

Role of Environmental Factors in the Development of Pediatric Eosinophilic Esophagitis

Mordechai Slae¹ · Rabin Persad¹ · Aldrich Jing-Tao Leung¹ · Raniah Gabr² ·
Dion Brocks² · Hien Quoc Huynh¹

Received: 24 February 2015 / Accepted: 28 May 2015
© Springer Science+Business Media New York 2015

Abstract

Background Despite accumulating data on the pathogenesis of eosinophilic esophagitis, not much is known about risk factors for the development of the disease. The role of factors such as smoking, breastfeeding, early antibiotic exposure and other factors that have been associated with other allergic diseases has not been well studied in children with eosinophilic esophagitis.

Aim To explore the role of environmental and medication exposures in the development of pediatric eosinophilic esophagitis.

Methods We conducted a cross-sectional case–control study, utilizing a parent and child questionnaire and medical chart review. Urine cotinine levels, measured by high-performance liquid chromatography, were obtained as objective evidence for smoking exposure.

Results One hundred and two children with eosinophilic esophagitis and 167 controls were recruited. The controls were mainly diagnosed with functional gastrointestinal disorders (33 %) and gastroesophageal reflux disease (29 %). Food allergy, specifically for peanuts and tree nuts, and allergy to pollen, tree, and grass were significantly higher among eosinophilic esophagitis children. Smoking exposure, both primary and secondary, was not associated with pediatric eosinophilic esophagitis when compared to controls (odds ratio 0.96, 95 % confidence interval 0.58–1.59). Furthermore, early smoking exposure in the first year of life was higher among controls. Common accepted risk factors for allergy and atopy, such as breastfeeding practices, antibiotics exposure, animals' exposure, and others, were not found to be associated with eosinophilic esophagitis in our study.

Conclusion Common risk factors in other allergic and atopic conditions were not found to be associated with eosinophilic esophagitis.

✉ Hien Quoc Huynh
hien.huynh@ualberta.ca

Mordechai Slae
slae@ualberta.ca

Rabin Persad
Rabin.persad@albertahealthservices.ca

Aldrich Jing-Tao Leung
ajleung@ualberta.ca

Raniah Gabr
gabr@ualberta.ca

Dion Brocks
dbrocks@ualberta.ca

Keywords Allergy · Eosinophilic esophagitis · Risk factors · Tobacco smoking · Urine cotinine

Abbreviations

EoE	Eosinophilic esophagitis
FGID	Functional gastrointestinal disorders
GERD	Gastroesophageal reflux disease
GI	Gastrointestinal

Introduction

Eosinophilic esophagitis (EoE) is a relatively newly recognized eosinophilic gastrointestinal disorder, of which the incidence is increasing [1, 2]. It is characterized by

¹ Pediatric GI and Nutrition, Department of Pediatrics, University of Alberta, Edmonton Clinic Health Academy (ECHA), 4th Floor, Room 4-579, 11405 - 87th Avenue, Edmonton, AB T6G 1C9, Canada

² Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, 2-142H Katz Group Centre, 87 Ave and 114 St, Edmonton, AB T6G 2J7, Canada

eosinophilic inflammation and remodeling of the esophageal mucosa, leading to feeding difficulties and failure to thrive in toddlers, dysphagia, food impaction, and perforation in older patients [3]. The pathogenesis of EoE is not completely understood, but likely involves reaction to food and environmental antigens [4]. This is supported by the use of elimination diets in EoE and the seasonal effects of EoE observed by some authors [3, 4]. EoE is associated with atopy. The majority of EoE patients have concurrent allergic diseases including seasonal allergies, food allergy, and asthma. A high percentage of EoE patients test positive to food and environmental allergens [5–7].

Environmental factors have been shown to affect allergic conditions. First-hand or second-hand exposure to tobacco smoke is a major risk factor for the development of asthma [8, 9], while smoking cessation improves asthma symptoms and control [10]. Tobacco smoke has also been shown to be associated with allergic sensitization and sensitization to food allergens [8]. Smoking or second-hand smoking as a trigger for EoE has not yet been studied thoroughly. Potentially, esophageal smoking exposure can occur through ingestion of airborne particles [11]. For example, mouse models of EoE have been developed through airway exposure to allergens and/or cytokines produced by Th2 cells giving rise to esophageal inflammation. Similarly, there is a role for aeroallergens in EoE, as evident by reports of seasonal variation in disease presentation [6]. Protective factors such as breastfeeding [12], having older siblings, early day care attendance [13], exposure to farm animals [14] and risk factors such as early life antibiotic exposure and acetaminophen exposure [15, 16] and fast food consumption [17] were found to be associated with the development of allergic diseases. However, these factors have not been well studied in EoE. Hence, we aimed to determine whether smoking and other exposures, which have been linked with the development of atopic/allergic diseases, are also associated with EoE.

