2023

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Keywords: Epigenomics, social epigenomics, asthma, allergy, psychosocial stress, socioeconomic status

Respiratory illnesses, such as asthma and allergy disorders, are disproportionately more common among minority racial/ethnic groups and those of low socioeconomic status. In the United States, asthma prevalence and severity are highest among Puerto Ricans (19.2%), American Indians/Alaska Natives (13%), and Black Americans (12.7%) and higher in families living below the poverty threshold than among those living above it (11% vs 8%–9%).[1] Many studies of asthma/allergy inequalities assume that genetic differences underlie racial/ethnic differences in these disorders, pointing to genetic ancestry differences

Published in *Journal of Allergy and Clinical Immunology* 2023
doi:10.1016/j.jaci.2023.01.032

Submitted October 15, 2022; revised January 13, 2023; accepted January 18, 2023.

between races, but most genetic variants fail to explain racial/ethnic differences and are usually studied only in White populations.[2] In reality, racial and ethnic groups—terms that are often used interchangeably and in overlapping ways—can exhibit varying levels of genetic ancestry, cultural traits, and environmental exposures that all may be entangled together. Thus, any genetic finding differing by race/ethnicity can be confounded by social and environmental factors that also track with different ancestries. However, epigenetic mechanisms (i.e., heritable and stable changes in gene expression) may prove important in explaining these inequalities, as they are influenced by a combination of environmental, social, and genetic factors.

Modifiable environmental risk factors are important in shaping early development of immune systems and lung function, including secondhand smoke exposure, low birth weight, preterm birth, poor air quality, and poor housing conditions, among others.[3] Importantly, these environmental risks are not randomly distributed but are instead shaped by structural forces such as the social policy of redlining, as a result of which families of color were historically excluded from wealthier neighborhoods, leading to higher exposure to hazardous waste, air pollution (e.g., closer to highways with more traffic), poor housing conditions with more environmental toxins such as mold and asbestos, and more potential pest allergens (including from cockroaches and mice). As a result of structural racism, these families are also more likely to have jobs exposing them to hazardous chemicals, such as aerosols or diesel exhaust, and lower access to high-quality medical care. Relatively strong associations have been demonstrated between epigenetic modifications and many of these environmental exposures, including tobacco smoke, airborne particulates, microbial allergens, diesel exhaust particles, polycyclic aromatic hydrocarbons, and dust mites, as reviewed previously.[4] For example, exposure to tobacco smoke in adults has been associated with reduced DNA methylation in the promoter of stress-related gene monoamine oxidase B (MAOB) in human blood cells, and prenatal exposure to smoking has also been associated with reduced methylation at repetitive element AluYb8. Additionally, the inhalation of both diesel exhaust particles and a fungal allergen in mice was associated with changes in IgE levels, potentially mediated through altered methylation at key immune function genes.[4] Although the full causal relevance of these findings

is still undetermined, they imply that DNA methylation may be an important mediator between environmental exposures and asthma and allergy phenotypes.

Even when chemical and physical environmental exposures are accounted for, social determinants such as psychosocial stress due to poverty or racism/discrimination can have an important effect on these phenotypes. For example, non-Hispanic Black and Puerto Rican children have a higher prevalence of asthma and more asthma-related hospitalizations than White American children, even after adjustment for environmental and socioeconomic factors,[1] potentially because they are exposed to more psychosocial stress. Very few epigenetic studies of asthma/allergy inequalities consider psychosocial stressors, which have also been linked to epigenetic changes in pathways relevant to asthma and allergies.[3]

