Diseases of the Esophagus (2017) **0**, 1–8
DOI: 10.1093/dote/dox122

DISEASES OF THE ESOPHAGUS

ISDE The International Society for Diseases of the Esophagus

Original Article

Pollen-food allergy syndrome is a common allergic comorbidity in adults with eosinophilic esophagitis

D. Letner,[1] A. Farris,[1] H. Khalili,[1,2] J. Garber[1,2]

[1] *Gastrointestinal Unit, Massachusetts General Hospital and* [2] *Department of Medicine, Harvard Medical School, Boston, Massachusetts, USA*

SUMMARY. **Eosinophilic esophagitis (EoE) is associated with atopic diseases including asthma, allergic rhinitis, and atopic dermatitis; however, limited data exist on the correlation between pollen-food allergy syndrome (PFAS) and EoE. We analyzed 346 adults with EoE treated at a single center between 2002 and 2016. Demographic and EoE-specific data including clinical features and measures of EoE disease severity and treatments were collected. The presence of other atopic diseases, family history, prevalence of peripheral eosinophilia and elevated IgE, and details of PFAS triggers were collected. Twenty six percent of the 346 subjects in our cohort had both EoE and PFAS (EoE–PFAS). Compared to subjects with EoE alone, subjects with EoE–PFAS had an increased frequency of allergic rhinitis (86.7% vs. 64.2%, $P < 0.001$) and family history of allergies (71.1% vs. 53.3%, $P = 0.003$), and comprised a higher proportion of EoE diagnoses made in the spring ($X^2 < 0.001$). 43.3% of subjects with concurrent EoE and PFAS opted for treatment with elimination diet, and these measures failed to induce remission in 46.2% of cases. In most cases, elimination diet failed despite strict avoidance of PFAS trigger foods in addition to common EoE triggers including dairy, wheat, and eggs. EoE–PFAS was also associated with higher serum IgE at the time of EoE diagnosis (460.6 vs. 289.9, $P < 0.019$). Allergic rhinitis and a family history of food allergy were independently associated with having EoE–PFAS. The most common triggers of PFAS in adults with EoE are apples (21.1%), carrots (15.5%), and peaches (15.5%). Along with asthma, allergic rhinitis and atopic dermatitis, PFAS is a common allergic comorbidity that is highly associated with EoE. Further studies aimed at understanding mechanistic similarities and differences of PFAS and EoE may shed light on the pathogenesis of these closely related food allergy syndromes.**

KEY WORDS: **eosinophilic esophagitis, IgE, oral allergy syndrome, pollen-food allergy syndrome.**

INTRODUCTION

Eosinophilic esophagitis (EoE) is an increasingly recognized allergic disease in which infiltration of the esophageal epithelium by eosinophils leads to chronic dysphagia, recurrent food impactions, and progressive esophageal stenosis and fibrosis.[1] There is significant overlap in genetic and environmental risk factors for EoE with other atopic diseases, and up to 80% of patients with EoE have concurrent atopic diseases including atopic dermatitis, asthma, allergic rhinitis, and IgE-mediated food allergy.[2]

The causal role of food antigens in triggering and maintaining EoE disease activity is supported by key studies demonstrating that disease remission is achieved in more than 90% of children[3] and approximately 75% of adults[4] placed on an elemental diet, and in more than two thirds of children and adults who eliminate wheat, dairy, egg, soy, peanuts/tree nuts, and fish/shellfish (six-food elimination diet, SFED).[5,6] Although several lines of evidence indicate that EoE is not primarily mediated by food-specific IgE,[7-10] the precise role of IgE and the relationship between IgE-mediated food allergies and EoE is presently not well understood. Important overlapping mechanisms between specific food allergies and EoE may exist for at least a subset of EoE patients.[11]

Address correspondence to: John Garber, MD, Gastrointestinal Unit, Massachusetts General Hospital, 55 Fruit Street, Jackson 712, Boston, MA 02114, USA.
E-mail: jjgarber@mgh.harvard.edu
Specific author contributions: Dorothea Letner performed data extraction, analysis and interpretation of data, statistical analyses, wrote the manuscript, and approved the final version of the manuscript; Alexandra Farris performed data extraction and approved the final version of the manuscript; Hamed Khalili performed analysis and interpretation of data, statistical analyses, and approved the final version of the manuscript; John Garber contributed to study conception and design, performed data extraction, analysis and interpretation of data, wrote the manuscript, and approved the final version of the manuscript. All authors approved the final version of this manuscript, including the authorship list.

