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Reply to Beck *et al.* and to Owora

From the Authors:

We are grateful for the comments by Beck and colleagues and Dr. Owora about our manuscript on the evolution of eczema, wheeze, and rhinitis, in which we suggested that the time may have come to rethink the framework of the atopic march (1). Both letters critique our definitions of outcomes and suggest that physician diagnoses are needed for more accurate estimates. We acknowledge that our findings are limited to questionnaire-based definitions (1). However, most population-based studies, which originally described atopic march, used similar definitions. Furthermore, most of our knowledge about epidemiology of atopic diseases, for example through the International Study of Asthma and Allergies in Childhood (ISAAC) (2) and more recently Global Asthma Network (GAN) (3), used the same extensively validated tools. Also of note, we have previously demonstrated greater misclassification of early-life eczema when using physician diagnosis compared with parental report by validated questionnaires (4).

For our analyses, we focused on wheeze rather than asthma. Although not all wheeze is asthma, wheeze is its most important symptom. The use of the term asthma may introduce bias into the analyses of temporal patterns of comorbidities. First, preschool wheezers (even those with severe symptoms) are rarely diagnosed as having asthma (5, 6), contributing to the impression that asthma diagnosis follows eczema, even in those in whom early-life wheeze precedes eczema, or they develop contemporaneously. Second, among children with identical wheezing patterns, those with a history of eczema may be more likely to have asthma diagnosis than those without (7). Therefore, wheeze is better suited to capturing symptom progression.

Beck and colleagues suggest that food allergy should be included in the definition of atopic march, that IgE-sensitization (with or without barrier dysfunction) drives atopic march, and that without sensitization there is no atopy or march. We defined atopic march as originally proposed, referring to the sequential development of symptoms from eczema in infancy to airway diseases in later childhood (8). We agree that food allergy is important, but as one component of atopic multimorbidity, rather than any march. Few population-based birth cohorts have data on food allergy confirmed by oral food challenge. In one of our cohorts with such data, we observed a fivefold increase in oral food challenge–confirmed peanut allergy in patients with multimorbidity persistence (1). In another recent analysis, we found a strong association between peanut allergy and machine learning–derived multimorbidity cluster, but not with single-disease clusters (9). However, most individuals with multimorbidity are not peanut allergic, and some peanut-allergic children do not have multimorbidity (1).

We agree that barrier dysfunction and sensitization are important, but IgE sensitization is not independent of barrier dysfunction and in some cases may be a consequence thereof (10). Sensitization was not part of the original definition of atopic march, and its inclusion does not strengthen the case for the existence of any specific sequence among sensitized individuals. Although patients with eczema, wheeze, and rhinitis are often sensitized, many sensitized individuals do not have any symptoms (11), and in a proportion of patients with these diseases, sensitization is a chance finding. For example, using conservative estimates of multimorbidity prevalence of 8%, and sensitization of 40%, by chance alone, 3.2% ($0.08 \times 0.4 = 0.032$) will have both. Thus, sensitization may be irrelevant to symptoms (i.e., benign) or may be contributing to different clinical presentations, from single disease to multimorbidity (12, 13). However, at this time, we do not have simple methods to differentiate at a population level whether sensitization is an important disease driver or whether it cooccurs with symptoms due to chance (12). Importantly, multimorbidity occurs with or without sensitization, markers of impaired barrier function, and/or food allergy, with little difference in temporal patterns of symptom development between these groups. Our descriptive and sequence analyses indicate that the progression resembling atopic march may exist, but as one of numerous heterogeneous sequences, which is by no means typical of the progression. Thus, there is no "march," but numerous different individual trajectories leading to the development of multimorbidity (1, 14).

Owora asserts that we understated the importance of the probability of transitioning from eczema to multimorbidity. On the contrary, we explicitly state that it was one of the highest transition probabilities. However, we pointed out that most children with eczema (>75%) do not transition to multimorbidity. In a related point, Owora suggests the use of a unidirectional latent Markov model to model transitions ignores the likelihood of bidirectional transitions between multiple latent states. Markovian models are stochastic models that enable the analysis of the transitions between successive states in sequences, and the latent Markov model does allow for bidirectionality as defined by progression and remission and, therefore, multiple transition patterns. The transition probabilities that we present in the manuscript demonstrate progression to and remission from all disease states, thereby allowing for heterogeneous sequences. However, as with many models, ours is a simplification of reality, but a more complex model must be balanced against interpretability.

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Owora also suggests that hypothesis testing pertaining to the cooccurrence patterns of allergic diseases should be undertaken. We direct readers to Table E5, where these results are presented (1). Differences between observed and expected probabilities suggest that only specific combinations of symptoms/diseases occurred more frequently than expected by chance alone (multimorbidity and wheeze followed by rhinitis in late school age), thereby suggesting that these are not independent; all other cooccurrence patterns occurred as frequently as expected by chance.