Recent social epigenomic studies have demonstrated the role of DNA methylation in mediating psychologically stressful experiences, such as chronic stress related to stigmatization or exposure to violence.[5] Many epigenome-wide association studies (EWAS) have now explored effects of adverse early-life environments such as war trauma, child abuse, bullying, or immigrant-related stress, often finding small but widespread differences in methylation in children.[5] Adverse social exposures early in life may alter children's immune function, inflammatory pathways, and the hypothalamic-pituitary-adrenal (HPA) axis in ways that predispose them to development of asthma or allergy phenotypes.[3] For example, prenatal maternal stress has been associated with increased proinflammatory cytokines in cord blood and subsequently with changes in fetal lung structure related to wheezing at 2 years of age.[6] Chronic psychological stress, even postnatally, can lead to increased release of cortisol, causing an imbalance in inflammatory cytokines with cascading effects on immune function throughout the child's life. Additionally, psychosocial stressors can enhance the effect of chemical or physical environmental exposures. For example, increased exposure to nitrogen oxides, such as those found in traffic-related air pollution, was associated with asthma and wheeze phenotypes only in children whose parents reported stressful life events, as reviewed previously.[3] Thus, studies of asthma/allergy inequalities should consider interacting effects of environmental risk factors and psychosocial stress on epigenetics.

To identify trends specifically in EWAS of asthma and allergy inequalities, we conducted a brief systematic review of all empirical EWAS of asthma or allergies in humans that were published on PubMed in the past 10 years. Among the 48 identified studies, we noted that 50% included non-White participants (mostly Black or Latinx), with fewer (31%) including more than 1 racial group in the same study and 15% not reporting the race/ethnicity of participants at all (**Figure 1**). These racial/ethnic groups are presumed to be mostly self-identified categories, and only 1 of them used genetic ancestry testing; moreover, many authors failed to specify how these classifications were determined. Given the high prevalence of asthma/allergies in minority racial/ethnic groups, it was not surprising that these studies were more diverse than were general epigenomic studies, in which 87% of participants in the United States–based Encyclopedia of DNA Elements (ENCODE) consortium were "European" (typically self-reported), although only 42% reported race/ethnicity at all.[7] If future studies hope to identify causes of inequalities in allergy/asthma, more diversity within and across studies will be needed. Specifically, if studies aim to address the etiology of racial/ethnic inequalities directly, study designs must make efforts to recruit participants from multiple racial/ethnic groups within the same study rather than focusing only on risk factors within a single racialized group.

Another limitation that we identified across these EWAS was a separate focus on either genetic, environmental, or social factors. Rarely were these factors studied simultaneously, limiting the ability to disentangle effects or study interactions among them. Further, among the reviewed studies that included any environmental data, the focus was limited to the usual suspects of exposure to smoking in the home or in utero, air pollution, and sometimes pets in the home. Only a quarter of the EWAS adjusted for any measures of socioeconomic factors that may shape relevant exposures early in life, and these were limited to education and income. None of the articles in our review included genetic data alongside any measure of socioeconomic status. Finally, we noted that fundamental causes of disease were usually left out of these epigenomic studies entirely. Specifically, no studies in our systematic review included measures of racism in any analysis, nor did they mention racism or structural racism anywhere in the article.