© The Authors 2017. Published by Oxford University Press on behalf of International Society for Diseases of the Esophagus.
All rights reserved. For permissions, please e-mail: journals.permissions@oup.com

Downloaded from https://academic.oup.com/dote/advance-article-abstract/doi/10.1093/dote/dox122/4566194
by Harvard Law School Library user
on 17 November 2017

Pollen-food allergy syndrome (PFAS), a term that encompasses and is sometimes used interchangeably with oral allergy syndrome (OAS), is an IgE-mediated hypersensitivity reaction to specific foods that results from sensitization to cross-reactive environmental allergens, most commonly derived from trees, grass, weeds, and pollen.[12] Patients with PFAS develop oral-pharyngeal pruritus, angioedema and itching, tingling or throat tightness within minutes of ingesting the trigger food.[13] An important study by van Rhijn *et al*. characterized aeroallergen sensitization patterns in adult EoE patients, and found that approximately three-quarters expressed at least one aeroallergen-specific IgE, and 30 out of the 79 EoE subjects in this study displayed birch pollen (rBet v 1) sensitization with cross-reactivity to food-allergens.[14] In parallel, there has been intense interest in determining whether seasonal variations influence the likelihood of EoE diagnosis and clinical activity of established disease,[15] and a seasonal correlation between peak levels of grass pollen and onset of EoE symptoms and subsequent diagnosis was recently described.[16] Whether and to what extent environmental sensitizations may trigger or perpetuate disease in patients with EoE is unknown.

We analyzed a large cohort of adult subjects diagnosed with EoE at our center to better define the prevalence of PFAS in subjects with EoE, and we examined clinical, histologic, and laboratory differences among patients who had EoE with evidence of PFAS (EoE–PFAS) compared to those who had EoE with no documentation of PFAS.

MATERIALS AND METHODS

This cohort study was approved by the Institutional Review Board at Partners Healthcare and Massachusetts General Hospital.

Patient selection

We conducted a retrospective chart review of patients within the Partners Healthcare network through a query of the Partners Healthcare Research Patient Data Registry (RPDR), a centralized clinical data repository and query system covering every patient seen across affiliated institutions within the Partners Healthcare system. We searched for a diagnosis of eosinophilic esophagitis and any assessment of 'food allergy' status within the electronic medical records between 1980 and 2016 and performed a manual chart review of the medical record for each potential case to confirm the diagnosis of EoE. We excluded patients diagnosed with EoE under the age of 18. An allergist-immunologist and a gastroenterologist saw the majority of patients.

Inclusion criteria

Patients were included in this study if the diagnosis of EoE could be confirmed by pathology and endoscopy reports demonstrating >15 eosinophils per high-power field (HPF) despite PPI therapy. Subjects were excluded from the study if they were diagnosed with EoE prior to the age of 18, did not have a positive biopsy with >15 eosinophils per HPF, did not have an adequate trial of PPI therapy at the time of their positive esophageal biopsy (including a minimum of omeprazole 40 mg QD or 20 mg BID, esomeprazole 40 mg QD or 20 mg BID, lansoprazole 30 mg QD, dexlansoprazole 30 or 60 mg QD, rabeprazole 20 mg QD, or pantoprazole 40 mg QD for at least 8 weeks), or there was insufficient clinical information available to assess the presence or absence of PFAS.

Clinical definitions

The date of diagnosis was based on the earliest date that the patient had a positive biopsy despite PPI therapy. Symptoms of EoE were assessed by physician-guided questions at the time of diagnostic endoscopy or by chart review by a GI physician within 2 weeks of the endoscopy report prior to treatment changes. Symptoms of PFAS were defined as tingling of the mouth, throat or lips, slight swelling and bumpiness of the mouth, throat or lips immediately after the consumption of the trigger food, and/or itching, redness, or slight swelling of the hands after peeling or handling the trigger food. A PFAS reaction was confirmed by a review of medical records. We retrieved information on age at diagnosis, sex, race, and family history of atopy and food allergies in first- and second-degree relatives for each subject by a chart review. In addition, we collected information on values for serum IgE and absolute eosinophil counts (AEC). The upper limit of normal serum IgE was considered to be >100 IU/mL and the upper limit of normal AEC was considered to be >500 K/uL in accordance with reference values set by our hospital's core immunology and hematology laboratories. We recorded these values closest to the date of diagnosis as well as recorded if patients had ever had a high serum IgE or AEC.

Histologic and endoscopic assessments

Pathology reports from the index endoscopy were reviewed to assess peak eosinophil counts, defined as the number of interepithelial eosinophils per high-powered field. The EoE endoscopic reference score (EoE-EREFS) score was first proposed in 2013 to classify the endoscopic features of EoE based on the

Downloaded from https://academic.oup.com/dote/advance-article-abstract/doi/10.1093/dote/dox122/4566194
by Harvard Law School Library user
on 17 November 2017

Table 1 Demographics and baseline characteristics for adult EoE study subjects

	Total EoE	EoE with PFAS	EoE without PFAS	*P* value
Number, (%)	346	90 (25.9%)	256 (74.1%)	NA
Age at diagnosis, median (range)	38.3 (18–78.1)	36.2 (18.3–61)	39.08 (18–78.1)	0.12
Male, no. (%)	221 (63.8%)	60 (66.7%)	161 (62.9%)	0.49
Race				
White, no. (%)	316 (91.3%)	82 (91.1%)	233 (91.0%)	
Nonwhite, no. (%)	30 (8.7%)	8 (8.9%)	23 (9.0%)	
Other atopic diseases				
Asthma, no. (%)	156 (45%)	47 (52.2%)	109 (42.4%)	0.11
Allergic rhinitis, no. (%)	243 (70%)	78 (86.7%)	165 (64.2%)	<0.001
Atopic dermatitis, no. (%)	95 (27.4%)	29 (32.2%)	66 (25.7%)	0.231
Family history				
EoE or history of esophageal dilation, no (%)	46 (13.3%)	17 (18.9%)	21 (11.3%)	0.067
Food allergy, no (%)[a]	201 (57.9%)	64 (71.1%)	137 (53.1%)	0.003

