA from January 1, 2005 to December 31, 2020 was undertaken at Sydney Children's Hospital Randwick. Children with EA and EoE (cases) were matched (1:2) to children with only EA (controls) to compare PPI exposure. Other early-life factors such as infantile antibiotic exposure and personal or family history of atopy were also analyzed using simple and multivariable logistic regression.

Results: Of 184 children with EA, 46 (25%) developed EoE during this period. Thirty-eight EoE participants were matched to 76 controls. Children with EoE and EA received PPI for significantly higher durations ($p = .018$) and at significantly higher cumulative doses ($p = .017$) than controls. Food allergy (adjusted odds ratio [aOR], 7.317; 95% confidence interval [CI], 2.244–23.742), family history of atopy (aOR, 3.504; 95% CI, 1.268–9.682), and infantile antibiotic exposure (aOR, 1.040; 95% CI, 1.006–1.075) were also significantly associated with an increased risk of developing EoE in the EA cohort.

Conclusions: Prolonged duration and high cumulative dose of PPI exposure were significantly associated with subsequent EoE development in children with EA. Food allergy, family history of atopy, and infantile antibiotic exposure in EA were also significantly associated with an increased risk of EoE development.

Abbreviations: CHARGE, coloboma, heart defects, atresia choanae, growth retardation, genital abnormalities, ear abnormalities; EA, esophageal atresia; EoE, eosinophilic esophagitis; GERD, gastroesophageal reflux disease; H2RA, histamine-2 receptor antagonist; PPI, proton pump inhibitor; SCH, Sydney Children's Hospital Randwick; VACTERL, vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, rectal anomalies, limb abnormalities.



KEYWORDS
acid suppression, esophagus, food allergy, proton pump inhibitor

1 | INTRODUCTION

Esophageal atresia (EA) is the most common congenital esophageal anomaly with an incidence of 2.99 per 10,000 livebirths worldwide.[1] Surgical correction is required soon after birth.[2] An acid suppressant, usually a proton pump inhibitor (PPI), is routinely prescribed postnatally and continued until at least 12 months of age in accordance with current international guidelines[3] for prophylactic management of gastroesophageal reflux disease (GERD) and its complications.[4]

Eosinophilic esophagitis (EoE) is an immune-mediated disease of the esophagus.[5] Esophageal dysfunction results from inflammation and subepithelial fibrosis; which causes feeding difficulties, vomiting, abdominal pain, and failure to thrive in children, while adolescents and adults may experience dysphagia and food bolus obstruction.[3,6] Untreated EoE can result in esophageal strictures.[7] The gold standard for EoE diagnosis ≥15 eosinophils per high power field (HPF) in biopsy, in the presence of esophageal dysfunction.[8] The current incidence is estimated at 5–10 cases arising per 100,000 individuals annually, although the rate is increasing. The etiology of EoE remains largely unknown.[9]

Currently, the known risk factors for EoE are Caucasian ancestry, male sex, and atopy.[10,11] Other suspected risk factors include early acid suppressant exposure, early antibiotic exposure, preterm birth, Cesarean birth, genetic factors, lack of breastfeeding, and aeroallergen exposure.[12,13] The prevalence of EoE was recently reported to be 18% in the EA cohort and 0.06% in the general population.[9,14] The increased prevalence of EoE in EA compared with the general population has been attributed to both EoE and EA being associated with *Forkhead Box (FOX)* gene cluster mutations,[15] dysmotility and strictures prolonging food bolus clearance and peptic mucosal injury due to GERD, increasing exposure to allergens that trigger EoE.[16,17]

Given the routine prescription of PPI following EA repair,[3] and emerging evidence that early acid suppressant exposure could increase the risk of EoE development,[12] further research is warranted to untangle the complexities between PPI exposure and EoE within the EA population. Additionally, no study has examined risk factors for EoE development in the EA cohort specifically.

What is Known

- Children with EA are more likely to develop EoE.
- Children with EA routinely receive long-term PPI therapy.
- Early exposure to PPIs has been postulated to increase risk of EoE in the general population.

What is New

- Prolonged proton pump inhibitor (PPI) use and high cumulative PPI exposure are significantly associated with increased risk for the subsequent development of eosinophilic esophagitis (EoE) in children with esophageal atresia (EA).
- Food allergy, family history of atopy, and infantile antibiotic exposure also demonstrated a significant positive association with development of EoE in children with EA.

