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Association between Atopic Dermatitis and Eosinophilic Esophagitis: A Cross-Sectional Study in the All of Us Research Program

Gloria F. Chen, BA¹, Jeffrey M. Cohen, MD²

¹Yale School of Medicine, New Haven, CT

²Department of Dermatology, Yale School of Medicine, New Haven, CT

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Dear Editor,

Eosinophilic esophagitis (EoE) is a chronic inflammatory disease of the esophagus that has recently been proposed as a manifestation of the atopic march¹. The atopic march is a stereotyped progression of allergic diseases, beginning with atopic dermatitis (AD) and followed by food allergy, asthma and allergic rhinitis². This study evaluated the association between AD and EoE among participants of the All of Us Research Program (AoURP), a National Institutes of Health research program that prioritizes recruitment from demographic categories underrepresented in biomedical research.

A cross-sectional study of the AoURP cohort was performed. Using electronic health record (EHR) data shared in AoURP, AD cases were identified by Systematized Nomenclature of Medicine (SNOMED) 43116000, excluding SNOMED 88996004. EoE cases were identified using SNOMED 235599003. Food allergy, asthma and allergic rhinitis were identified by SNOMED 419452009, 195967001 and 61582004 respectively. All participants diagnosed with AD were compared to a control group of all AoURP participants without AD diagnoses in the EHR.

Individuals with and without AD were compared using Pearson's χ^2 test for categorical variables and one-way analysis of variance for continuous variables. The relationship between AD and EoE was assessed via logistic regression, controlling for age, sex, ethnicity, race and atopic comorbidities. Mediation analysis for atopic comorbidities was conducted using logistic regression with 500 cycles of bootstrapping.

Corresponding author: Jeffrey M. Cohen, MD, Department of Dermatology, 15 York St, New Haven, CT 06510, jeffrey.m.cohen@yale.edu, 203-785-4092.

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Among 240,635 participants in AoURP with EHR data available, 10,605 were diagnosed with AD (mean age 58, standard deviation 17). Individuals with AD were significantly more likely to be diagnosed with EoE than individuals without AD (0.8% v. 0.3%, $p<0.001$) (Table 1). Controlling for age, sex, ethnicity, race, food allergy, asthma and allergic rhinitis, the adjusted odds ratio of EoE in individuals with AD was 1.82 (95% confidence interval [CI] 1.42–2.30, $p<0.011$) (Table 2).

The proportion of AD's association with EoE that was mediated by food allergy was 0.04 (95% CI 0.01–0.07, $p<0.004$); the proportion mediated by asthma was 0.21 (95% CI 0.16–0.28, $p<0.001$); and the proportion mediated by allergic rhinitis was 0.38 (95% CI 0.31–0.50, $p<0.001$).

In this large, diverse cohort, AD was significantly associated with EoE after adjusting for age, sex, race, ethnicity and atopic comorbidities. This evidence supports the theory that EoE is a late member of the atopic march.

Food allergy, asthma and allergic rhinitis were each found to partly mediate the positive association between AD and EoE; a combined 63% of the association between AD and EoE is attributable to atopic comorbidities. These results are compatible with the concept that sensitization to allergens via atopy predisposes to EoE, such as through inflamed skin in AD^{1,3}. The relatively low mediation effect of food allergy was unexpected and may be explained by the low number of food allergy diagnoses in AoURP. Potential for misclassification when relying on EHR data is a limitation of this study. Additionally, the composition of AoURP differs from the US population.

All atopic conditions are characterized by type 2 inflammatory responses, as well as common genetic and environmental factors¹. EoE similarly involves a type 2 inflammatory response and shares genetic susceptibility loci with other atopic diseases^{1,3}. Dupilumab, an anti-IL-4 receptor alpha antibody used in AD, is now approved for EoE, suggesting common immunopathology for the conditions⁴.

Demonstrating that AD represents a risk factor for EoE may encourage screening for EoE in individuals with AD who develop esophageal symptoms to prevent serious sequelae such as dysphagia, esophageal strictures and food impaction. Better characterizing the relationship between AD and EoE will facilitate optimal management of both conditions, and future studies may investigate whether certain treatments are ideal in individuals with both AD and EoE.

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Table 1.

Demographics and Clinical Characteristics of AD Cases versus Controls

	AD Cases	Controls	P
n	10605	230030	
Age, mean (SD)	57.51 (16.72)	54.23 (16.58)	<0.001
Sex (%)			<0.001
Female	7030 (66.3)	138701 (60.3)	
Male	3296 (31.1)	84853 (36.9)	
Nonconforming/Unknown	279 (2.6)	6476 (2.8)	
Hispanic/Latino (%)	1545 (14.6)	43175 (18.8)	<0.001
Race (%)			<0.001
Asian	370 (3.5)	6110 (2.7)	
Black	1730 (16.3)	47895 (20.8)	
White	6442 (60.7)	121856 (53.0)	
Multiracial	180 (1.7)	3938 (1.7)	
Another single population	53 (0.5)	1610 (0.7)	
None of these	98 (0.9)	2380 (1.0)	
Skip	1732 (16.3)	46241 (20.1)	
Food allergy (%)	98 (0.9)	362 (0.2)	<0.001
Allergic rhinitis (%)	4758 (44.9)	36061 (15.7)	<0.001
Asthma (%)	3502 (33.0)	36741 (16.0)	<0.001
Eosinophilic esophagitis (%)	82 (0.8)	576 (0.3)	<0.001

AD = atopic dermatitis, SD = standard deviation

Table 2.

Association of Atopic Dermatitis with Eosinophilic Esophagitis Adjusted for Age, Sex, Ethnicity, Race, and Food Allergy, Allergic Rhinitis, and Asthma Comorbidities

	Unadjusted Odds Ratio (95% CI)	P	Adjusted Odds Ratio (95% CI)	P
Eosinophilic esophagitis	3.10 (2.44–3.89)	<2e-16	1.82 (1.42–2.30)	1.21e-06

CI = confidence interval