[a]Allergies were defined as presence of food allergy in a first- or second-degree family member.

presence of edema, rings, exudates, furrows, and stricture.[17] The EREFS score was built into the standard electronic medical record (EMR) documentation for endoscopy reports at our institution in 2015. Endoscopy reports for all subjects included in this study were reviewed and, if documented by the endoscopist performing the EGD, the composite EREFS and subscores were recorded.

Statistical analysis

For all statistical analyses, patients were separated and compared based on their PFAS status. Continuous variables were compared with two-tailed t-tests. Categorical variables were compared using chi-squared analyses. Binary logistic regression modeling was used to ascertain the effects of statistically significant variables in predicting the presence of EoE–PFAS while controlling for the other variables in the equation. For all associations, a P value of <0.05 was considered statistically significant. Statistical analysis was performed in R (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

PFAS a common allergic comorbidity in adults with EoE

Our initial search identified 1128 potential EoE subjects. After reviewing all inclusion criteria, we confirmed 346 adult subjects with EoE for subsequent analysis. Baseline characteristics of all patients in our adult EoE cohort are listed in Table 1. Consistent with previous reports,[18] there was a male predominance (63.7%), although at a slightly lower male:female ratio (1.9:1) than previously reported,[19-21] and the majority of patients were white. The mean age of diagnosis for the entire EoE cohort was 38.3 years. Of the 346 subjects included in our study, 90 (25.9%) also had documented PFAS symptoms, while 256 (74%) had no documentation of PFAS (Fig. 1). The diagnosis of

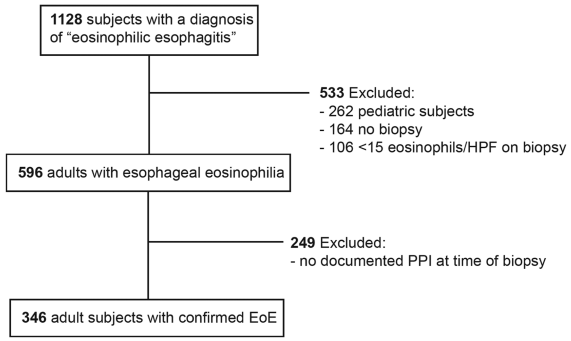

Fig. 1 Study flow chart.

concurrent PFAS was most often made by an allergist (84.8%) or primary care physician (13%) and only rarely made by a gastroenterologist (2.2%). Compared to EoE patients without PFAS, EoE–PFAS patients had a higher frequency of allergic rhinitis (86.7% of EoE–PFAS vs. 64.2% EoE alone, $P < 0.001$), but not asthma (52.2% of EoE–PFAS vs. 42.4% EoE alone, $P = 0.11$) or atopic dermatitis (32.2% EoE–PFAS vs. 25.7% EoE alone, $P = 0.231$), and a higher frequency of a family history of food allergies (71.1% vs. 53.3%, $P = 0.003$). The presence or absence of concurrent PFAS was not correlated with any significant differences in age at diagnosis, family history of EoE or esophageal dilation, or race (all $P_{\text{comparisons}} > 0.05$). On multivariate analysis, the presence of allergic rhinitis (OR 3.0, 95% CI 1.39–7.24) and family history of atopic disease (OR 2.195, 95% CI 1.193–4.161) were each associated with significantly increased risk of PFAS in the EoE population after controlling for age of EoE diagnosis, gender, and race (Table 2).

Outcome of dietary elimination in patients with EoE and PFAS

Compared to EoE subjects without concurrent PFAS, EoE–PFAS subjects were similarly likely to opt for a trial of empiric elimination diet (43.3% for EoE–PFAS vs. 46.1% for EoE without PFAS, $P = 0.481$).

Downloaded from https://academic.oup.com/dote/advance-article-abstract/doi/10.1093/dote/dox122/4566194
by Harvard Law School Library user
on 17 November 2017

Table 2 Multivariate logistic regression model of factors predicting the presence of EoE with PFAS

	Beta coefficient	Odds ratio	*P* value	95% confidence interval	
				Lower	Upper
Allergic rhinitis	1.110	3.033	0.008	1.388	7.235
Family history of atopy	0.786	2.195	0.013	1.193	4.161

