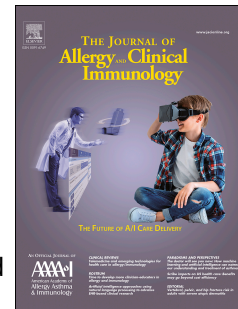


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Atopic dermatitis and the atopic march: considering racial and ethnic diversity in atopic disease progression.

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Jayanta Gupta has nothing to report.

Yaqian Zhun has nothing to report.

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Atopic Dermatitis (AD) is a common, pruritic, skin disease characterized by acute disease flares as well as remissions.<sup>1, 2</sup> The worldwide prevalence of childhood AD ranges from 7% to 25%.<sup>1, 3, 4</sup> AD is also common in adults, which may begin in adulthood or persist from childhood, and has a prevalence of about 10%.<sup>1</sup> AD is observed across all races and ethnicities and in the US is likely more common in Black children than White children.<sup>1, 2, 5</sup> AD has been associated with the sequential progression to asthma and/or allergic rhinitis (AR) called the “atopic march” which is thought to occur due to a common atopic pathophysiology linked to epithelial barrier defect, genetic predisposition, environmental, and immunological factors.<sup>2, 3, 5</sup> How the march is defined may vary depending on the report.<sup>2</sup> The march classically includes the onset of asthma and AR after AD, but can include other illnesses like food allergies (FA), eosinophilic esophagitis, allergic conjunctivitis, pet allergies, etc. as well as specific sequential progressions of these illnesses in individuals with AD.<sup>2, 3</sup> Understanding the march is thought to be critically important for preventing the onset of these other atopic illnesses among those with AD. Patients can develop asthma or AR prior to skin manifestations of AD, and the march to other atopic illnesses in adult-onset AD is also not commonly seen.<sup>4</sup>

In this issue of JACI, Biagini et al observed different orders, for risk of asthma, and rates of onset for FA and AR in Black versus White children in a well-designed longitudinal inception cohort of children with AD from the US (Cincinnati, Ohio).<sup>6</sup> Most children were enrolled by age 2 with outcomes determined at enrollment and approximately 2 years later. Allergic outcomes included sensitization (by skin prick testing), FA (by parental report of a physician diagnosis), AR (by parental report of symptoms), and asthma risk, rather than diagnosis, based on the pediatric asthma risk score (PARS). The PARS is calculated based on history of parental asthma, eczema, wheezing when healthy, early wheezing, allergies, and race).<sup>6</sup> Between the first and second visits, the rates of developing FA and AR were about 3 times higher among White children compared to Black children, and risk of asthma was almost 2.5-fold higher among Black children than White children.<sup>6</sup> Specifically, the mean PARS (Fig 2 in manuscript) among Black children was about 7.5 and among White children was 4.5, but, notably, the PARS includes two points for *Black/African American* race and zero points for *White* race.<sup>6</sup> Importantly, environmental exposures such as traffic related air pollution (TRAP) were also higher among Black children in Biagini et al.<sup>6</sup> TRAP was previously associated with asthma in children living in the Cincinnati area.<sup>7</sup> The investigators appropriately conclude that Black and White children with AD have different atopic marches in their study cohort.<sup>6</sup>

As most prior studies on the atopic march included primarily White individuals or those of European descent, this study adds important and much-needed racial diversity to the existing literature.<sup>2, 5</sup> However, the use of race and ethnicity is often not clearly defined in biomedical research. The appropriate use of race and ethnicity in biomedical research has undergone much debate and the conflation of race and ethnicity with ancestry and biological constructs occurs too frequently. Race and ethnicity are often considered imperfect, and not necessarily appropriate, proxies for a variety of social (e.g., socioeconomic status), environmental, and genetic/biological factors. Without *a priori* deliberate thought about the use and meaning of race/ethnicity in the study design and interpretation of data in research, the meaningfulness of race/ethnicity designations is often unclear. Therefore, transparency about the use and meaning of race/ethnicity in research is critical.<sup>8</sup> The complexities of the implications of observed racial/ethnic differences in AD research can be appreciated in some of the following examples that are relevant to the topic at hand. A large prospective study of children with AD found disparities in healthcare utilization between White and Black children suggesting that the

identification of atopic diseases based on a healthcare provider's diagnosis may be affected by differences in healthcare utilization rather than true differences in disease onset.<sup>9</sup> Other studies have not found differences in asthma prevalence between White and Black children with AD.<sup>9</sup> A previous cohort study of children in Cincinnati by many of the same investigators in the Biagini *et al* study, showed that environmental TRAP exposure was associated with asthma. In the current study TRAP exposure was more common in Black children revealing that, at least in this cohort, environmental exposures also vary by race.<sup>6, 7</sup> Simple statistical adjustment of an often incomplete set of exposures to address these complexities can be inadequate when attempting to account for confounding and especially when attempting to make causal inference.