The primary objective of this study was to determine whether early prolonged exposure to PPI is associated with subsequent EoE development in children with EA. The secondary objective was to determine whether other early-life factors such as male sex, personal and family history of atopy, exclusive breastfeeding, infantile antibiotic exposure, and long-gap EA are associated with EoE development in children with EA.

2 | METHODS

This study was a single-center retrospective clinical data review undertaken on all children who had their EA repaired at Sydney Children's Hospital between January 1, 2005 and December 31, 2020. Children who died within the first year of life or lacked data for the variables of interest were excluded. Controls were children with EA who did not develop EoE. Ethics approval and waiver of consent were obtained from the Sydney Children's Hospitals Network Human Research Ethics Committee (2020/ETH03114) on 18/01/2021.

2.1 | Data collection

Clinical and demographic information was retrieved from electronic medical records. Data was collected up to the date of EoE diagnosis for children with EA who developed EoE, and up to the last follow-up appointment for those without EoE. Data collected included patient demographics; type of EA and gap length; details of endoscopy and biopsy results at the time of EoE diagnosis; results of other investigations including pH-impedance testing and contrast study if applicable; medication use including acid suppressive medications, antibiotics, and prokinetics; breastfeeding and/or formula use; comorbidities; atopy and food allergy history; number of strictures requiring dilation; and other surgeries.

2.2 | Definitions

Personal history of atopy included history of asthma, eczema, and/or allergic rhinitis. Family history of atopy included any history of these conditions in a first-degree relative. Long-gap EA was defined as EA with a gap of ≥2.5 cm between the proximal and distal esophageal pouches. Children were defined to be exclusively breastfed if they only received breastmilk and no formula before transitioning to solids. Diagnosis of EoE was based on the presence of ≥15 eosinophils/HPF in biopsy in addition to symptoms of esophageal dysfunction. GERD was defined based on symptoms as well as results of pH-impedance testing and endoscopy where performed.

2.3 | Calculation of PPI exposure

Each period of PPI exposure was considered the duration bound by a commencement date and cessation date. Individual periods were added to calculate the total duration of PPI exposure for each patient. Cumulative dose of PPI, expressed in milligrams (mg), was calculated using prescription records and defined as the cumulative dose of PPI used over the study period for each patient. As per standard practice at Sydney Children's Hospital Randwick (SCH), all children with EA were uniformly commenced on compounded omeprazole suspension at birth then continued for varying periods depending on clinical judgment. As some patients grew older, their PPI was changed to esomeprazole if they were still symptomatic on omeprazole. All children received PPI from birth until at least 12 months of age, at which stage weaning was attempted depending on symptoms and results of endoscopy and/or pH impedance testing.

2.4 | Calculation of antibiotic exposure

Only antibiotic exposure in the first year of life was considered, as this is a crucial period for immune maturation and microbial colonization.[18] Infantile antibiotic exposure was expressed as the number of antibiotic courses received during the first year of life. The duration for one antibiotic course was 3 days.[19] Concurrently administered antibiotics were considered separate courses. Administration route and antibiotic type were not considered.

2.5 | Matching of cases to controls for analysis of PPI exposure and stricture occurrences

Children with EA and EoE (cases) were matched 1:2 to children with only EA (controls) for sex, presence of long-gap EA, and prematurity, as these factors have been reported to influence disease risk.[3,15,20,21] PPI and stricture data for each matched control was considered only up to the age at which the corresponding case was diagnosed with EoE, in order that identical periods of time were analyzed between cases and controls. Children with missing PPI data were excluded from case matching.