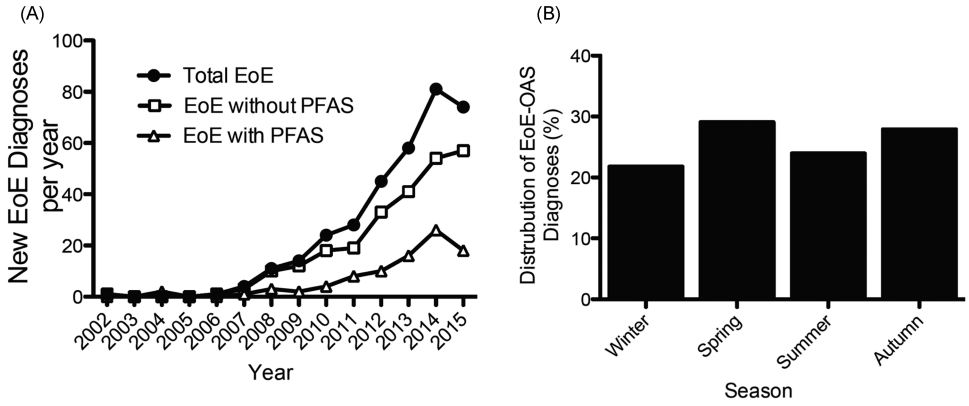

Fig. 2 (A) Number of EoE cases diagnosed by year, (B) Proportion of new EoE cases with concurrent PFAS, by season of diagnosis.

Among the 39 EoE–PFAS subjects in our study who were treated with dietary elimination, the most common foods eliminated were dairy (76.9%), wheat (59.0%), and eggs (59.0%), followed by soy (48.7%), nuts (46.2%), seafood (33.3%), and corn (12.8%). Overall, 56.4% of EoE–PFAS subjects achieved remission (41.0%) or were in the process of identifying food triggers at the time of this study (15.4%), while 46.2% of subjects failed to achieve remission by empiric elimination diet. Among the 18 subjects who failed to respond to elimination diet, 11 reported strictly avoiding their PFAS trigger, whereas in the 5 remaining cases subjects either were not specifically avoiding their PFAS trigger, or the degree to which they were avoiding their PFAS trigger was unclear. Of note, in all but one case of EoE–PFAS failing empiric elimination diet, subjects had multiple triggers of PFAS symptoms including a combination of apples, bananas, grapes, carrots, celery, nectarines, and eggplant.

Patients with concurrent EoE and PFAS are more often diagnosed in the spring and autumn seasons

Given the known seasonal variation in environmental allergens, including proteins derived from trees, grasses, and pollen, we examined whether there were any significant effects of seasonal variation on diagnosis of EoE during the course of our study. Consistent with experiences reported at other institutions, we observed a steady and significant increase in the number of EoE diagnoses over the course of the study (Fig. 2A). We divided the year into four seasons: winter (December, January, February), spring (March, April, May), summer (June, July, August) and autumn (September, October, November) according to previously published studies of seasonal variation in disease risk.[22,23] We found that EoE–PFAS cases comprised a significantly greater proportion of new EoE diagnoses in the spring (29.1%, $X^2 \leq 0.001$, Fig. 2B), which correlates with the start of birch pollen season for the Northeastern US climate zone.[24]

Higher serum IgE but not peripheral eosinophil counts in EoE–PFAS

Of the 90 patients with EoE–PFAS, 28.9% had a history of elevated serum IgE, compared to 10.2% of patients with EoE without PFAS ($P < 0.001$) (Table 3). In addition, patients with EoE–PFAS had significantly higher serum IgE levels nearest to the time of EoE diagnosis compared to subjects with EoE alone (460.6 vs. 289.9, $P = 0.019$). There were no significant differences in peak esophageal eosinophil counts (Table 3) at diagnosis according to the presence of absence of concurrent PFAS. During upper endoscopy, patients with EoE–PFAS were more likely to have esophageal exudates compared to those with EoE alone ($P = 0.027$), but there were otherwise no significant differences in the presence of edema, rings, furrows or strictures (Fig. 3).

Birch pollen cross-reactive foods are the most common triggers of PFAS associated with EoE

Subjects with EoE and PFAS were reactive to a large number of foods (Table 4, Supplemental Table), with

Downloaded from https://academic.oup.com/dote/advance-article-abstract/doi/10.1093/dote/dox122/4566194
by Harvard Law School Library user
on 17 November 2017

Table 3 Laboratory and Histologic Features of EoE based on presence or absence of PFAS

	Total EoE	EoE with PFAS	EoE without PFAS	*P* value
Histologic features				
Peak eosinophil count (median, eos/HPF)				
Mid	27	24.06	28.08	0.599
Distal	32.5	33.60	32.17	0.107
Lab values				
Peripheral eosinophilia				
Ever elevated eosinophils, no (%)	35 (10.1%)	5 (5.56%)	30 (11.67%)	0.097
AEC nearest to time of diagnosis	0.566	0.274	0.676	0.101
Serum IgE				
Ever elevated IgE, no (%)	52 (15%)	26 (28.9%)	26 (10.15%)	<0.001
Serum IgE near time of diagnosis (IU/mL)	358.2	460.6	289.90	0.019

