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Eosinophilic esophagitis and allergic comorbidities in a US-population-based study

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TO THE EDITOR:

Eosinophilic esophagitis (EoE) is an atopic disease characterized by eosinophilic inflammation in the esophagus[1], with the highest disease burden in the US and Western industrialized countries[2]. However, prevalence estimates differ substantially between studies, ranging from as low as 2.3/100,000 in Denmark to as high as 90.7/100,000 in part of the US [2]. The aforementioned prevalence studies are based on electronic medical records or pathology reports, health insurance claims, patients referred to third level health care systems, or subspecialty physician-administered questionnaires[3], therefore they tend to reflect specific population prevalence, with consequent potential for socioeconomic and comorbidity selection biases[2]. To the best of our knowledge, no US population-based EoE prevalence estimates have been previously reported.

Foods have been shown to cause EoE through the use of elimination diets or elemental formulas fulfilling Koch's postulate, like in IgE-mediated food allergies (IgE-FA) and food protein-induced enterocolitis syndrome (FPIES)[4]. IgE-FA and EoE are considered T helper cell type 2 (Th2) reactions, with lymphocytes predominantly producing Th2 cytokine (IL-4, IL-5, IL-13) playing a major role in disease pathogenesis, whereas in FPIES monocytes play

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a larger role.[5] While previous work has acknowledged frequent comorbidity of IgE-FA with EoE and FPIES, much remains unknown about the current prevalence, demographic characteristics and associations between these 3 different food allergies in the general population.

In this study we sought to provide the first nationally-representative estimates of the lifetime prevalence and atopic comorbidities of EoE in both US children and adults.

A cross-sectional, population-based survey was administered between October 2015 and September 2016 to a sample of 53,575 US households. Self-report responses were obtained for 40,443 adults, while parent-proxy responses were provided for 38,408 children. Informed consent was obtained from all participants. The Northwestern University IRB approved all study activities. Detailed information about survey development and design has been previously reported.[6] Briefly, the survey was developed by pediatricians, pediatric allergists, and survey methodologists with support from an expert panel. The survey instrument was pretested on 345 pilot interviewees whose data and feedback were incorporated into the final 2015–2016 survey.

The outcome measure of interest was the lifetime prevalence of physician-diagnosed EoE. Participants were asked “Have you/Has your child ever been diagnosed by a physician with Eosinophilic Esophagitis (EoE)? Questions asking about the presence of other physician-diagnosed chronic atopic comorbidities utilized the same question stem.

In addition, we analyzed the reported physician-diagnosed IgE-FA, asthma, atopic dermatitis, allergic rhinitis and FPIES as per the definitions published previously. [6] Eligible study participants included adults (≥18 years old) able to complete the survey in English or Spanish via web or telephone, who resided in a US household. Point prevalence estimates were based on participants recruited from NORC at the University of Chicago’s, probability-based *AmeriSpeak Panel*, with a survey completion rate of 51.2%. To improve the precision of estimates, these data were augmented via small-area estimation with additional participants recruited from *Survey Sampling International* as detailed in Gupta et al [7] Prevalence estimates were calculated using Stata 14 via complex survey-weighted proportions.

Prevalence estimates are presented in Table I, whereas allergic comorbidities are presented in Table II.

Lifetime, physician-diagnosed EoE was estimated to affect 0.16 % (95% CI 0.12–0.22%) of children younger than 18 years and 0.18% (0.14–0.23) of adults (18+ years) in the US. (Table I). Consequently 0.17% (0.14–0.22%) of the entire US population was estimated to have lifetime physician-diagnosed EoE corresponding to roughly 548,695 people (based on 2016 US census) and this is in line with the current estimated US prevalence of EoE between 1–2/1000[2].

Among children with parent-reported, physician-diagnosed EoE (n=74) there was a significantly higher prevalence of atopic comorbidities compared to the children without parent-reported physician-diagnosed EoE, as 32.4% had ≥1 current IgE-FA (meeting

stringent symptom-report reaction criteria used in recent studies (CITE REFS 6 AND 7), 19.1% reported FPIES, 27.8% physician-diagnosed asthma, 27.5% atopic dermatitis/eczema, and 43.5% seasonal rhinitis (Table II). Significantly higher prevalence rates of atopic diseases were also reported among adults with EoE (n=89) as 37.3% had ≥1 comorbid current IgE-FA, 13.3% reported FPIES, 47.8% physician-diagnosed asthma, 22.9% atopic dermatitis/eczema, and 41.6% (29.3–55.1%) seasonal rhinitis (Table II).

These data confirm, as previously reported, that patients with EoE and their parents have significantly higher prevalence of IgE-mediated and atopic diseases such as allergic rhinitis, asthma and IgE-FA compared to patients not affected by EoE[8]. We also observed a statistically significant increased comorbidity with FPIES, a relationship that has not previously been investigated or reported.