2.6 | Statistical analysis

Analysis was performed using IBM SPSS Statistics Version 26 (IBM Corp.). Descriptive statistics were used to express participant demographics and clinical

characteristics. Depending on variable distribution, mean ± standard deviation or median (range) were used as appropriate to report the central tendency of continuous variables. Categorical variables were reported as a number (percentage). Demographics and clinical characteristics were compared using Fisher's exact test for categorical variables, Student's *T* test for normally distributed continuous variables, and Mann–Whitney *U* test for non-normally distributed continuous variables. Mann–Whitney *U* test was used to analyze differences in total duration of PPI exposure, cumulative PPI dose, and number of strictures between matched EoE cases and controls due to non-normal distribution. Univariate logistic regression was performed to assess individual associations between other independent variables and EoE to obtain unadjusted odds ratios (OR) with 95% confidence intervals (CI). The α level used was 0.05. A multivariable logistic regression model was developed to adjust for potential confounders. Variables significant upon univariate analysis and those known to be clinically relevant were entered into the model. Adjusted odds ratios (aOR) were obtained. A *p* value of ≤0.05 was considered statistically significant. Children without data for the relevant variables were excluded from logistic regression analysis.

3 | RESULTS

A total of 195 participants were identified to have their EA surgically repaired at SCH between January 1, 2005 and December 31, 2020. Of the 195 participants, 3 were excluded for death in the first year of life. Eight other participants were excluded for lacking data on PPI exposure and early life factors. Data was obtained for 184 participants, consisting of 46 children with EA and EoE, and 138 children with EA only (Figure 1).

Table 1 outlines the demographics and clinical characteristics of participants in the whole cohort. Descriptive statistics revealed statistically significant differences between children with EA with EoE and those without EoE for long-gap EA and exclusive breastfeeding.

3.1 | Characteristics of children with EA at time of EoE diagnosis

The median age of diagnosis for EoE was 25.5 (8–177) months. The median for the maximum number of eosinophils per HPF found at the time of EoE diagnosis was 30 (15–100) eosinophils/HPF.

3.2 | Formula feeding

None of the children with EoE nor children from the control group were on any specialized formulas, including amino acid and extensively hydrolyzed formulas, or elimination diets at the time of diagnosis of EoE. Children who were formula-fed were only on a standard full cream milk or standard milk-based formula.

3.3 | Comparison of PPI exposure and stricture occurrences between cases and controls

EoE cases were matched to controls in a 1:2 ratio. Eight children with EoE who had missing PPI data were excluded from matching. Thirty-eight (83%) children with EoE were matched with 76 controls for sex, long-gap EA, and prematurity. Mann–Whitney *U* test showed that the total duration (months) of PPI exposure of EoE cases (Median = 19.5, $n = 38$) was significantly higher than that of controls (Median = 12.0, $n = 76$, $U = 1052$, $z = 2.358$, $p = .02$). Those who developed EoE (Median = 6145.0, $n = 38$) received a higher cumulative dose (mg) of PPI than controls (Median = 3038.1, $n = 76$, $U = 1017$, $z = 2.380$, $p = .02$). Data on PPI dose per kilogram was unavailable. For number of stricture occurrences, there was no statistically significant difference found between EoE cases (Median = 1, $n = 38$) and controls (Median = 1, $n = 58$, $U = 943$, $z = 1.224$, $p = .22$) (Table 2).

3.4 | Potential risk factors for EoE development in the EA cohort

The variables that demonstrated statistically significant positive associations with EoE in univariate and multivariate logistic regression included food allergy (aOR, 7.317; 95% CI, 2.255–23.742), family history of atopy (aOR, 3.504; 95% CI, 1.268–9.682) and infantile antibiotic exposure (aOR, 1.040; 95% CI, 1.006–1.075) (Table 3). Adjustment attenuated the associations observed for long-gap EA (aOR, 2.528; 95% CI, 0.853–7.492) and exclusive breastfeeding (aOR, 0.586; 95% CI, 0.149–2.308). Male sex (OR, 1.091; 95% CI, 0.559–2.131) and Cesarean delivery (OR, 1.237; 95% CI, 0.579–2.641) did not demonstrate statistically significant associations with development of EoE on univariate analysis and were therefore not included in the multivariate regression model. Nagelkerke R^2 was 0.356.