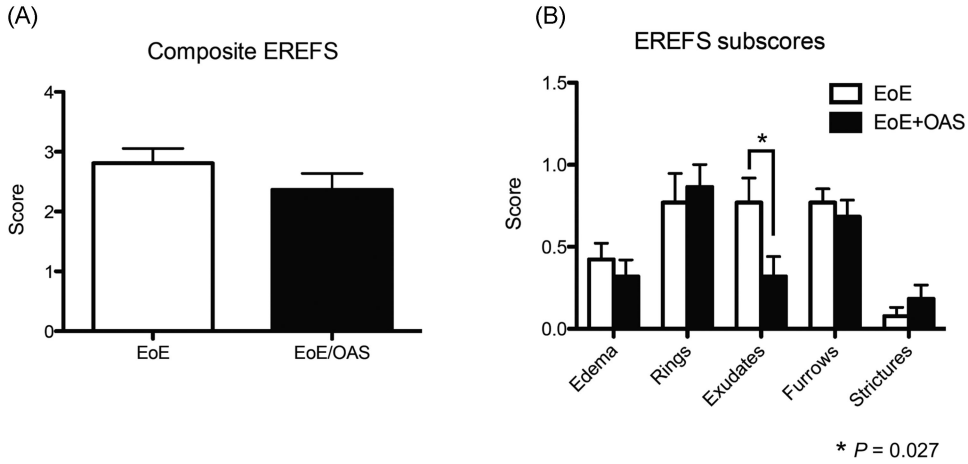

Fig. 3 **(A)** Composite EoE endoscopic reference scores (EREFS) in EoE vs. EoE-PFAS, (B) Comparison of EREFS subscores in EoE subjects with and without concurrent PFAS.

Table 4 Most common food triggers of PFAS and allergen cross-reactivity in adults with EoE

		Trees		Grass	Weeds		
Food	%	Birch	Cedar		Mugwort	Ragweed	Goosefoot
Apples	21.1	PR-10					
Carrots	15.6	PR-10		Profilin	Profilin		
Peaches	15.6		PR-10		Profilin		Profilin
Bananas	12.2					Profilin	Profilin
Pears	12.2	PR-10					
Kiwi	10.0		PR-5				
Almonds	8.9	PR-10					
Celery	8.9	PR-10		Profilin	Profilin		
Cherries	8.9	PR-10	PR-5				
Tree nuts	8.9	PR-10					
Hazelnuts	7.8	PR-10					
Walnuts	7.8	PR-10					
Peanuts	6.7	PR-10					
Cantaloupe	5.6				Unknown	Unknown	

the most common triggers being apples (21.1%), carrots (15.5%), and peaches (15.5%). Thirty-nine subjects (43.3%) developed PFAS symptoms to a single food, while 42 (46.7%) identified 2–5 trigger foods, and 9 subjects (10%) had >5 food triggers. Of note, common food triggers of EoE were rarely associated with PFAS in our cohort: soy and eggs were OAS triggers in 3 patients (3.3%) each, and only 1 subject experienced PFAS with milk, and none reported PFAS triggered by wheat.

DISCUSSION

EoE is an increasingly recognized complex disorder with both environmental and genetic risk factors, and the range of atopic and nonatopic disease associations is still being fully defined.[25–27] PFAS is an IgE-mediated allergic reaction that leads to oropharyngeal symptoms after ingestion of uncooked fruits or vegetables bearing antigens that cross-react with common environmental antigens present in pollens derived

Downloaded from https://academic.oup.com/dote/advance-article-abstract/doi/10.1093/dote/dox122/4566194
by Harvard Law School Library user
on 17 November 2017

from trees, grasses, and weeds. EoE patients exhibit high rates of sensitization to environmental allergens,[14] and two separate studies—one in a cold/very cold climate zone,[16] and the other in a mixed-humid climate zone[28]—demonstrated a correlation between daily pollen concentrations and the timing of onset of EoE symptoms and diagnosis. As a potential link between environmental- and food-specific sensitization, PFAS in the context of EoE remains poorly understood and we therefore sought to better understand the nature of concurrent PFAS and EoE.

We found that the adult EoE population is significantly enriched for coexisting PFAS, with approximately one quarter (25.9%) of EoE patients having concurrent PFAS, compared to prevalence estimates ranging from 0.1 to 4.3% in the general population.[29,30] EoE–PFAS patients had significantly higher rates of allergic rhinitis, but not asthma or eczema, and more often had documented elevations in serum IgE but not eosinophil counts. More than half (56.7%) of subjects in our study experienced PFAS symptoms triggered by more than one food. The most frequent food triggers in our study—apple, carrot, peach, banana—share cross-reactivity to antigens in the pathogenesis-related (PR)-10 family of heat-labile proteins,[31] which are widely distributed throughout the plant kingdom, and include the major birch pollen allergen Bet v 1.[32] Our findings are consistent with and complementary to those of van Rhijn and colleagues, who, using a multiplexed panel to detect IgE antibodies against 112 different food and aeroallergen components, observed high overall rates of sensitization (59 of 74 subjects), with a predominance of Birch pollen (rBet v 1) sensitization with food allergens.[14]

Although EoE subjects in our study exhibited PFAS symptoms to a wide variety of foods (Supplemental Table), wheat, dairy, egg, and soy, which are among the most common triggers of EoE,[33] were rarely associated with typical PFAS symptoms. The lack of overlap between PFAS and EoE dietary triggers in this cohort suggests that the shared genetic and environmental factors that predispose to both EoE and PFAS diverge with respect to specific sensitization and further highlight the complex and likely indirect role that IgE plays in EoE pathogenesis.