Methods

Participants

EoE patients and controls aged 1–18 years were recruited through pediatric gastroenterology clinics and endoscopy unit where they were seen for diagnosis or follow-up. All underwent upper GI endoscopy for various indications. The study was approved by University of Alberta Research Ethics Boards (Pro00028193); parent consent and child (≥ 7 years) assent were obtained. EoE patients were defined according to accepted criteria based on esophageal histopathology findings with peak eosinophils count ≥ 15 per high power field after at least 6–8 weeks trial of

anti-reflux proton-pump inhibitors therapy [3]. Controls were children aged 1–18 years, undergoing endoscopy for various indications. We excluded children with other hypereosinophilic conditions, such as parasitic infection, hypereosinophilic syndrome, eosinophilic gastroenteritis, inflammatory bowel disease, and those with multi-systemic diseases (can have many confounding risk factors). Also excluded from the controls were children with recent (4 weeks) use of systemic or topical corticosteroids or other immunosuppressive agents at time of endoscopy (can mask EoE by altering histological findings).

Questionnaires and Chart Review

Parents completed questionnaires either online or by hard copy. Included were 74 questions regarding demographics, medical and allergic background, active and passive smoking exposure of the child, breastfeeding and food introduction history, vaccinations and drug allergies, family allergic background, type of area of living, farm animals' exposure, exposure to pets, early age and current antibiotic treatment frequency, nonsteroidal anti-inflammatory drugs and acetaminophen treatment, fast food consumption frequency, day care attendance, birth order, and number of siblings. A child questionnaire was developed and administered for the children aged 9 years and older, completed confidentially by them either online or by hard copy. Questions included the child's current or past smoking status, and friends', parents', and other household members' current smoking status. Medical background and endoscopy results were obtained by chart review.

Smoking exposure is defined as either first-hand smoking or exposure to any smoker in the same household or smoker whom the child has close contact with, e.g., friends and caregivers. Pregnancy smoking exposure was defined as smoking by either the mother and/or her partner during pregnancy. We deemed the risk of reporting positive exposure to smoking in the absence of smoking in the household to be low. Therefore, if there was disagreement in reporting smoking status between the child and parents, we elected to use the positive exposure in our analysis.

Urine Cotinine Assay

Urine was collected in sterile manner and transferred within short time to deep freeze (-80°C). The samples were collected at the time of questionnaire completion or within few days. A previously published liquid chromatography-mass spectrometric assay method was used for the quantification of total cotinine in urine [18]. The validated lower limit of quantification of the assay was 2 ng/mL where the coefficient of variation and percentage error was

<12 and 6 %, respectively. Levels above the limit of quantification were considered positive exposure.

Statistics

The sample size calculation was based on smoking exposure as the main outcome. Based on a Canadian nation-wide asthma study, we assumed a smoking exposure of 40 % in the general pediatric population and speculated an increase of 15 % in the cases group. Using the University of British Columbia clinical significance calculator, the number needed for EoE group would be 100 and 200 for the control to achieve an odds ratio of 1.83 (95 % confident interval of 1.13–3.0) and absolute risk reduction of 0.15 (95 % confident interval of 0.03–0.27). We have chosen an unequal 2–1 because there are more patients undergoing gastroscopy for reasons other than EoE.

Descriptive statistics were used to analyze the differences between the demographic and clinical characteristics of children with EoE and controls. Proportions and Chi-square tests were used for categorical variables and means, and Student's *t* tests were used for continuous variables, log-transformed in case of an abnormal distribution. For non-normal distributions, median and Mann–Whitney *U* test were used. Logistic regression was used to assess the association between smoking and EoE. When comparing the odds ratio of smoking exposure between EoE and control subjects, a multivariable model was developed to adjust for potential confounders. Variables entered in the model included: (1) known confounders based on the literature; (2) those with an unadjusted odds ratio of 0.7 and less, or 1.5 or higher; or (3) those with a *p* value of 0.2 or less. Variables were then removed from the model if this did not change the odd ratios of the others by 10 % or more. Statistical analysis was done with SPSS version 21.

Results

We enrolled 269 participants: 102 diagnosed with EoE and 167 controls. The demographics of the EoE and control patients are summarized in Table 1. Controls included functional gastrointestinal disorders (FGID) (33.0 %), gastroesophageal reflux disease (GERD) (28.7 %), and others.