4 | DISCUSSION

The current study is the first study in children with EA to demonstrate that the total duration and the cumulative dose of PPI exposure are significantly associated with subsequent EoE development in children with EA. It is also the first study in this population to demonstrate

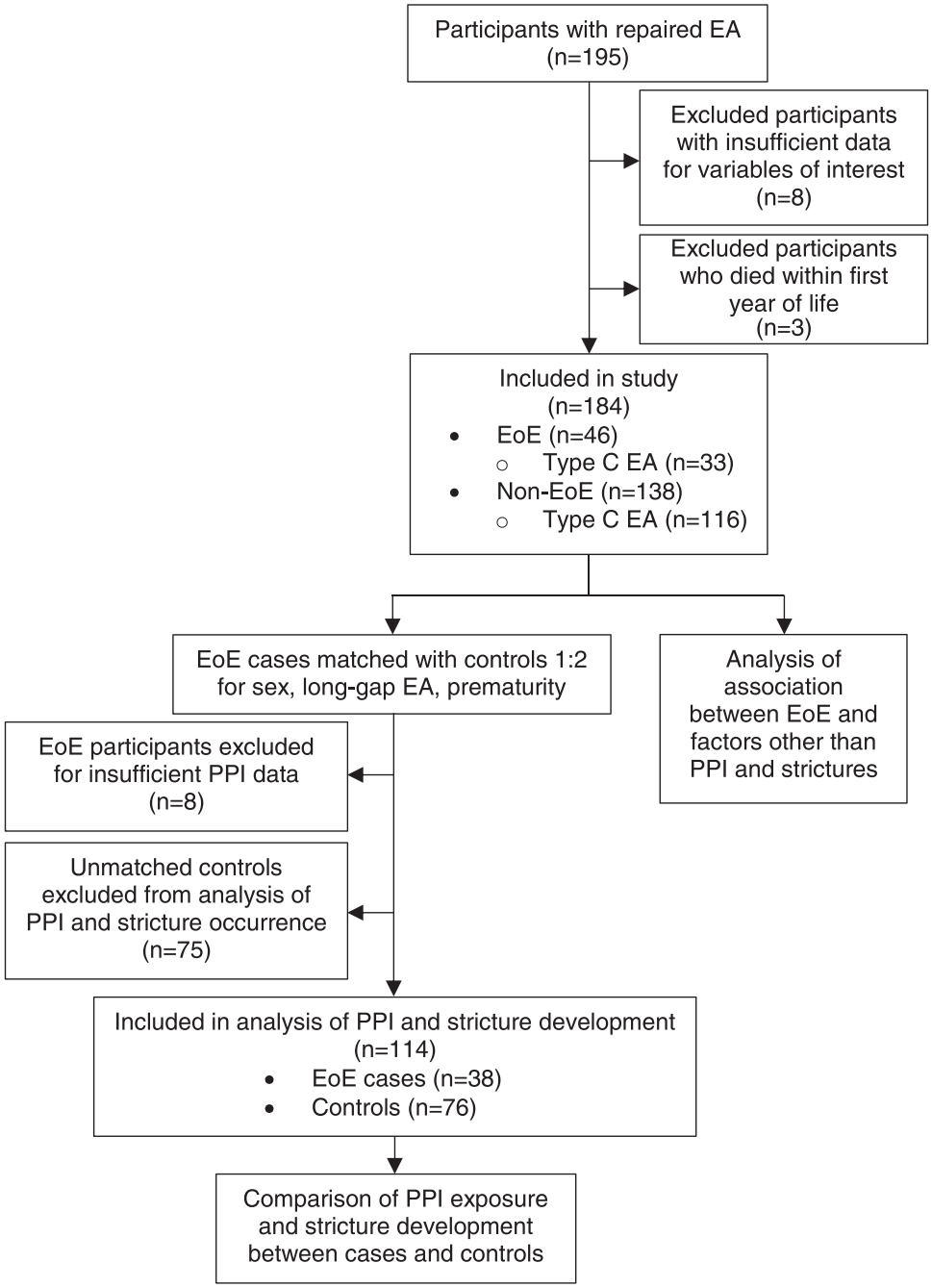


FIGURE 1 Study flowchart. Data were collected on 184 participants with PPI and stricture development investigated by a matched case-control cohort. EA, esophageal atresia; EoE, eosinophilic esophagitis; n, number of participants; PPI, proton pump inhibitor.

positive associations with subsequent EoE development for atopy and infantile antibiotic exposure.

