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Racial disparity in treatment of gastroesophageal reflux disease in children with food allergy

Mahboobeh Mahdavinia, MD., PhD., Lucy A. Bilaver, PhD., Susan Fox, PA., Andrea A. Pappalardo, MD., Aame B. Andy-Nweye, MD., Hemant P. Sharma, MD., Amal H. Assa'ad, MD., Ruchi S. Gupta, MD., MPH, Mary C. Tobin, MD., on behalf of the FORWARD team



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Title: Racial disparity in treatment of gastroesophageal reflux disease in children with food allergy

Short title: Risk factors for GER in children with FA

Authors: Mahboobeh Mahdavinia MD.,PhD. ¹, Lucy A Bilaver PhD. ², Susan Fox PA.¹, Andrea A. Pappalardo MD.⁴, Aame B Andy-Nweye MD.¹, Hemant P. Sharma MD.⁶, Amal H. Assa'ad MD.⁵, Ruchi S. Gupta MD.,MPH ^{2,3} and Mary C. Tobin MD.¹ ; on behalf of the FORWARD team

¹Division of Allergy and Immunology, Department of Medicine and Department of Pediatrics, Rush University Medical Center, Chicago, Ill

² Center for Food Allergy and Asthma Research and Institute for Public Health and Medicine, Northwestern University Feinberg School of Medicine, Chicago, Ill

³ Advanced General Pediatrics and Primary Care, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Ill

⁴University of Illinois at Chicago, Department of Medicine and Pediatrics, Chicago, Ill

⁵ Division of Allergy & Immunology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

⁶ Division of Allergy and Immunology, Children's National Health Systems, Washington, DC

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Corresponding Author: Mahboobeh Mahdavinia, MD., PhD. *

Allergy and Immunology Division

Internal Medicine Department

Rush University Medical Center

1725 W. Harrison St. Suite 117, Chicago IL, 60612, USA

Phone: 312-942-6296, Fax: 312-563-2201, Email: Mahboobeh_mahdavinia@rush.edu

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Clinical Implications:

Almost 20% of children with Food allergy have reported GER, which was associated with age above 9-years-old, milk allergy and eczema. Black children with FA and GER were less likely to be treated for GER compared to their white counterpart.

Racial disparity in treatment of gastroesophageal reflux disease in children with food allergy

IgE mediated food allergy (FA) is a life threatening condition that currently afflicts more than 8% of the US children.(1) Unfortunately, the health-related outcomes of FA span beyond food reactions and can result in anxiety, diminished quality of life (QoL), and impaired psychosocial development.(2, 3) FA can also be associated with gastrointestinal conditions such as gastroesophageal reflux disease (GERD). (4) Gastroesophageal reflux (GER) is reported in 2-8.2% of children of different ages and can lead to poor weight gain and malnutrition impacting child's health and quality of life.(5, 6) In children, FA and GER may manifest with similar symptoms making the diagnosis challenging. (4) Furthermore, both conditions impact the food related behaviors in children.(4) While there are reports indicating an association between the two conditions, no prior study has systemically investigated the rate and impact of the GER in children with FA. In this study we sought to investigate the prevalence and associated risk factors of reported GER in children with FA. We also aimed to understand whether Black and White children with FA have a differential risk of reported GER and gastrointestinal symptoms in association with FA comorbidities (AD, asthma and allergic rhinitis) and specific types of food allergens. (7)

Data were sourced from the FORWARD (Food Allergy Outcomes Related to White and African American Racial Differences) which is a large multicenter collaborative prospective cohort on FA.(7) The study was approved by the Institutional Review Boards of all involved institutes and includes Black and White children, 0 to 12 years of age with an allergist confirmed diagnosis of IgE-mediated FA. Diagnosis of FA was based on positive clinical symptoms (i.e., of an IgE-mediated reaction to a specific food and evidence for sensitivity to that specific food(s). The present study utilized parent-reported data from FORWARD's intake and 6-month follow up survey collected from January 2018 to January 2021. Parent/guardian report of acid reflux was assessed by the following question: "Was your child diagnosed with acid reflux (GER)?" The diagnosis of GER was then confirmed and supported by chart review performed by the investigators. In addition, parents/guardians reported on treatment received for GER, the "top 9" food allergens (i.e., peanuts, tree nuts, milk, egg, wheat, soy, finfish, shellfish, sesame), and presence and/or history of atopic comorbidities (e.g. eczema and asthma). Six months after intake, parents/caregivers were asked if children were being followed by a gastroenterology (GI) doctor. The diagnosis of comorbid conditions and other gastrointestinal conditions such as eosinophilic esophagitis was confirmed by detailed chart review and by the primary allergist who made the diagnoses. For demographic information, parents/guardians were asked to report race, ethnicity, date of birth, gender, yearly household income categorized as less than \$50,000 per year, \$50,000 to \$99,000, or \$100,000 or greater, and highest level of parental education categorized as less than bachelor's degree, bachelor's degree, or more than bachelor's degree.