Smoking Exposure

Questionnaires were completed by 263 parents and 152 children. In 45 cases, there was a disagreement between

Table 1 Demographics, eosinophilic esophagitis versus controls

Group	Control	EoE	<i>p</i> value
Number of participants	167	102	
Caucasian mother	85 %	86 %	0.15
Caucasian father	83 %	80 %	0.82
Male gender	55 %	78 %	<0.001
Mean height for age <i>z</i> scores (CDC)	−0.11	0.21	0.18
Mean weight for age <i>z</i> scores (CDC)	0.18	0.10	0.67
Mean BMI <i>z</i> scores (CDC)	0.22	−0.03	0.28
Mean birth weight (kg)	3.79	3.71	0.73
Mean age at time of survey (years)	10.0	10.9	0.11
Mean age at first scope (years)	9.2	8.6	0.33

Bold values are statistically significant (*p* < 0.05)

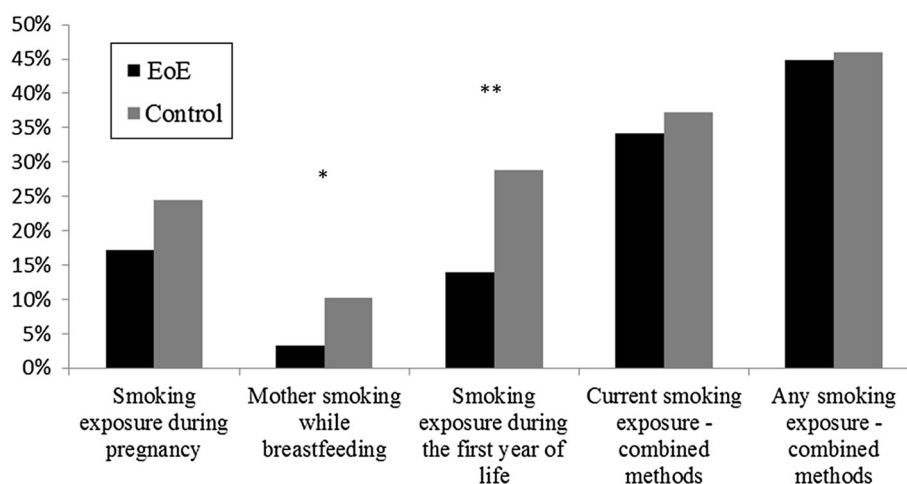
BMI body mass index, *CDC* center for disease control and prevention, *EoE* eosinophilic esophagitis

child's and parent's questionnaire, with only either reporting exposure. In these cases, smoking exposure was considered positive. When we compared EoE to controls, past smoking exposure during pregnancy, during breastfeeding, and first year of life were all lower among EoE (Fig. 1). In contrast, present smoking exposure reported by the questionnaires, including first- or second-hand smoking exposure, was almost equal in the EoE group and the controls (35.3 and 33.5 %, respectively, *p* = 0.76). Similarly, present exposure as detected by urinary cotinine was equal as follows: of the 269 cases, 198 samples were available for urinary cotinine testing. Positive exposure rates were 27 % in the EoE and 26 % in the controls (*p* = 0.86). When comparing the questionnaires detection of present exposure to the urinary cotinine results, 33 smokers were identified by the two modalities, 18 more by urinary cotinine, and 34 by self-report. The overall agreement between the questionnaires and urine cotinine was 74 %.

We combined the identified current smoking exposures from both questionnaires and the urine test and compared the rates of present smoking exposure between the EoE and the control groups (see Fig. 1). Once again exposure rates were found similar (37.3 vs. 34.1 %, EoE vs. controls, *p* = 0.60). Batching together either past or present exposure resulted again in comparable rates (44.9 vs. 45.9 %, EoE vs. controls, *p* = 0.87). The general rate of the whole sample current smoking exposure was 35.3 % and any smoking exposure was 44.6 %.

Since we observed a difference between cases and controls in smoking exposure in the first year of life (Fig. 1, Chi-square), we divided the participants into 3 groups according to the timing of exposure: exposure in the first year of life, exposure later in life but not in the first year of life, and no-exposure group, in order to explore whether the association of lower smoking exposure rates

Fig. 1 Comparison of past and current smoking exposure, EoE versus controls. * $p = 0.008$. ** $p = 0.006$, Chi-square test. EoE eosinophilic esophagitis. Combined methods = urine cotinine + questionnaires



with EoE was specific for exposure in the first year of life. On this analysis, while controlling for possible confounders, once again exposure in the first year of life appeared to be associated with a lower risk of having EoE (Table 2), while smoking exposure later in life was not different between the groups (though p value did not reach statistical significance, $p = 0.06$).

Breastfeeding

Breastfeeding rates were 92.0 % among EoE and 85.6 % among controls. Of these, 52.8 and 42.9 %, respectively, were solely breastfed, without formula supplementation. None of these differences were statistically significant ($p > 0.05$). Similarly, median age of formula introduction in breastfed babies was older among EoE, compared to controls, but not significant (2.5 and 2 months, respectively, Mann–Whitney U test, $p > 0.05$). However, mean breastfeeding length was significantly longer among EoE, 9.7 months, compared to 9.1 months for controls ($p = 0.02$ on t test after log transformation). Breastfeeding duration and formula introduction age by age groups are shown in Fig. 2.