There are several strengths and limitations to our study. First, we analyzed one of the largest single-center cohorts of adult EoE patients, who were included only if they had a diagnosis confirmed by stringent criteria,[34] including direct evidence of esophageal biopsies with >15 eosinophils/HPF despite treatment with a high-dose PPI. While asthma, allergic rhinitis, and atopic dermatitis have each been firmly established to be associated with EoE in multiple epidemiological studies,[35] our study adds to the very small existing literature on EoE and PFAS/OAS, and provides a detailed survey of the specific foods that trigger PFAS symptoms in EoE patients. Finally, our study is the first to demonstrate that PFAS was present in a higher proportion of new EoE diagnoses made in the spring, which coincides with the start of birch pollen season in the Northeastern US. Several studies have described seasonal variation in the diagnosis of EoE, with higher rates of diagnosis correlating with typical allergy seasons.[36–38] However these findings have not been consistent, and some studies suggest that there is no association.[39-41] Hypothesizing that geographic and climate zone differences could account for some of the conflicting results of seasonal variation of EoE diagnosis, an important recent study by Jensen and colleagues observed that climate zones with greater seasonal variation also demonstrated stronger variation in EoE diagnoses.[42] In our study, using a cohort of EoE patients primarily residing in the Northeastern US, we found that EoE with concurrent PFAS comprised a significantly higher proportion of EoE diagnoses made in the spring and summer, and raises the possibility that PFAS might account for some of the variability in observations of seasonality in EoE diagnoses.

An important limitation of our study is that the diagnosis of PFAS, and identification of trigger foods, is made on clinical history and by patient report, and may be a source of bias and heterogeneity based on lack of uniformity in both clinician assessment and individual patient's ability to accurately recall symptoms and associate these with specific foods. While double-blind, placebo-controlled food challenge (DBPCFC) and, to a lesser degree, open food challenge (OFC) are considered the gold standards for diagnosing food allergies, these are often not practical in epidemiological studies of food allergy,[43,44] and there are data suggesting that these tests may not perform as well for PFAS compared to traditional food allergy. In one study of 53 subjects with OAS triggered by melon, less than half had positive OFC or DBPCFC results.[45] There are also data to suggest that a careful clinical history may perform as well or better than these tests in diagnosing PFAS; in one study, a good clinical history of OAS symptoms to apple had a negative predictive value of 100% and a positive predictive value of 92% compared to OFC.[46]

Our study was limited to adults with EoE. Previous studies by Sugnanam and colleagues[47] demonstrated that reactivity to aeroallergens increases with age, and the age-specific sensitization profile (both IgE- and non-IgE-mediated) transitions from food allergen sensitivity to inhalant allergen sensitivity as age increases in subjects with EoE. Based on this, we suspected that an observed association of PFAS with EoE might be restricted to adults and possibly the small proportion of older pediatric EoE cases who are aeroallergen sensitized and we therefore limited our initial analysis to subjects ≥18 years old.

Up to a third of EoE patients who undergo treatment with SFED fail to resolve their symptoms

Downloaded from https://academic.oup.com/dote/advance-article-abstract/doi/10.1093/dote/dox122/4566194
by Harvard Law School Library user
on 17 November 2017

and eosinophilia.[5,6] Although noncompliance with dietary interventions certainly accounts for some of the observed lack of response, it is also possible that environmental, rather than food, antigens, or foods that are not typically included in 6- or 8-food elimination diets may be important, and overlooked, triggers of ongoing esophageal eosinophilia in this subset of patients who do not respond to elimination diet. Although there is good evidence that food antigens drive disease in the majority of EoE patients, the high prevalence of environment/food cross-sensitization in the EoE population raises the possibility of alternate, or additional, pathways to the development of eosinophilic inflammation. While our study does not suggest a mechanistic relationship between EoE and environmental and food antigen cross reactivity, it raises the possibility that coexisting PFAS—specifically, the ongoing exposure to the environmental allergens—might be playing a significant role in the subset of EoE patients in whom esophageal eosinophilia does not resolve with empiric, multiple food elimination diets.

ACKNOWLEDGMENTS

The authors are grateful to the patients and support staff of the pediatric and adult multidisciplinary EoE clinics at Massachusetts General Hospital.