Data were exported from Research Electronic Data Capture (REDCap) databases for the purpose of the current analyses. Bivariate relationships were first assessed using chi-square statistics while multivariate logistic regression was used to determine the adjusted association between other variables and GER adjusted for demographics, socioeconomic factors, atopic history variables and recruitment site. Standard errors were clustered by family to account for up to two children with food allergy enrolled in the study. Statistical analyses were performed using SAS V9.4 (SAS Institute, Cary, NC).

A total of 714 children with diagnosed FA were included in the analysis (256 Black and 458 White). Demographic, household socioeconomic status, and clinical characteristics are presented by race in Table E1.

Across the cohort 18.6% (133/714) of children had parent/caregiver-reported GER at intake. Table 1 present the fully adjusted odds of GER in the FORWARD cohort. Race was not associated with GER among FA children. Younger children (ages 0-2 years) at intake had lower odds of GER (OR [95% confidence interval (CI)] = 0.30 [0.15-0.59]) compared with children ages 9-12 yrs. Current tree nut allergy was associated with lower odds of GER (OR=0.52 [0.31-0.79]) while current milk allergy was associated with 2.00 times the odds of GER (OR=2.00 [1.22-3.28]). Current eczema was also associated with higher odds of GER (OR=1.84 [1.03-3.29]. All other food allergies, gender, current or past asthma, household socioeconomic status, and site were not associated with GER.

Table E2 examined bivariate associations between atopic comorbidities and GER stratified by race. Among White children, GER was associated with a higher prevalence of milk, soy, and multiple FA and a lower prevalence of tree nut allergy ($p<0.05$). Among Black children, GER was associated with a higher prevalence of current eczema ($p<0.05$).

Race was associated with treatment for GER (Table 2). Among those with GER, Black children were less likely to be treated for GER than white children (18.1% of white and 43.6% of black children were untreated, $P=0.002$). Whites were more likely to be on multiple medications for GER than Black children (White 19.2%, Black 2.6%, $p<0.05$). Overall 56% of children with reported GER were evaluated by a gastroenterologist (GI) at some point. One-third (30.5%) of White children and 18.2% of Black children who reported GER, relayed being followed currently by GI at their 6-months follow up survey, but the difference was not statistically significant ($p=0.267$).

Among our FA cohort, 18.6% of children had reported GER. This is markedly higher than the reported rates for GER among all children.(6) While we found that Black and White children with FA have similar rates of reported GER, Black children were less likely to be treated compared to White children. Untreated GER can impact a child's quality of life, have a negative impact on comorbid conditions such as asthma, and has the potential to lead to long-term consequences such as Barrett's esophagus.(5, 8) Socioeconomic factors and poor access to care evidenced by significantly lower income and parent education in Black children might play a role in the observed disparity in GER treatment between black and white children. Another potential detrimental but preventable factor that can impact this disparity is provider's implicit (unconscious) attitudes and bias. Implicit bias towards Black and Medicaid insured children impacting management strategies has been reported in several other pediatric diseases, such as asthma.(9)

Our data demonstrates that milk allergy is associated with GER. It is noteworthy that milk allergy and GER in young children have overlapping symptoms such as feeding difficulties and food aversion.(4) Therefore, it is important to consider and appropriately evaluate for GER in the presence of milk allergy and vice versa. Elimination of milk, a major source of nutrients in the young child can result in poor growth.(3) Therefore, confirmation of IgE allergy to milk by physician diagnosis is critical so that milk is not unnecessarily eliminated. The lower rate of tree nut allergy in children with GER has never been reported before and calls for larger studies to confirm this finding.

We found that among FA children, GER is significantly associated with eczema. While the connection between food allergy and eczema is well-known, the association of GER and eczema among FA children, needs to be further explored to understand the possible pathophysiologic pathway linking these conditions.