Allergic Background

Allergic background is reported in Tables 3 and 4. Anaphylactic food allergy was significantly higher among the EoE cases (Table 3), interestingly, distinctively for peanuts (reported by 7 % of the EoE vs. 0 %, of the controls, p value = 0.001) and tree nuts (4 vs. 1.8 %, p value = 0.432), but indifferent for cow's milk, wheat, eggs, soy, fish, and shellfish (data not shown). Other reactions such as cough, wheezing, swelling, rash, vomiting and diarrhea, abdominal pain, and nasal symptoms were reported higher in EoE compared to controls for peanuts, but not for other foods (data not shown).

Of EoE or controls who reported environmental allergies, 79 % were allergic to pollen/trees/grass, followed by 39 % for dust, 33 % for molds, and 20 % for furry animals. However, of these allergen groups, only pollen/trees/grass seemed to associate with EoE group when compared to controls (Table 4).

There was no difference between the groups in vaccination rate (94.9 and 93.8 %, EoE and controls, $p = 0.67$), vaccination reaction rate (9.3 and 7.6 % $p = 0.64$), and drug allergy rate (13.0 and 19.6 %, $p = 0.16$).

Table 2 Multiple regression analysis for smoking exposure as a risk factor for eosinophilic esophagitis compared to controls

Variable	Crude odds ratio			Adjusted odds ratio		
	Odds ratio	95 % CI	Significance	Odds ratio	95 % CI	Significance
Smoking exposure during first year of life	0.53	0.27–1.02	0.06	0.48	0.23–1.02	0.06
Smoking exposure, but not on the first year of life	1.66	0.86–3.03	0.14	1.83	0.90–3.69	0.09
Environmental allergy	2.70	1.6–4.55	<0.001	1.86	1.01–3.42	0.05
Asthma	1.86	1.11–3.11	0.02	1.54	0.84–2.83	0.16
Atopic dermatitis (eczema)	2.92	1.73–4.93	<0.001	2.35	1.3–4.25	0.005

EoE eosinophilic esophagitis

Fig. 2 Comparison of formula introduction age (a) and breastfeeding duration (b) by age groups, EoE versus controls. * $p = 0.23$. ** $p = 0.002$, Chi-square test. EoE eosinophilic esophagitis

