Published in final edited form as:

Ann Allergy Asthma Immunol. 2022 August ; 129(2): 140–141. doi:10.1016/j.anai.2021.12.002.

No allergy left behind – the importance of food allergy in longitudinal cohorts

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Keywords

children; sensitization; IgE; food allergy; epidemiology

In recent years, the prevalence of IgE-mediated food allergy appears to be rising. Our ability to confirm this epidemiologic trend is limited. Over the past several decades, multiple cohorts have been established to investigate the etiologic risk factors and natural history of asthma and allergic diseases.[1] The allergic march includes the development of eczema, food allergy, allergic rhinitis, and asthma. One of the great tools of clinical epidemiology, the longitudinal cohort, has been successful in describing the allergic march, but this approach has been severely underutilized to study food allergy. The focus of most cohorts has been on eczema, allergic rhinitis and asthma with fewer studies focusing on food allergy. While cohort studies have greatly improved our knowledge of most atopic diseases, the common deemphasis of food allergy leaves us with an incomplete understanding of the allergic march – and about the epidemiology of food allergy per se.

This omission is likely due to the lack of widely accepted epidemiological method to accurately assess food allergy outcomes, making interpretation across cohorts challenging.

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Conflict of Interest: None

This has led to a significant knowledge gap in our understanding of the etiologic risk factors and natural history of food allergy.

Two major factors contribute to the paucity of food allergy outcomes in cohort studies. First, the current gold standard for diagnosis of food allergy, the double-blind placebo-controlled oral food challenge (DBPCFC) presents several challenges that make implementation in cohort studies unrealistic. It is time, resource and labor intensive[2]; participants and researchers may be reluctant to pursue a procedure that carries risk of anaphylaxis; and the test provides a diagnosis at a single timepoint for a disease that is inherently dynamic (i.e., tolerance to food can change over time). Due to these challenges existing cohort studies rarely include DBPCFC food allergy outcomes, with a few recent and notable exceptions (HealthNuts[3] and EuroPrevall-iFAAM[4]). When DBPCFC are not used, many cohorts often omit the study of food allergy diagnosis or rely on more simple surrogate markers such as allergen sensitization or parent-reported food allergy, both of which are prone to inaccuracies.

The second factor contributing to the omission of food allergy outcomes in cohort studies is the lack of a widely-accepted epidemiologic definition of food allergy that can supplant the use of DBPCFC. Food allergy outcomes have been defined by parent-report and/or self-report, which are not always reliable and often yield a higher prevalence due to inclusion of food intolerances and non-IgE mediated food allergy. More extensive symptom and clinical history-based surveys are of interest, but, to date, are of differing quality and often lack necessary details to more definitively establish food allergy. Some cohorts have assessed sensitization using skin prick testing or serum food specific IgE (sIgE) data; however, elevated sIgE or positive skin testing alone does not reliably predict food allergy. The addition of case review by an expert panel of allergists have been used to improve the likelihood of accurate food allergy diagnosis. Despite the multiple methods that have been implemented, none are widely accepted and rigorously validated against DBPCFC.

Even in clinical practice, food allergy can be difficult to diagnose, yet DBPCFC is only used in extenuating circumstances and the option to pursue an unblinded food challenge is often forgone. In clinic, a diagnosis of food allergy is often made on history and skin prick and/or elevated sIgE testing alone. For example, a child with history of recent peanut anaphylaxis with positive skin prick and/or elevated sIgE testing would be diagnosed with peanut allergy without undergoing a confirmatory oral food challenge. It is often possible to glean from clinical encounters the most convincing aspects that support a food allergy diagnosis without the addition of oral challenge. We believe that a validated epidemiologic method could function in a similar capacity for cohort studies and is crucial to rigorously investigate food allergy when widespread implementation of DBPCFC is not realistic.

The obstacles in epidemiologic study of food allergy are not unique. We can learn from several decades of studying asthma, another clinically defined syndrome, which in the past required confirmation of airway hyperreactivity often by methacholine-challenge in older children and adults. Similar to DBPCFC, the methacholine challenge is another time, resource and labor-intensive procedure. Over the years, in observational and cohort studies, the diagnosis of asthma has ishifted to include epidemiologic definitions, which include data

from surveys and electronic medical records in combination with medication usage and/or measure of pulmonary function. The development of epidemiologic asthma definitions hinged on validation with airway hyperreactivity and agreement with doctor diagnosis. Currently, the use of epidemiologic definitions of asthma diagnoses are widely accepted and utilized in multiple cohorts.[5] The use of these epidemiologic methods allowed us to define the phenotypes of asthma. If the scientific community had continued to assert that asthma could only be diagnosed by documenting methacholine hyperreactivity or reversible airflow obstruction, we would know far less about origins and types of asthma than we currently do.

The development and implementation of similar epidemiologic methods to investigate food allergy is urgently needed. We propose that we can learn from our collective experience with asthma and apply this knowledge to food allergy. The creation of validated epidemiologic method to define a food allergy outcome (both at diagnosis and over time) would allow established cohorts to study food allergy with relative ease, optimizing resource utilization and allowing for more rapid data collection, thus speeding up the pace of scientific discovery for patients without significant financial burden.

In summary, we encourage allergy researchers to focus on designing and implementing epidemiologic methods to define IgE-mediated food allergy outcomes. These methods should aim to be reasonably accurate in diagnosis, easy to implement in cohort studies and validated with oral food challenge. Widespread acceptance of epidemiologic methods to define food allergy will advance our understanding of the etiologic factors and natural history of food allergy and its role in the allergic march. With better understanding of these issues, we will be one step closer to developing programs for the primary prevention of food allergy.

Financial Disclosure:

No funding was received for this project. Dr. Arroyo is supported by NIH R25 AI147369; Dr. Mehta by T32 AI007306; and Dr. Camargo by UH3 OD023253. Dr. Camargo has served on Scientific Advisory Boards for Bryn, Hikma, and kaleo, Inc. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. Dr. Robinson is employed by both MGH and Sanofi - with employment at Sanofi unrelated to this work.

Abbreviations:

DBPCFC	Double blind placebo-controlled food challenge

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