This study provides important information about GER/GER treatments and their risk factors in food allergy, however there are limitations. The main limitation of this study is that GER diagnosis and treatment history was as reported by guardian/parent through questions about GER diagnosis and treatments. However, detailed chart review showed 91% agreement between physician notes regarding diagnosis of GER and answer to this question. Chart review showed that more than half of these children (56%) were evaluated by a gastroenterologist who confirmed the diagnosis. In our total cohort 17 children were diagnosed with eosinophilic esophagitis (EoE). We have screened for EoE and eosinophilic gastrointestinal disease (EGID) through parents' survey and chart review. However, one cannot completely differentiate GER from EoE without endoscopic evaluation and there is a chance that some of reported GER was due to undiagnosed EoE.

Furthermore, other diagnoses which can mimic GER including H.pylori or hiatal hernia were much less frequently evaluated or reported in patients charts.

These data point to the need for evaluating the children with FA in terms of gastrointestinal symptoms, especially older children above age of 9, and those with milk allergy or eczema. Furthermore, there is a significant disparity in terms of GER management between Black and White children. Given the high rate of reported GER among FA children and the observed racial disparity in GER treatment, allergists need to consider GER, ensure effective education and treatment options, and guide/empower families in need to seek further evaluation, and treatment, when necessary.

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Table 1. Adjusted Odds Ratios of GER at Intake

	Odds Ratio	95% CI	P-value
Variable			
Child Demographics			
Race			
White	1.72	(0.90-3.26)	0.100
Black	1.00		
Age at Intake			
0-2 yrs	0.32	(0.16-0.65)	0.002
3-5 yrs	0.61	(0.34-1.07)	0.084
6-8 yrs	0.60	(0.32-1.13)	0.112
9 -12 yrs	1.00		
Gender			
Male	1.10	(0.72-1.66)	0.669
Female	1.00		
Household Socioeconomic Status			
Household Income			
Less than \$50,000	1.00		
\$50,000-\$99,000	0.90	(0.40-1.98)	0.783
\$300,000 or more	0.74	(0.33-1.67)	0.470
Decline to answer	0.70	(0.26-1.87)	0.470
Highest Parental Education			
Less than Bachelor's degree	0.76	(0.39-1.49)	0.417
Bachelor's degree	0.81	(0.49-1.34)	0.405
More than Bachelor's degree	1.00		
Clinical Characteristics			
Type of Current Food Allergy			
Peanut	1.22	(0.77-1.95)	0.390
Tree nut	0.49	(0.30-0.78)	0.003
Fin Fish	0.53	(0.27-1.05)	0.071
Shell Fish	1.60	(0.84-3.04)	0.152
Milk	2.04	(1.23-3.39)	0.006
Egg	1.36	(0.83-2.23)	0.225
Soy	1.26	(0.58-2.75)	0.557
Wheat	1.04	(0.44-2.44)	0.929

Sesame	1.09	(0.59-1.99)	0.785
Other FA	1.53	(0.88-2.66)	0.129
Current or Past Asthma			
Current Asthma	0.81	(0.21-3.17)	0.761
Past Asthma	1.24	(0.32-4.74)	0.754
Never Asthma	1.00		
History of Atopic Dermatitis (Eczema)			
Yes	1.84	(1.03-3.28)	0.039
No	1.00		
History of Environmental Allergies			
Yes	1.18	(0.74-1.88)	0.492
No	1.00		
History of Parental Atopy			
Yes	0.89	(0.57-1.39)	0.607
No	1.00		
Site			
Rush	1.46	(0.59-3.66)	0.414
CCHMC	2.40	(1.04-5.53)	0.040
Children's National Health Systems	1.84	(0.79-4.31)	0.159
Lurie Children's	1.00		

Note: Odds ratios and confidence intervals are calculated by logistic regressions adjusting for demographic, socioeconomic, site and atopic disease history variables. Regression excludes 5 observations due to missing data.

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Table 2. Treatment for GER by Race

	White Children		Black Children		P. Value
	N	%	N	%	
Treatment for GER^a					
H2 blockers only	36	38.3	9	23.1	
Proton pump inhibitors only	23	24.5	11	28.2	
Other medication only	0	0.0	1	2.6	
Multiple medications	18	19.2	1	2.6	
Not treated	17	18.1	17	43.6	0.002
GI doctor^a					
Yes	18	30.5	4	18.2	
No	41	69.5	18	81.8	0.267

^a Treatment for GER was an alternatively exclusive question in the survey, and only one answer was accepted. The p.values are calculated by Chi-square.

^b Report of current follow-up with a GI doctor were available for 81 of 133 children with GER who had 6-month post intake survey data.

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