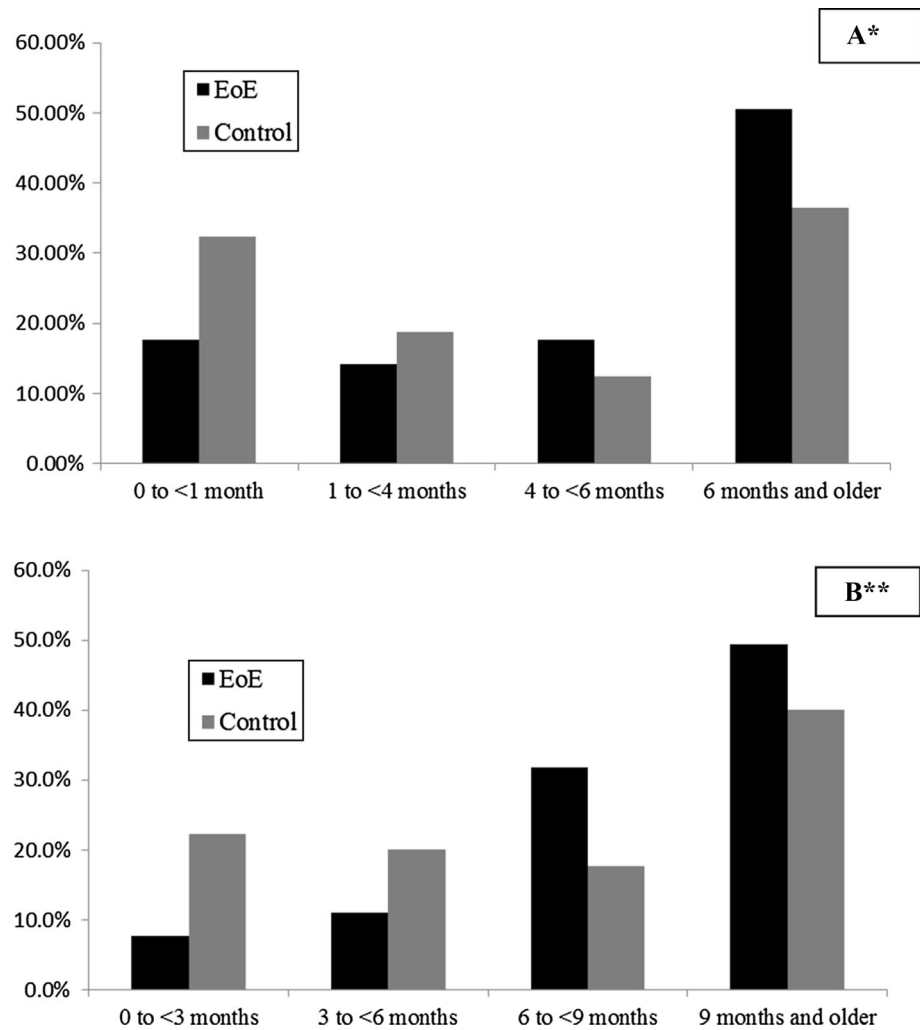


Table 3 Associated allergic conditions, eosinophilic esophagitis versus controls

Associated allergic conditions	Control (%)	EoE (%)	<i>p</i> value	Odds ratio	95 % CI	
					Lower	Upper
Atopic dermatitis (eczema)	38	57	0.002	2.92	1.73	4.93
Allergic conjunctivitis	35	55	0.002	2.25	1.34	3.77
Asthma	33	47	0.02	1.85	1.11	3.11
Allergic rhinitis	35	62	<0.001	3.04	1.80	5.13
Food allergy—anaphylaxis	2.5	10	0.008	4.417	1.35	14.49

EoE eosinophilic esophagitis

Other Exposures

Past or current pets' exposure and farm animals' exposure were similar between EoE and controls. The rates of antibiotic exposure in first year of life and recent antibiotic exposure were similar. Urban versus rural area of living (self-reported and by postal code decoding) was found in similar rate. Both ibuprofen and acetaminophen frequencies of use were found higher among the controls. First-time food introduction age was similar between the groups, with the

exception of wheat introduction, which was delayed among the EoE group. For these and other parameters, see Table 5.

Discussion

In this study, we compared a group of EoE children to a group of children who underwent upper gastrointestinal endoscopy for FGID, GERD, and other indications. Study groups were comparable with similar demographics. The

Table 4 Environmental allergies, eosinophilic esophagitis versus controls

Allergen	Control (%)	EoE (%)	<i>p</i> value	Odds ratio	95 % CI	
					Lower	Upper
Environmental allergies	34	58	<0.001	2.70	1.60	4.55
Pollen, trees, grass	21.6	32.4	0.049	1.740	0.999	3.032
Dust mite	10.2	15.7	0.182	0.609	0.293	1.267
Mold	8.4	12.7	0.248	0.626	0.282	1.393
Furry animals	6.0	5.9	0.972	1.019	0.359	2.893

EoE eosinophilic esophagitis

overall current smoking exposure rate in our children was 44.6 %, similar to rates reported by a national Canadian pediatric study [13] and rates reported in the USA [19]. Either by objective measure, using urinary cotinine, or through the subjective questionnaire, and the combination, smoking exposure was not found to confer a significant risk for EoE development. In fact, early smoking exposure during the first year of life was higher among the controls in our study, which is similar to finding by another EoE study of higher maternal smoking rates while breastfeeding among controls [20]. Likewise, it is known that smoking exposure is inversely associated with ulcerative colitis, and several mechanisms have been suggested for this phenomenon, such as reduction in gut blood flow, reduction in mucosal cytokine levels, and alteration of gut microbiota, motility, or permeability [21]. The fact that smoking exposure after the first year of life did not protect from EoE points toward a more time-specific effect. Being an antigen-driven disease, mainly food antigens, pediatric EoE is likely to be susceptible to processes which take place at the first year of life, when food tolerance is been formed. Repeated and further studies are required to confirm and explore this finding, such as smoking exposure in adult-onset EoE.

The use of both objective and subjective measures to detect smoking exposure was strength of this study. Utilization of separate questionnaire for parents and children provided additional cases to parent questionnaire alone. Some exposure cases were also identified only by urine testing, demonstrating either lack of disclosure or unaware exposure. Urine cotinine is the biomarker of choice for first- and second-hand smoking exposure [22]. It has a half-life of 15–19 h, as compared to 2–3 h for nicotine. Nonetheless, it does not capture remote exposure, which is better documented by questionnaires. The agreement between self-reported smoking exposure and cotinine levels has been examined in previous studies and reviewed by Fluresco et al. [23]. Misclassification values vary up to 73 % and are higher when studying correlation between a biomarker and parental report on child's exposure, rather than between a biomarker and adult self-exposure report. Taken together, the two methods are complementary.