Children with EA routinely undergo long-term PPI therapy following EA repair as prophylaxis against common complications of EA, such as GERD and anastomotic strictures.[3,22] The results of this study suggest that in children with EA, being exposed to high cumulative doses of PPIs and having prolonged PPI use are both significantly associated with the development of EoE. This is congruent with the emerging evidence in the general pediatric population that there is an increased risk of EoE development in individuals who undergo acid suppressive therapy.[21,23–26] A possible explanation for these findings is that acid suppressants inhibit gastric parietal cell function and elevate the gastric pH, thereby impairing peptic digestion of dietary allergens, potentiating sensitization, and facilitating the development of allergic diseases like EoE.[27] Sensitization may also occur due to PPIs increasing mucosal permeability in the gastrointestinal tract and enabling antigen penetration.[28] Alternatively, the association between extensive

TABLE 1 Overall participant demographics and clinical characteristics.

Characteristic	EoE *n* = 46 [number (percentage) or mean ± SD or median (range)]	Non-EoE *n* = 138 [number (percentage) or mean ± SD or median (range)]	*p* Value
Sex			
Male	25 (54)	72 (52)	0.87
Female	21 (45)	66 (4)	0.87
Missing	0 (0)	0 (0)	
Age[a] (years)	2 (14)	5 (17)	<0.001[i]
Type of EA-TEF			
Type A	8 (17)	14 (10)	0.20
Type B	2 (4)	2 (1)	0.26
Type C	33 (71)	116 (84)	0.08
Type D	2 (4)	3 (2)	0.60
Type H	1 (2)	3 (2)	1.00
Missing	0 (0)	0 (0)	
EA-TEF gap length			
Long-gap[b]	13 (28)	20 (14)	<0.05[i]
No long-gap	33 (72)	118 (86)	<0.05[i]
Missing	0 (0)	0 (0)	
Repair of EA-TEF			
Primary repair[c]	36 (78)	109 (79)	0.51
Delayed repair[d]	1 (2)	4 (2)	1.00
Foker procedure[e]	8 (17)	15 (10)	0.31
Scharli procedure[f]	1 (2)	3 (2)	1.00
Missing	0 (0)	7 (5)	
Prematurity			
Preterm birth	18 (39)	42 (30)	0.36
Term birth	27 (59)	90 (65)	0.36
Missing	1 (2)	6 (4)	
Birthweight (grams)	2589.3 ± 708.2	2621.0 ± 726.5	0.80
Missing	1 (2)	18 (13)	
Birth mode			
Cesarean birth	21 (45)	52 (37)	0.70
Vaginal birth	16 (35)	49 (36)	0.70
Missing	9 (20)	37 (27)	
Mode of feeding			
Exclusively breastfed	3 (6)	32 (23)	0.008[i]
Not exclusively breastfed	38 (83)	83 (60)	0.008[i]
Missing	5 (11)	23 (50)	

TABLE 1 (Continued)

Characteristic	EoE $n = 46$ [number (percentage) or mean ± SD or median (range)]	Non-EoE $n = 138$ [number (percentage) or mean ± SD or median (range)]	*p* Value
H2RA exposure	19 (41)	45 (32)	0.29
Prokinetic exposure	10 (21)	41 (29)	0.34
Comorbidities/congenital abnormalities			
VACTERL syndrome	10 (21)	30 (21)	1.00
CHARGE syndrome	1 (2)	3 (2)	1.00
Vertebral anomalies	6 (13)	30 (21)	0.28
Anorectal anomalies	3 (6)	14 (10)	0.57
Cardiac anomalies	30 (65)	78 (56)	0.39
EA-TEF complications			
GERD			
History of GERD[g]	43 (93)	117 (84)	0.29
Abnormal pH-impedance test[h]	8 (17)	18 (13)	0.32
Normal pH-impedance test[h]	21 (46)	26 (19)	0.32
Procedures			
Gastrostomy	17 (37)	35 (25)	0.19
Fundoplication	7 (15)	18 (13)	0.81
Aortopexy	4 (8)	20 (14)	0.33

Abbreviations: CHARGE, coloboma, heart defects, atresia choanae, growth retardation, genital abnormalities, ear abnormalities; EA, esophageal atresia; EoE, eosinophilic esophagitis; GERD, gastroesophageal reflux disease; H2RA, histamine-2 receptor antagonist; *n*, number of participants; VACTERL, vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, rectal anomalies, limb abnormalities.