Beck and colleagues highlighted that our findings may not be generalizable to other ethnicities. We fully agree and have acknowledged this in our manuscript. This is important, given that we used machine learning algorithms, which can have racial bias when models are trained using racially imbalanced data sets (15). This could increase health inequalities experienced by minority groups through inaccurate diagnosis, prediction, and treatment (16). It is therefore of crucial importance to understand how patterns of atopic multimorbidity vary in different ethnic groups and the mechanisms underlying these.

In the Editorial accompanying our manuscript, Dhamarge and colleagues suggest that the totality of evidence including our study confirms the "validity of the atopic march, when this is interpreted to broadly describe the temporal associations between allergic phenotypes that may evolve along multiple pathways, incorporating the progression from sensitization to overt clinical allergic disease or from one allergic condition to others" (17). We respectfully disagree with this interpretation. The term "march" implies an exclusive sequence of events in a stepwise manner, "moving along steadily and in step with others," rather than any progression from any condition to the other along multiple pathways. Our results identified multimorbidity of eczema, wheeze, and rhinitis as an important phenotype, which affects ~8% of the population and has unique genetic associates (1, 18, 19). However, all analyses (descriptive statistics, frequentist methods, data-driven modeling [1], and Bayesian machine learning framework [18]) confirmed that very few individuals (if any) are marching. In most patients, multimorbidity is established before school age and is stable to adolescence/adulthood (1).

The framework of atopic march has undeniably been useful in highlighting the connection between atopic diseases, leading to a more holistic approach to management. However, as evidence evolves, so should our definitions. We need to reform the taxonomy of atopic diseases from the traditional symptom/medication-based criteria toward a mechanism-based framework (20). On this journey, absolute clarity on terms that we use is important, particularly if this impacts clinical practice. The way we say things matters. Our data do not question the existence of atopic multimorbidity—on the contrary, we identified this to be an important phenotype. The question is whether individual patients are following a typical sequence, or march, and the answer to this is unequivocal—the overwhelming majority do not. We propose that most patients with multimorbidity are not transitioning from one disease to another but have clinical expression of specific pathophysiological mechanism(s) in multiple organs. The syndrome that we agreed to call asthma may partly differ in causality (and therefore treatment) between patients with multimorbidity and with those with lower respiratory symptoms only, and the case may be similar for eczema and rhinitis. Therefore, we suggest that until we uncover the mechanisms underpinning different symptom patterns, terms such as multisystem atopic disorder may be better suited to describe multimorbidity than atopic march. ■

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Erratum: The Impact of Insulin Resistance on Loss of Lung Function and Response to Treatment in Asthma

There are errors in the article by Peters and colleagues (1) appearing in the November 1, 2022 issue of the *Journal*. The name of one of the coauthors, Melody G. Duvall, M.D., was inadvertently omitted from the author byline. Dr. Duvall is affiliated with the Division of Pulmonary and Critical Care Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA. In the author contribution section Dr. Duvall should have been included in the list of those who conceived and designed the study.

In addition, Dr. Elliot Israel is listed as being affiliated with the University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin as well as with Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts. This is incorrect; Dr. Israel is not affiliated with the University of Wisconsin School of Medicine and Public Health.

For the convenience of our readers, *AJRCCM* is replacing the online version of the article with a revised version. ■

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1. Peters MC, Schiebler ML, Cardet JC, Johansson MW, Sorkness R, DeBoer MD, *et al.* National Heart, Lung, and Blood Institute Severe Asthma Research Program-3. The impact of insulin resistance on loss of lung function and response to treatment in asthma. *Am J Respir Crit Care Med* 2022;206:1096–1106.

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Erratum: Prognostic Value of Exercise as Compared to Resting Pulmonary Hypertension in Patients with Normal or Mildly Elevated Pulmonary Arterial Pressure

There are errors in the letter by Douschan and colleagues (1) published in the December 1, 2022 issue of *AJRCCM*. Because of production errors by the typesetter, the word *hemodynamics* has been incorrectly substituted by *hypertension* in the title and throughout the text. The *Journal* is replacing the online article with one that has been corrected. ■

Reference

1. Douschan P, Avian A, Foris V, Sassmann T, Bachmaier G, Rosenstock P, Zeder K, Olschewski H, Kovacs G. Prognostic value of exercise as compared to resting pulmonary hemodynamics in patients with normal or mildly elevated pulmonary arterial pressure. *Am J Respir Crit Care Med* 2022;206:1418–1423.

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