In conclusion the data in this study suggest that EoE has a prevalence of 1–2 in every 1000 US children and adults as previously estimated[2]. Moreover we confirmed an association between EoE and atopic diseases, including IgE-FA, eczema[8]. This is not surprising as EoE is considered an atopic disease believed to be a late manifestation of the atopic march[8]. However, for the first time, we showed an association between EoE and FPIES, suggesting that FPIES or FPIES-like symptoms may be common in children with EoE. FPIES is considered a non-IgE mediated food allergy where children have activation of monocytes during acute reactions. [9]. Co-existence of IgE-FA and FPIES have been previously described and a subset of children with atypical FPIES, characterized by detectable food-specific IgE antibodies, may switch to IgE-FA to the food that previously caused FPIES reactions [9]. Similarities between FPIES and EoE in comorbidity may point to the common pathogenetic mechanism in a subgroup population. Further study will be necessary to understand the scope of such relationship.

Our report has several limitations. The survey was not specifically developed to estimate EoE prevalence and we have no details of the trigger foods, age at diagnosis and symptoms. While the survey asked about physician-diagnosed EoE, no specific case definition was provided; we have no information about the criteria used to establish EoE diagnosis, and whether endoscopy and count of eosinophils in esophageal biopsies were performed to confirm diagnosis. Therefore, it is possible that EoE diagnosis was used incorrectly and led to under or over-estimation of true EoE prevalence. However, the fact that incidence of EoE and its comorbidity is similar to what reported before suggest that this survey-based approaches may have captured a population carrying a real EoE diagnosis. Future prospective studies need to be done to confirm EoE and FPIES comorbidity and to elucidate the underlying pathophysiology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

FA	Food allergy
FPIES	Food protein-induced enterocolitis syndrome

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TABLE 1

Estimated prevalence of Eosinophilic Esophagitis (EoE) in the US population

Reported physician-diagnosed current or past EoE	Prevalence estimate (95% CI)
All ages, N = 163	0.17 (0.14–0.22)
Children	
Age < 18 y, N = 74	0.16 (0.12–0.22)
<2 y (N = 15)	0.02 (0.11–0.35)
3–5 y (N = 12)	0.17 (0.08–0.36)
6–10 y (N = 24)	0.16 (0.09–0.27)
11–13 y (N = 12)	0.17 (0.08–0.37)
14–17 y (N = 11)	0.11 (0.04–0.30)
Adults	
Age ≥ 18 y, N = 82	0.18 (0.14–0.23)
18–29 (N = 23)	0.17 (0.11–0.28)
30–39 (N = 26)	0.25 (0.16–0.39)
40–49 (N = 6)	0.16 (0.02–0.14)
50–59 (N = 9)	0.16 (0.02–0.14)
60+ (N = 18)	0.19 (0.09–0.35)

TABLE 2

Allergic comorbidities in children and adults with EoE

	% among those with EoE	% among those without EoE	*P* value
Children			
Lifetime			
IgE-FA	32.44 (20.48–47.22)	7.59 (7.11–8.10)	<.001
FPIES	19.11 (9.32–35.20)	0.48 (0.39–0.59)	<.001
Asthma	26.83 (14.92–43.41)	12.17 (11.37–13.01)	.008
Atopic dermatitis/eczema	27.53 (15.81–43.44)	5.8 (5.25–6.48)	<.001
Allergic rhinitis	43.48 (28.62–59.61)	12.74 (11.97–13.56)	<0.001
Insect sting allergy	2.83 (0.69–10.85)	2.23 (1.93–2.57)	.74
Medication allergy	3.94 (1.57–9.58)	4.15 (3.71–4.65)	.91
Biological parental reported history of atopy			
IgE-mediated food allergy	59.54 (44.52–72.96)	19.32 (18.24–20.46)	<.001
Asthma	36.17 (23.37–51.28)	18.30 (1719–19.46)	.003
Atopic dermatitis/eczema	41.31 (27.50–56.64)	15.54 (14.50–16.63)	<.001
Allergic rhinitis	59.73 (4.47–73.31	40.02 (38.52–41.54))	.009
Adults			
Physician-diagnosed comorbid atopic conditions			
Lifetime			
IgE-mediated food allergy	37.28 (26.16–49.95)	10.72 (10.36–11.09)	<.001
FPIES	13.31 (6.75–24.56)	0.19 (0.15–0.25)	<.001
Asthma	47.82 (34.93–61.01)	1.19 (11.74–12.65)	<.001
Atopic dermatitis/eczema	22.99 (13.13–37.10)	6.70 (6.36–7.05)	.001
Allergic rhinitis	41.66 (29.35–55.10)	21.39 (20.84–21.95)	<0.001
Insect sting allergy	7.40 (2.61–19.26)	3.82 (3.57–4.08)	.2
Medication allergy	13.41 (12.98–13.87)	11.63 (5.50–22.96)	.7
Biological parental reported history of atopy			
IgE-mediated food allergy	29.97 (18.87–44.05)	12.82 (12.34–13.33)	.003
Asthma	30.24 (19.83–43.17)	13.50 (13.03–13.99)	.0002
Atopic dermatitis/eczema	34.05 (22.04–48.52)	9.53 (9.11–9.97)	<.001
Allergic rhinitis	47.78 (34.11–61.79)	28.68 (28.01–29.37)	0.004

Note: A two-sided $P < .05$ was considered as statistically significant.