



Published in final edited form as:

Ann Allergy Asthma Immunol. 2023 May ; 130(5): 540–541. doi:10.1016/j.anai.2023.01.038.

Multifood allergy: More than meets the eye

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Food allergy (FA) is on the rise, and many people have allergies to more than one food (hereafter referred to as multi-FA).¹ However, few studies to date have evaluated the epidemiology of and medical and psychosocial burdens within this intriguing population. Previous studies have found increased FA-related adverse events among patients with multi-FA, with increased rate and severity of food allergic reactions and emergency department visits.^{2,3} Patients with multi-FA have been reported to have increased prevalence of atopic comorbidities² and asthma morbidity for reasons that are not well understood.⁴ Both adult and pediatric patients, as well as their care-givers, with a greater number of FA report lower quality of life (QoL) compared with patients with fewer FAs.^{5,6} Lower QoL among patients with multi-FA may be due to factors such as need for greater vigilance in daily FA management, increased dietary and social restrictions used to manage FA, increased economic burden of FA management, and greater perceived or actual risk of allergic reactions.

Whether patients with multi-FA represent a unique endotype within FA is not well established. There may be distinct biological mechanisms underlying multi-FA, such as epigenetic changes resulting in altered B-cell methylation, which could lead to differential B- and T-cell development, B-cell lineage determination, and dysregulation of signaling pathways.⁷ Some studies have found multi-FA to be more prevalent among non-Hispanic Black and Asian vs non-Hispanic White children² and among inner-city populations with asthma,⁴ suggesting that social and environmental risk factors and other comorbidities may also predispose patients to develop multi-FA.⁸

Because of the increased burdens associated with multi-FA and the possibility of distinct pathophysiological mechanisms, there is an emerging need for clinicians and researchers to accurately identify and study these patients. For clinicians, it is important to identify and intervene on these patients to provide appropriate medical and psychosocial support. Improved understanding of patients with multi-FA may lead to tailored screening practices, anticipatory guidance, and management advice. For researchers, it is important to specifically study these patients, because distinct biologic mechanisms may guide the development of multi-FA treatments. Although currently the only Food and Drug Administration–approved FA treatment is peanut oral immunotherapy monotherapy, options for simultaneously treating multi-FA, such as multifood oral immunotherapy, possibly in

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Disclosures: The authors have no conflicts of interest to report.

conjunction with a global biologic such as omalizumab, are being investigated in clinical trials.⁹

In this issue of the *Annals of Allergy, Asthma & Immunology*, Warren et al¹⁰ describe the prevalence, characteristics, social determinants, psychosocial burden, and distribution of multi-FA in a large, nationally representative sample of 38,408 children and 40,443 adults using a US population-based survey. They found that 40% of children and 48% of adults in the cohort had multi-FA. They also determined that the lifetime-reported prevalence of physician-diagnosed atopic comorbidities, health care utilization, and perceived FA severity and FA-related psychosocial burden increased sequentially as the number of FAs increased. They used latent class analysis with 9 dichotomized indicators of FA prevalence and carefully characterized FA-related psychosocial burden within each class. Results of the latent class analysis revealed 4 major multi-FA phenotypic clusters in both pediatric and adult patients, which are as follows: milk and egg-dominant, seafood-dominant, peanut and tree nut-dominant, and broadly multifood allergic groups. These clusters were key and central to relationships with atopic comorbidities, sociodemographic factors, and psychosocial burden.

The authors found that non-Hispanic Black children and adults were more likely to have multi-FA compared with their White counterparts, consistent with prior reports.² Interestingly, there were also racial and ethnic differences in latent class membership, with non-Hispanic Black and Hispanic adults more likely to be in the broadly multifood allergic class compared with the milk and egg-dominant class and non-Hispanic Black, non-Hispanic Asian, and Hispanic children more likely to be in the seafood-dominant class compared with the milk and egg-dominant class. They also found that children and adults born in the United States were less likely to be in the broadly multifood allergic class than their non-native US-born counterparts. Taken together, the heterogeneity and differences in FA latent class membership are likely on the basis of a complex relationship of pathophysiological mechanisms, atopic comorbidities, and socioeconomic and demographic factors that require further study.

The study is one of the largest population-based surveys in children and adults and characterizes 4 major multi-FA phenotypes that may help inform clinical management, future research, and targeted therapies. This is important given the high prevalence of disease and physical and psychological burden in patients with multi-FA and the increased risk and burden of life-threatening anaphylaxis. The data are compelling; however, one significant limitation in the study is that the primary source of data relies on survey report, which can lead to bias and over-reporting of disease burden. In particular, the study did not have available data on clinical and allergen-specific immunoglobulin E confirmation of FA, which are critical in diagnosing true immunoglobulin E-mediated disease. This limitation could also lead to overestimation of the prevalence of other associated atopic conditions, such as latex, drug, or sting or venom allergy. The nature of the questions asked could be an additional source of bias and overestimate disease prevalence by misclassification, misdiagnosis, or misinterpretation.

With FA on the rise, this study provides persuasive evidence that multi-FA is an important FA phenotype that has significant associated disease burden and perhaps even distinct risk factors, pathophysiological mechanisms, and disease trajectory compared with single FA. A multidisciplinary approach in patient management may be necessary, because avoiding multiple food groups can have nutritional, developmental, and psychosocial consequences. The differences in latent class membership by atopic comorbidities, race, ethnicity, and place of birth could point to social determinants of health and disparities that may have implications for FA prevention, diagnosis, and management. The QoL impairments in patients with multi-FA highlight the importance of establishing care with an Allergist to accurately diagnose FA and having regular follow-up appointments, including being offered food challenges, to periodically reassess whether any FAs have resolved. This study provides a compelling rationale for accurately identifying the large number of children and adults with multi-FA in clinical practice and research studies, providing appropriate testing, giving anticipatory guidance and support, and developing effective targeted therapies to minimize disease burden.

Funding:

This research is supported by the National Institutes of Health K23 AI143962 (Bartnikas).

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