[a]Age denoted the age of the child at their last appointment at the EA clinic between January 1, 2005 and December 31, 2020.

[b]Long-gap EA was defined as a gap >2.5 cm or >2 vertebral bodies between the proximal and distal esophageal pouches.

[c]Primary repair was EA repair that occurred within 7 days of birth.

[d]Delayed repair was EA repair that occurred after 7 days.

[e]Foker procedure referred to the surgical repair of long-gap EA-TEF whereby traction sutures were placed on esophageal pouches and attached to the chest wall to elongate the pouches with tension before attempting anastomosis.

[f]Scharli procedure referred to the surgical transposition of the stomach used to replace the missing lower esophagus in EA-TEF.

[g]History of GERD was defined as having had GERD at any point during the study period; this was defined based on endoscopy, pH-impedance results, and/or documented signs/symptoms indicative of GERD.

[h]Impedance test results were from the time of EoE diagnosis for children with EoE, or the last impedance test between January 1, 2005 and December 31, 2020 for children without EoE.

[i]Statistically significant result.

PPI exposure and EoE development could be attributed to dysbiosis and diminished gut microbiome diversity. A recent study showed that prolonged use of PPI in EA altered the composition of the early infant gut,[29] thereby predisposing individuals to allergic diseases.[30–32]

While our findings agree with the literature on the associations between PPI exposure and subsequent EoE development, the current study also adds to the existing body of knowledge by reproducing these results in the context of children with EA for the first time. Furthermore, previous studies focused on PPI exposure during infancy only and also did not quantify level of exposure.[21,23–26] Our investigation on PPI exposure extends much later into childhood and offers novel findings that having greater PPI exposure (in dosage and/or duration) may be associated with an increased risk of developing EoE in children with EA. This is important as children with EA routinely receive PPI treatment for at least 1 year under the current guidelines, and therefore the more pertinent issue in this unique cohort is not whether having any PPI exposure at all increases the risk of EoE (as answered by previous studies) but whether the risk can potentially be stratified according to the degree of PPI exposure. The results suggest that clinicians should carefully monitor PPI use and avoid unnecessarily prolonging PPI exposure. Recent studies showed that prophylactic treatment with

TABLE 2 Comparison of PPI exposure and stricture formation between EoE cases and controls.

	EoE Median	*n*	Controls Median	*n*	*U*	*z*	*p* Value
PPI exposure							
Total duration of PPI exposure (months)	19.5	38	12.0	76	1052.0	2.358	0.02[a]
Cumulative dose of PPI received (mg)	6145.0	38	3038.1	76	1017.0	2.380	0.02[a]
Stricture formation							
Number of strictures	1	38	1	58	943.0	1.224	0.22

Abbreviations: EoE, eosinophilic esophagitis; mg, milligrams; *n*, number of participants; PPI, proton pump inhibitor.
[a]Statistically significant result.

TABLE 3 Univariate and multivariate analysis of independent variables using logistic regression.

	Unadjusted		Adjusted	
Independent variable	OR (95% CI)	*p* Value	aOR (95% CI)	*p* Value
Sex	1.091 (0.559–2.131)	0.80		
Long-gap EA-TEF	2.324 (1.047–5.161)	0.04[b]	2.528 (0.653–7.492)	0.09
Type A EA-TEF	1.865 (0.727–4.781)	0.20		
Nonprimary repair	1.376 (0.598–3.179)	0.46		
Prematurity	1.447 (0.717–2.920)	0.30		
Low birth weight	1.053 (0.521–2.126)	0.89		
Cesarean delivery	1.237 (0.579–2.641)	0.58		
H2RA exposure	1.454 (0.732–2.889)	0.29		
Prokinetic exposure	0.644 (0.292–1.419)	0.28		
Infantile antibiotic exposure	1.034 (1.006–1.062)	0.02[b]	1.040 (1.006–1.075)	0.02[b]
Exclusive breastfeeding	0.205 (0.059–0.711)	0.01[b]	0.586 (0.149–2.308)	0.45
CHARGE syndrome	0.970 (0.098–9.566)	0.98		
VACTERL syndrome	0.981 (0.436–2.209)	0.96		
Cardiac anomalies	1.370 (0.683–2.749)	0.38		
Ano-rectal anomalies	0.593 (0.162–2.165)	0.43		
Food allergy	8.500 (3.436–21.028)	<0.001[b]	7.317 (2.244–23.742)	0.001[b]
Personal history of atopy[a]	2.821 (1.390–5.728)	0.005[b]	1.463 (0.536–3.989)	0.46
Family history of atopy[a]	2.581 (1.302–5.115)	0.007[b]	3.504 (1.268–9.682)	0.02[b]
History of GERD	3.675 (0.457–29.569)	0.22		
Gastrostomy	1.641 (0.805–3.346)	0.17		
Fundoplication	1.137 (0.442–2.927)	0.79		
Aortopexy	0.538 (0.174–1.666)	0.28		