While allergic background and male gender bias found in our study are known risk factors for EoE [7, 24], there are some nuances in our findings. In our study, family allergic background was found to be more common on the paternal side (data not shown), which correlates with the male dominance in EoE and may be explained by a genetic factor transferred from male to male. Accordingly, a unique single nucleotide polymorphism of the thymic stromal lymphopoietin receptor, present only in males, was found to be associated with EoE [25]. As for the cases allergic background, we found that peanuts and tree nuts dominated food allergies. Upon reviewing history of environmental allergies, we found that of different allergens, it was pollen/trees/grass that were significantly associated with increased risk of EoE and not dust mite, mold, and animal dander. This finding correlates with the findings of van Rihjn et al. [26]. In their study of adult EoE patients, they observed high rates of aeroallergen sensitization with cross-reactivity to food allergens among the cases. Of note, birch pollen predominated sensitization in EoE patients. It also correlates with reports of seasonal variation in EoE, which is probably related to outdoor allergens.

Other environmental and medication exposures studied were not found to be associated with EoE. Most parameters related to breastfeeding were not significantly different between the groups; breastfeeding length was significantly longer among EoE, questioning the protective role of extending breastfeeding in EoE. Antibiotics exposure—either in the first year of life or recent—did not differ between the groups. In contrast, Jensen et al. [20] reported higher antibiotic exposure during the first year of life, 81 % in EoE and 73 % in GERD, compared to 42 % in healthy controls. Our rates for both EoE and controls were similar to their controls rates (41 %). In Jensen's study, thirty-one pediatric EoE patients were compared to 26 pediatric healthy controls and 26 pediatric GERD patients. The authors also report lower exclusive breastfeeding rates among EoE children compared to controls (6 % EoE, 23 % GERD, and 19 % healthy controls). Our findings were 52.8 and 42.9 % for EoE and controls, probably representing

Table 5 Different exposures representing indices (additional data were collected), eosinophilic esophagitis versus controls

Exposures	Control	EoE	<i>p</i> value	Odds ratio	95 % CI	
					Lower	Upper
Day care attendance	44 %	43 %	0.9	0.97	0.59	1.61
Age at day care attendance (months)	26.0	20.0	0.15	1.02	1.00	1.05
Single child	10 %	7 %	0.17	0.91	0.35	2.39
Firstborn child	40 %	49 %	0.44	1.55	0.88	2.73
Intra-uterine growth retardation	5 %	3 %	0.48	0.49	0.10	2.51
Cow's milk, age at first exposure (months)	14.0	12.3	0.11	1.03	0.98	1.08
Other dairies, age at first exposure (months)	13.1	14.7	0.51	0.99	0.98	1.01
Wheat, age at first exposure (months)	9.2	13.1	0.05	0.97	0.94	1.01
Eggs, age at first exposure (months)	14.0	15.3	0.43	0.99	0.97	1.01
Soy, age at first exposure (months)	25.0	27.8	0.68	1.00	0.99	1.01
Peanuts, age at first exposure (months)	24.2	21.3	0.21	1.01	0.99	1.03
Tree nuts, age at first exposure (months)	28.6	28.9	0.93	1.00	0.99	1.01
Fish, age at first exposure (months)	23.4	28.2	0.13	0.99	0.97	1.00
Shellfish, age at first exposure (months)	41.9	45.8	0.53	1.00	0.99	1.01
Present pets' exposure	67 %	55 %	0.2	0.61	0.37	1.02
Past pets' exposure	69 %	63 %	0.49	0.78	0.45	1.34
First year pets' exposure	63 %	62 %	0.5	0.94	0.56	1.58
Farm animals' exposure	23 %	23 %	1	1.14	0.57	2.28
Antibiotic use in first year						
First exposure after the first year	41 %	41 %	0.61	1.00		
Exposure at first month	10 %	5 %		0.53	0.18	1.55
First exposure between 2 and 6 months	22 %	23 %		1.04	0.53	2.05
First exposure between 7 and 12 months	28 %	31 %		1.11	0.60	2.06
Current antibiotics use						
Less than once a year	44 %	49 %	0.37	1.00		
Once a year	25 %	17 %		0.62	0.31	1.25
Two to three times per year	18 %	23 %		1.20	0.61	2.37
4 or more times per year	13 %	11 %		0.74	0.32	1.72
NSAIDs frequency of use						
Less than once per 6 months	34 %	53 %	0.01	1.00		
Once per 6 months or more	34 %	26 %		0.50	0.27	0.91
Once a month or more	33 %	21 %		0.42	0.22	0.79
Acetaminophen frequency of use						
Less than once per 6 months	38 %	50 %	0.07	1.00		
Once per 6 months or more	34 %	34 %		0.76	0.43	1.34
Once a month or more	28 %	16 %		0.45	0.23	0.89
Average number of fast food meals per week	0.8	1.0	0.13	1.19	0.95	1.50
Urban area of living (self-reported)	68 %	66 %	0.81	0.94	0.55	1.60