Biagini *et al* identify racial differences in the risk of asthma and rate of progression to AR within the atopic march, whereas previous studies have not consistently found such differences.<sup>2, 3</sup> In fact, a recent review noted that the majority of children with early onset AD do not develop other atopic illnesses, and most children with AD do not report early onset (< age 2) disease.<sup>2</sup> Notably, many of these studies evaluate asthma onset or diagnosis, and these evaluations often happened when children were older (e.g., 6 years of age or later). In contrast, Biagini *et al* evaluate the risk of asthma via the PARS score, which may not accurately reflect asthma development. Prior studies have reported the prevalence of asthma to be nearly 30%, and, in one study of repetitive cross sectional analyses, the prevalence of asthma appears to stabilize around age 6.<sup>2, 5</sup> However, in another recent study using an electronic medical records based inception cohort in the Philadelphia region, Black children with AD were more likely to progress to asthma, and White children were more likely to progress to AR.<sup>10</sup> Overall, the asthma progression appeared to occur sooner than AR.<sup>10</sup> Different findings among these studies could be related to the difficulty in making an asthma diagnosis in younger children, an issue that has been affected by changing diagnostic criteria, trends in diagnosis, and access to healthcare as well as the use of parental report for the AR diagnosis which, on its own, can also be challenging.<sup>2</sup> The consistency across studies is that there is an increased risk of asthma and AR in young children with AD, and, in newer studies mostly from the USA, there is likely a difference in the frequency of AR and asthma in White versus Black children with AD.<sup>2, 5, 6, 10</sup> However, recent US prevalence studies show that, regardless of AD, Black children are more likely to have asthma than White children.

We know that AD can be associated with other allergic illnesses, associations which have been consistently established for food allergies, asthma, and AR. While attempts have been made to “stop the march” or prevent the onset of other atopic illnesses in those with AD, these studies have not been consistently successful, and, as described by Biagini *et al*, this may have to do with heterogeneity in the etiology and pathophysiology of AD. Future studies may need to evaluate the march in the context of AD endotypes and possible interactions among exposures or risk factors, both genetic and environmental.<sup>6</sup> Certainly important to our understanding of the atopic march is better evaluations of racial and ethnic differences and the specific contributions from social, environmental, and/or ancestral/genetic factors in causing these differences. The Biagini *et al* study is an important step in that direction.

## References

1. Chiesa Fuxench ZC, Block JK, Boguniewicz M, Boyle J, Fonacier L, Gelfand JM, et al. Atopic Dermatitis in America Study: A Cross-Sectional Study Examining the Prevalence and Disease Burden of Atopic Dermatitis in the US Adult Population. *J Invest Dermatol* 2019; 139:583-90.
2. Paller AS, Spergel JM, Mina-Osorio P, Irvine AD. The atopic march and atopic multimorbidity: Many trajectories, many pathways. *J Allergy Clin Immunol* 2019; 143:46-55.
3. Davidson WF, Leung DYM, Beck LA, Berin CM, Boguniewicz M, Busse WW, et al. Report from the National Institute of Allergy and Infectious Diseases workshop on "Atopic dermatitis and the atopic march: Mechanisms and interventions". *J Allergy Clin Immunol* 2019; 143:894-913.
4. Hill DA, Spergel JM. The atopic march: Critical evidence and clinical relevance. *Ann Allergy Asthma Immunol* 2018; 120:131-7.
5. Kapoor R, Menon C, Hoffstad O, Warren B, Leclerc P, Margolis DJ. The prevalence of atopic triad in children with physician-confirmed atopic dermatitis. *J Am Acad Dermatol* 2008; 58:68-73.
6. Biagini JM, Kroner JW, Baatyrbek Kyzy A, Gonzales A, He H, Stevens M, et al. Longitudinal atopic dermatitis endotypes: An atopic march paradigm that includes Black children. *J Allergy Clin Immunol* 2021.
7. Brunst KJ, Ryan PH, Brokamp C, Bernstein D, Reponen T, Lockey J, et al. Timing and Duration of Traffic-related Air Pollution Exposure and the Risk for Childhood Wheeze and Asthma. *Am J Respir Crit Care Med* 2015; 192:421-7.
8. Ioannidis JPA, Powe NR, Yancy C. Recalibrating the Use of Race in Medical Research. *JAMA* 2021; 325:623-4.
9. Wan J, Margolis DJ, Mitra N, Hoffstad OJ, Takeshita J. Racial and Ethnic Differences in Atopic Dermatitis-Related School Absences Among US Children. *JAMA Dermatol* 2019.
10. Gabrysiewicz SJ, Chang X, Dudley JW, Mentch F, March M, Holmes JH, et al. Unsupervised modeling and genome-wide association identify novel features of allergic march trajectories. *J Allergy Clin Immunol* 2021; 147:677-85.e10.

#### Figure 1 Legend:

Schematic diagram of the emerging relationships between atopic dermatitis, associated co-morbid illness, race, environmental factors, and socioeconomic status.