Abbreviations: aOR, adjusted odds ratio; CHARGE, coloboma, heart defects, atresia choanae, growth retardation, genital abnormalities, ear abnormalities; CI, confidence interval; EA, esophageal atresia; GERD, gastroesophageal reflux disease; H2RA, histamine-2 receptor antagonist; OR, odds ratio; VACTERL, vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, rectal anomalies, limb abnormalities
[a]Atopy included asthma, eczema, and/or allergic rhinitis.
[b]Statistically significant result.

PPIs in EA patients did not prevent the formation of anastomotic strictures.[33,34] No association was also found between the duration of postoperative acid suppression and anastomotic stricture development.[35] Moreover, studies found significant variation in the implementation of the guidelines, possibly due to lack of awareness thereof and/or the lack of strong evidence underlying the recommendations.[36,37] Hence, the routine use of PPIs for the first year of life as recommended by the current guidelines may need to be revisited.[3] Symptoms in the EA cohort are often nonspecific and do not help to distinguish between GERD, EoE, dysmotility, and stricture. Hence regular monitoring using endoscopy with biopsies and pH-impedance testing where clinically indicated would enable more timely and accurate diagnosis of EoE, as well as help avoid unnecessary and often prolonged PPI exposure at high doses based on symptomatology alone.[38]

In this study, food allergy and family history of atopy were shown to significantly increase the risk of developing EoE in children with EA by over seven-fold and three-fold, respectively. This adds to the mounting evidence that the risk of developing EoE is greater in individuals with a history of allergic diseases.[23,26,39] The association between food allergy and EoE has been supported by the alleviation of inflammation observed upon avoidance of dietary allergens and implementation of elemental diets composed of amino acids.[40,41] To date, the allergens most commonly associated with EoE are milk, egg, wheat, and soy.[23,42] In regard to atopy, infants with positive family history of atopy, especially maternal history, have been found to be predisposed to developing atopic diseases later in childhood.[43] Interestingly, only familial (and not personal) atopic history remained positively associated with EoE when adjusting for other factors in this study, potentially alluding to the complex genetic components underlying EoE and allergy diatheses. Genome-wide studies have identified various candidate genes implicated in both EoE and other atopic diseases: *TSLP, CCL26, FLG, CAPN14*.[11,44] Overexpression of *TSLP* has been observed in EoE, eczema, and asthma; it is hypothesized to contribute to allergen sensitization and EoE development by promoting Th2 cell development and potentiating the Th2 inflammatory response.[44] Similarly, *CAPN14* has been implicated in atopic diseases and its upregulation by the proallergic Th2 cytokine, interleukin-13, has also been observed in the esophageal epithelium in EoE.[11,45] Upregulation of *CAPN14* has been associated with impaired barrier integrity and function, which is thought to be a central component of EoE pathogenesis.[46] However, continued research is necessary to clarify the mechanisms by which genes and atopy affect the development of EoE.

This study additionally revealed a significant positive association between infantile antibiotic exposure and development of EoE in children with EA for the first time. Previous reports showed up to a six-fold increase in EoE risk for those with early antibiotic exposure.[12] This study adds to the mounting evidence that antibiotics in infancy contribute to dysbiosis[47] and may predispose to atopic diseases, including EoE.[12,23,26,27] As early life is a critical time during which intestinal bacterial colonization, microbiome development, and immune system maturation occur simultaneously,[18] antibiotic exposure in infancy may compromise these processes.[47] A recent murine model discovered that antibiotic treatment reduced microbiota protective for the esophagus, especially *lactobacillales*, and promoted the outgrowth of bacterial taxa implicated in atopic inflammation.[48] Antibiotic use was also associated with greater esophageal eosinophilic infiltration as well as the upregulation of allergen-specific IgE and pro-Th2 cytokines involved in the EoE pathophysiology.[49] While further research into the effects of antibiotic exposure on EoE development is required, it is important that antibiotic overuse in infants with EA be avoided where there is no clear indication.