References

1 Furuta G T, Katzka D A. Eosinophilic Esophagitis. N Engl J Med 2015; 373: 1640–8.
2 Sherrill J D, Rothenberg M E. Genetic dissection of eosinophilic esophagitis provides insight into disease pathogenesis and treatment strategies. J Allergy Clin Immunol 2011; 128: 23–32; quiz 3–4.
3 Markowitz J E, Spergel J M, Ruchelli E, Liacouras C A. Elemental diet is an effective treatment for eosinophilic esophagitis in children and adolescents. Am J Gastroenterol 2003; 98: 777–82.
4 Peterson K A, Byrne K R, Vinson L A *et al.* Elemental diet induces histologic response in adult eosinophilic esophagitis. Am J Gastroenterol 2013; 108: 759–66.
5 Gonsalves N, Yang G Y, Doerfler B, Ritz S, Ditto A M, Hirano I. Elimination diet effectively treats eosinophilic esophagitis in adults; food reintroduction identifies causative factors. Gastroenterology 2012; 142: 1451–9 e1; quiz e14–5.
6 Kagalwalla A F, Sentongo T A, Ritz S *et al.* Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis. Clin Gastroenterol Hepatol 2006; 4: 1097–102.
7 Simon D, Straumann A, Wenk A, Spichtin H, Simon H U, Braathen L R. Eosinophilic esophagitis in adults–no clinical relevance of wheat and rye sensitizations. Allergy 2006; 61: 1480–3.
8 Loizou D, Enav B, Komlodi-Pasztor E *et al.* A pilot study of omalizumab in eosinophilic esophagitis. PLoS One 2015; 10: e0113483.
9 Clayton F, Fang J C, Gleich G J *et al.* Eosinophilic esophagitis in adults is associated with IgG4 and not mediated by IgE. Gastroenterology 2014; 147: 602–9.
10 Mishra A, Schlotman J, Wang M, Rothenberg M E. Critical role for adaptive T cell immunity in experimental eosinophilic esophagitis in mice. J Leukoc Biol 2007; 81: 916–24.
11 Maggadottir S M, Hill D A, Ruymann K *et al.* Resolution of acute IgE-mediated allergy with development of eosinophilic esophagitis triggered by the same food. J Allergy Clin Immunol 2014; 133: 1487–9, 9 e1.
12 Webber C M, England R W. Oral allergy syndrome: a clinical, diagnostic, and therapeutic challenge. Ann Allergy Asthma Immunol 2010; 104: 101–8; quiz 9-10, 17.
13 Price A, Ramachandran S, Smith G P, Stevenson M L, Pomeranz M K, Cohen D E. Oral allergy syndrome (pollen-food allergy syndrome). Dermatitis 2015; 26: 78–88.
14 van Rhijn B D, van Ree R, Versteeg S A *et al.* Birch pollen sensitization with cross-reactivity to food allergens predominates in adults with eosinophilic esophagitis. Allergy 2013; 68: 1475–81.
15 Lucendo A J, Arias A, Redondo-Gonzalez O, Gonzalez-Cervera J. Seasonal distribution of initial diagnosis and clinical recrudescence of eosinophilic esophagitis: a systematic review and meta-analysis. Allergy 2015; 70: 1640–50.
16 Fahey L, Robinson G, Weinberger K, Giambrone A E, Solomon A B. Correlation between aeroallergen levels and new diagnosis of eosinophilic esophagitis in NYC. J Pediatr Gastroenterol Nutr 2017; 64: 22–5.
17 Hirano I, Moy N, Heckman M G, Thomas C S, Gonsalves N, Achem S R. Endoscopic assessment of the oesophageal features of eosinophilic oesophagitis: validation of a novel classification and grading system. Gut 2013; 62: 489–95.
18 Dellon E S. Epidemiology of eosinophilic esophagitis. Gastroenterol Clin North Am 2014; 43: 201–18.
19 Dellon E S, Gibbs W B, Fritchie K J *et al.* Clinical, endoscopic, and histologic findings distinguish eosinophilic esophagitis from gastroesophageal reflux disease. Clin Gastroenterol Hepatol 2009; 7: 1305–13; quiz 261.
20 Prasad G A, Alexander J A, Schleck C D *et al.* Epidemiology of eosinophilic esophagitis over three decades in Olmsted County, Minnesota. Clin Gastroenterol Hepatol 2009; 7: 1055–61.
21 Dellon E S, Jensen E T, Martin C F, Shaheen N J, Kappelman M D. Prevalence of eosinophilic esophagitis in the United States. Clin Gastroenterol Hepatol 2014; 12: 589–96 e1.
22 Iroh Tam P Y, Madoff L C, O'Connell M, Pelton S I. Seasonal variation in penicillin susceptibility and invasive pneumococcal disease. Pediatr Infect Dis J 2015; 34: 456–7.
23 Lewis J D, Aberra F N, Lichtenstein G R, Bilker W B, Brensinger C, Strom B L. Seasonal variation in flares of inflammatory bowel disease. Gastroenterology 2004; 126: 665–73.
24 Zhang Y, Bielory L, Georgopoulos P G. Climate change effect on Betula (birch) and Quercus (oak) pollen seasons in the United States. Int J Biometeorol 2014; 58: 909–19.
25 Abonia J P, Wen T, Stucke E M *et al.* High prevalence of eosinophilic esophagitis in patients with inherited connective tissue disorders. J Allergy Clin Immunol 2013; 132: 378–86.
26 Jensen E T, Eluri S, Lebwohl B, Genta R M, Dellon E S. Increased risk of esophageal eosinophilia and eosinophilic esophagitis in patients with active celiac disease on biopsy. Clin Gastroenterol Hepatol 2015; 13: 1426–31.
27 Dellon E S, Peery A F, Shaheen N J *et al.* Inverse association of esophageal eosinophilia with Helicobacter pylori based on analysis of a US pathology database. Gastroenterology 2011; 141: 1586–92.
28 Moawad F J, Veerappan G R, Lake J M *et al.* Correlation between eosinophilic oesophagitis and aeroallergens. Aliment Pharmacol Ther 2010; 31: 509–15.
29 Zuidmeer L, Goldhahn K, Rona R J *et al.* The prevalence of plant food allergies: a systematic review. J Allergy Clin Immunol 2008; 121: 1210–8 e4.
30 Anderson L B, Jr, Dreyfuss E M, Logan J, Johnstone D E, Glaser J. Melon and banana sensitivity coincident with ragweed pollinosis. J Allergy 1970; 45: 310–9.
31 Fernandes H, Michalska K, Sikorski M, Jaskolski M. Structural and functional aspects of PR-10 proteins. FEBS J 2013; 280: 1169–9.
32 Breiteneder H, Pettenburger K, Bito A *et al.* The gene coding for the major birch pollen allergen Betv1, is highly homologous to a pea disease resistance response gene. EMBO J 1989; 8: 1935–8.
33 Spergel J M, Brown-Whitehorn T F, Cianferoni A *et al.* Identification of causative foods in children with eosinophilic