EoE eosinophilic esophagitis

different population characteristics. Other trending factors (though not statistically significant) discovered in Jensen's study were associated with cesarean delivery and preterm birth. Maternal smoking rates were lower among EoE children (13 %, 19–23 % in controls), in agreement with our finding of lower rates of first-year smoking exposure among EoE. In our study, we also asked about first-time

food introduction age. There was no difference between the groups in relation to specific foods, apart from wheat introduction age which was delayed among the EoE group. The significance of this finding is unclear, given that milk introduction age, which is another common identified causative of EoE, was indifferent. The role of NSAID and acetaminophen in EoE as potential protective factor is

unclear since significant proportion of our control subjects have functional gastrointestinal disease and likely to use these medications. Further study is needed using well children as control subjects.

Although our control subjects were <200, our data clearly showed that smoking is not associated with having EoE, our primary outcome. Whether it is a protective factor will require a larger study. We used an objective measure (urinary cotinine) in the assessment of smoking exposure. However, for assessing other exposures, we used questionnaires. This method has limitations and might be associated with recall and non-response biases. Nevertheless, since we used symptomatic controls who have been labeled with a medical condition, the bias is likely to be similar for both groups. Another limitation of our study is the ethnic background. In our study, more than 80 % were Caucasian, and this may limit the external validity of our conclusions to populations with substantially different ethnic breakdown. Consequently, it is recommended that the study be repeated in other metropolitan centers. We were not able to confirm the allergic background of many of our control subjects because they have not undergone assessment by allergist. We therefore adopted a symptom-based approach in allergy assessment based on history. The male predominance as a confounding factor was not accounted for in our control group. Not accounting for this in our control group, would not have affected our conclusion on factors such as smoking exposure, food introduction, analgesics and antibiotics use, animal exposure, and breastfeeding practices. However, other factors such as childhood asthma and food allergy are more common in boys (the opposite is true in adulthood), and allergic rhinitis could be affected.

In summary, this large case-control study of pediatric EoE patients found that many of the exposures found to be commonly associated with other allergic conditions, like asthma, were not associated with EoE, potentially implying that the immune dysregulation in EoE differs from that in other allergic conditions. However, other risk factors should be sought and identified, perhaps with additional emphasis on exposure during pregnancy, such as chemical exposures, industrial and air pollution [27, 28], damp housing and mold exposure [29], use of gas stove or oven for heat [30], and the role of westernized and processed food.

Acknowledgments We would like to thank Karen J. Goodman, PhD, and Hsiu-Ju Chang, MSc, Department of Medicine, University of Alberta, for help with the statistics and Amr Abdel-Radi, University of Alberta, and Ronda Danchuk of Women and Children's Research Institute for help with data collection. We thank Dr Justine Turner for her invaluable suggestions and comments on the manuscript.

Conflict of interest MS was funded through the Stollery Children's Hospital Foundation and Alberta Innovates Health Solutions post-graduate fellowship. AL was supported by a summer-student grant by the University of Alberta. HH is a consultant for Sucampo, Janssens, and Abbvie, holds a grant from Janssens, and received fund from Actavis for educational events. None is directly related to this study. For the remaining authors, none were declared. This study was funded by the Women and Children's Health Research Institute (WCHRI), University of Alberta, Edmonton, AB, Canada.

Ethical Standard This study was approved by the University of Alberta Research Ethics Board (Pro00028193). All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. This article does not contain any studies with animals performed by any of the authors.

References

1. Soon IS, Butzner JD, Kaplan GG, deBruyn JC. Incidence and prevalence of eosinophilic esophagitis in children. *J Pediatr Gastroenterol Nutr.* 2013;57:72–80.
2. Dellon ES, Jensen ET, Martin CF, Shaheen NJ, Kappelman MD. Prevalence of eosinophilic esophagitis in the United States. *Clin Gastroenterol Hepatol.* 2014;12:589–596.
3. Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol.* 2011;128:3–20.
4. Rothenberg ME. Biology and treatment of eosinophilic esophagitis. *Gastroenterology.* 2009;137:1238–1249.
5. Assa'ad AH, Putnam PE, Collins MH, et al. Pediatric patients with eosinophilic esophagitis: an 8-year follow-up. *J Allergy Clin Immunol.* 2007;119:731–738.
6. Prasad GA, Alexander JA, Schleck CD, et al. Epidemiology of eosinophilic esophagitis over three decades in Olmsted County, Minnesota. *Clin Gastroenterol Hepatol.* 2009;7:1055–1061.
7. Spergel JM, Brown-Whitehorn TF, Beausoleil JL, et al. 14 years of eosinophilic esophagitis: clinical features and prognosis. *J Pediatr Gastroenterol Nutr.* 2009;48:30–36.
8. Hansen K, Mangrio E, Lindstrom M, Rosvall M. Early exposure to secondhand tobacco smoke and the development of allergic diseases in 4 year old children in Malmö, Sweden. *BMC Pediatr.* 2010;10:61.
9. Ho SM. Environmental epigenetics of asthma: an update. *J Allergy Clin Immunol.* 2010;126:453–465.
10. McLeish AC, Zvolensky MJ. Asthma and cigarette smoking: a review of the empirical literature. *J Asthma.* 2010;47:345–361.
11. Matt GE, Quintana PJ, Hovell MF, et al. Households contaminated by environmental tobacco smoke: sources of infant exposures. *Tob Control.* 2004;13:29–37.
12. Gdalevich M, Mimouni D, David M, Mimouni M. Breast-feeding and the onset of atopic dermatitis in childhood: a systematic review and meta-analysis of prospective studies. *J Am Acad Dermatol.* 2001;45:520–527.
13. Midodzi WK, Rowe BH, Majaesic CM, Saunders LD, Senthilselvan A. Early life factors associated with incidence of physician-diagnosed asthma in preschool children: results from the Canadian early childhood development cohort study. *J Asthma.* 2010;47:7–13.