Although a significant inverse association was initially found between exclusive breastfeeding and EoE development, this association attenuated upon adjustment for other factors. Currently, the literature on the association between exclusive breastfeeding and EoE development remains divided. One study reported a near-significant reduction of EoE risk in those exclusively breastfed and attributed this to microbiota alteration caused by the early introduction of formula.[12] Meanwhile, others revealed no association.[24,26] Further studies are therefore needed to gain deeper insight into the effects of exclusive breastfeeding on the development of EoE.

Our study also showed a positive association between long-gap EA and EoE, which however attenuated upon adjustment for other variables. Individuals with long-gap EA could be predisposed to EoE as they are more likely to remain on high-dose PPI for long periods due to propensity for developing anastomotic strictures and severe GERD.[50] Dhaliwal et al. reported over an 11-fold risk of developing EoE in children with long-gap EA in the only other study to investigate this factor, though they did not adjust for other variables or match cases to controls and had a smaller sample size.[15] Other factors that did not show any significant association with EoE in this cohort despite being reported as EoE risk factors in the literature included male sex and Cesarean delivery.

The current study was limited by incomplete data which is generally unavoidable in retrospective studies. Additionally, this was a single-center study; however, the study has a large sample size compared to the current literature, and the multidisciplinary EA clinic sees patients from a wide catchment area as it is the largest dedicated EA clinic in the southern hemisphere.

Another limitation was that the controls were not matched to cases by symptoms. It is possible that the EA patients were treated with high-dose PPIs for prolonged periods because of symptoms thought to be due to reflux. However, from the mechanisms explored above, we believe the likely contributing factor to the increased risk of developing EoE in children with EA shown in this study is prolonged PPI exposure rather than symptomatology in the EA cohort. The main strength of this study is that it was the first to examine the effects of PPIs and many other early-life factors on risk of subsequent EoE development in the EA cohort. Furthermore, it was the first to consider the extent of PPI exposure (duration and dosage), as previous studies only noted whether participants did or did not have exposure. This study, which has the largest number of EA patients with EoE compared to previous studies, was also the first to match EoE cases to controls and adjust for other variables when evaluating risk factors for EoE in the EA cohort.

4.1 | Future directions

As EA and EoE are both rare diseases, most studies thus far have had limited sample sizes. Hence, the current study's findings should be validated with prospective multicenter studies with a larger cohort size examining how PPI exposure and early life factors affect the risk of subsequent EoE development in children with EA. Future studies could also further investigate the potential genetic associations between EoE and EA, such as *FOX* gene cluster mutations, as well as pharmacogenomic associations between PPI, EoE, and genes such as *Cytochrome P450 2C19*.

5 | CONCLUSION

In summary, this study was the first to examine risk factors for the development of EoE in children with EA, and the first to identify associations between childhood PPI exposure and subsequent EoE development in these children. Previous studies in general pediatric cohorts have reported an increased risk of developing EoE for individuals with early PPI exposure. The current findings corroborate these results for the first time in an EA cohort. It is likely that PPIs are overprescribed (often for prolonged periods) in the EA cohort and should be prescribed more selectively based on objective evaluation for GERD using endoscopy with biopsies and pH-impedance testing off treatment, especially given the multifactorial etiology for esophageal and extra-esophageal symptoms in this cohort. The current study also showed that atopy and infantile antibiotic exposure were significantly associated with subsequent EoE development in children with EA. Clinicians should aim to avoid the coexistence of multiple potential risk factors by exercising caution when prescribing antibiotics in infancy, promoting breastfeeding, and avoiding prolonged high-dose PPI exposure where not clinically indicated. Close monitoring and long-term multidisciplinary follow-up of pediatric patients with EA (particularly those with multiple potential risk factors) could also facilitate earlier detection and management of EoE.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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