Downloaded from https://academic.oup.com/dote/advance-article-abstract/doi/10.1093/dote/dox122/4566194
by Harvard Law School Library user
on 17 November 2017

esophagitis treated with an elimination diet. J Allergy Clin Immunol 2012; 130: 461–7 e5.
34 Dellon E S, Gonsalves N, Hirano I *et al.* ACG clinical guideline: evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). Am J Gastroenterol 2013; 108: 679–92; quiz 93.
35 Spergel J M, Brown-Whitehorn T F, Beausoleil J L *et al.* 14 years of eosinophilic esophagitis: clinical features and prognosis. J Pediatr Gastroenterol Nutr 2009; 48: 30–6.
36 Wang F Y, Gupta S K, Fitzgerald J F. Is there a seasonal variation in the incidence or intensity of allergic eosinophilic esophagitis in newly diagnosed children? J Clin Gastroenterol 2007; 41: 451–3.
37 Iwanczak B, Janczyk W, Ryzko J *et al.* Eosinophilic esophagitis in children: frequency, clinical manifestations, endoscopic findings, and seasonal distribution. Adv Med Sci 2011; 56: 151–7.
38 Almansa C, Krishna M, Buchner A M *et al.* Seasonal distribution in newly diagnosed cases of eosinophilic esophagitis in adults. Am J Gastroenterol 2009; 104: 828–33.
39 van Rhijn B D, Verheij J, Smout A J, Bredenoord A J. Rapidly increasing incidence of eosinophilic esophagitis in a large cohort. Neurogastroenterol Motil 2013; 25: 47–52 e5.
40 Elitsur Y, Aswani R, Lund V, Dementieva Y. Seasonal distribution and eosinophilic esophagitis: the experience in children living in rural communities. J Clin Gastroenterol 2013; 47: 287–8.
41 Elias M K, Kopacova J, Arora A S e*t al*. The diagnosis of esophageal eosinophilia is not increased in the summer months. Dysphagia 2015; 30: 67–73.
42 Jensen E T, Shah N D, Hoffman K, Sonnenberg A, Genta R M, Dellon E S. Seasonal variation in detection of oesophageal eosinophilia and eosinophilic oesophagitis. Aliment Pharmacol Ther 2015; 42: 461–9.
43 Shu S A, Chang C, Leung P S. Common methodologies in the evaluation of food allergy: pitfalls and prospects of food allergy prevalence studies. Clin Rev Allergy Immunol 2014; 46: 198–210.
44 Asero R, Fernandez-Rivas M, Knulst A C, Bruijnzeel-Koomen C A. Double-blind, placebo-controlled food challenge in adults in everyday clinical practice: a reappraisal of their limitations and real indications. Curr Opin Allergy Clin Immunol 2009; 9: 379–85.
45 Rodriguez J, Crespo J F, Burks W *et al.* Randomized, double-blind, crossover challenge study in 53 subjects reporting adverse reactions to melon (Cucumis melo). J Allergy Clin Immunol 2000; 106: 968–72.
46 Anhoej C, Backer V, Nolte H. Diagnostic evaluation of grass- and birch-allergic patients with oral allergy syndrome. Allergy 2001; 56: 548–52.
47 Sugnanam K K, Collins J T, Smith P K *et al.* Dichotomy of food and inhalant allergen sensitization in eosinophilic esophagitis. Allergy 2007; 62: 1257–60.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Supplemental Table PFAS trigger foods in 90 adult EoE subjects.

Downloaded from https://academic.oup.com/dote/advance-article-abstract/doi/10.1093/dote/dox122/4566194
by Harvard Law School Library user
on 17 November 2017