14. Ege MJ, Mayer M, Normand AC, et al. Exposure to environmental microorganisms and childhood asthma. *New Engl J Med*. 2011;364:701–709.
15. Marra F, Lynd L, Coombes M, et al. Does antibiotic exposure during infancy lead to development of asthma? A systematic review and metaanalysis. *Chest*. 2006;129:610–618.
16. Beasley RW, Clayton TO, Crane J, et al. Acetaminophen use and risk of asthma, rhinoconjunctivitis, and eczema in adolescents: international study of asthma and allergies in childhood phase three. *Am J Respir Crit Care Med*. 2011;183:171–178.
17. Ellwood P, Asher MI, Garcia-Marcos L, et al. Do fast foods cause asthma, rhinoconjunctivitis and eczema? Global findings from the International study of asthma and allergies in childhood (ISAAC) phase three. *Thorax*. 2013;68:351–360.
18. Gabr RQ, Elsherbiny ME, Somayaji V, Pollak PT, Brocks. A liquid chromatography-mass spectrometry method for nicotine and cotinine: utility in screening tobacco exposure in patients taking amiodarone. *Biomed Chromatogr*. 2011;25:1124–1131.
19. Centers for Disease C, Prevention. Vital signs: nonsmokers' exposure to secondhand smoke—United States, 1999–2008. *MMWR Morb Mortal Wkly Rep*. 2010;59:1141–1146.
20. Jensen ET, Kappelman MD, Kim H, Ringel-Kulka T, Dellon ES. Early life exposures as risk factors for pediatric eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr*. 2013;57:67–71.
21. Rom O, Avezov K, Aizenbud D, Reznick AZ. Cigarette smoking and inflammation revisited. *Respir Physiol Neurobiol*. 2013;187: 5–10.
22. Stevens KR, Munoz LR. Cigarette smoking: evidence to guide measurement. *Res Nurs Health*. 2004;27:281–292.
23. Florescu A, Ferrence R, Einarson T, Selby P, Soldin O, Koren G. Methods for quantification of exposure to cigarette smoking and environmental tobacco smoke: focus on developmental toxicology. *Ther Drug Monit*. 2009;31:14–30.
24. Noel RJ, Putnam PE, Rothenberg ME. Eosinophilic esophagitis. *New Engl J Med*. 2004;351:940–941.
25. Sherrill JD, Gao PS, Stucke EM, et al. Variants of thymic stromal lymphopoietin and its receptor associate with eosinophilic esophagitis. *J Allergy Clin Immunol*. 2010;126:160–165 e163.
26. van Rhijn BD, van Ree R, Versteeg SA, et al. Birch pollen sensitization with cross-reactivity to food allergens predominates in adults with eosinophilic esophagitis. *Allergy*. 2013;68:1475–1481.
27. McConnell R, Berhane K, Gilliland F, et al. Asthma in exercising children exposed to ozone: a cohort study. *Lancet*. 2002;359:386–391.
28. Morgenstern V, Zutavern A, Cyrys J, et al. Atopic diseases, allergic sensitization, and exposure to traffic-related air pollution in children. *Am J Respir Crit Care Med*. 2008;177:1331–1337.
29. Quansah R, Jaakkola MS, Hugg TT, Heikkinen SA, Jaakkola JJ. Residential dampness and molds and the risk of developing asthma: a systematic review and meta-analysis. *PLoS ONE*. 2012;7:e47526.
30. Lanphear BP, Aligne CA, Auinger P, Weitzman M, Byrd RS. Residential exposures associated with asthma in US children. *Pediatrics*. 2001;107:505–511.