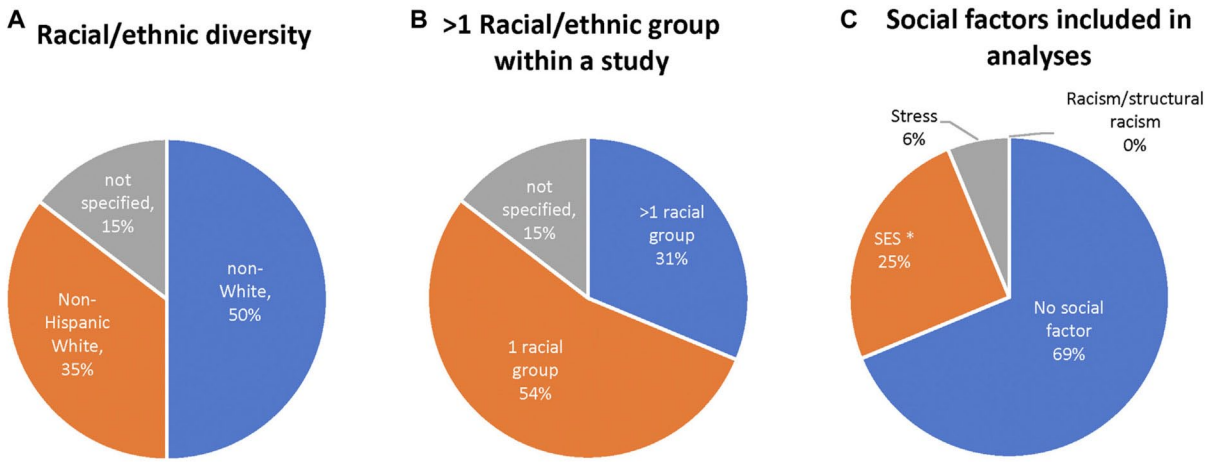

Figure 1. Results of a systematic review of EWAS of allergy and asthma. The brief systematic review was conducted in PubMed in October 2022 by using the search query "DNA Methylation" AND (asthma OR allergy) AND "epigenome-wide" OR "epigenome wide" AND ((y_10[Filter]) AND (humans[Filter]) AND (english[Filter]))) AND (Asthma[Title/Abstract] OR allergy[Title/Abstract]. Query results were filtered for relevant EWAS of asthma or allergies in humans, resulting in 48 analyzed studies. **A)** The racial/ethnic diversity within the articles is demonstrated. **B)** The percentages of articles including more than 1 racial group are shown. **C)** The social factors that were included in the analyses are described, with the majority of articles (69%) not including social factors at all. SES, Socioeconomic status.

Additionally, we noted that very few studies focused on the role of stress-related epigenetic changes as asthma/allergy risk factors. We found only 3 EWAS that examined associations between psychological stress and epigenetics of asthma or wheezing in children.[8-10] One of these studies found that in families with high maternal stress, both mothers and children exhibited genome-wide methylation differences from those with low maternal stress, particularly in functional regulatory regions (enhancer elements and transcription factor binding sites) and, importantly, at sites connecting stress response to pathways relevant to immune function and lung development. Specifically, increased cord blood methylation of the enhancer of the HPA response gene neuromedin U receptor 1 (NMUR1), which was also linked with a higher concentration of cytokines in cord blood, was found only in children who later developed persistent wheeze.[8] Notably, this study utilized whole genome bisulfite sequencing, and it identified significant sites not captured by the more

commonly used Illumina methylation array, indicating the need for broader whole genome sequencing in future EWAS. In the second study, 12 CpG sites measured in nasal epithelial cells were associated with exposure to stress or violence and also with atopic asthma across a metaanalysis of 3 cohorts.[9] The third study included only maternal depression and anxiety as potential confounders of methylation associations with wheezing, and it did not examine direct effects of this exposure.[10] A few additional studies have identified associations of stress with gene expression, primarily finding changes in HPA-related genes, such as melanocortin and glucocorticoid receptors, and other genes involved in the HPA response.[6] Taken together, these studies indicate that psychosocial stress is an important risk factor for asthma/allergy phenotypes and should be accounted for in future epigenomic studies.

In sum, we have found that too few EWAS of allergies and asthma measure any social factors or consider structural racism in understanding inequalities in these disorders. Social, genomic, and epigenomic data must all be integrated along with novel methods to account for joint influences in studies of more diverse populations if we hope to identify the root causes of racial/ethnic inequalities in asthma/allergies. This type of cross-disciplinary work will require collaborative funding mechanisms that support broad interdisciplinary teams with diverse expertise from the social sciences, environmental health, clinicians, geneticists, and biologists.

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We are grateful to Lucia Rejzek, who assisted with the systematic literature review conducted for this study.

Funding Supported by the University of California San Diego Academic Senate Research (grant RG103497).

Disclosure The authors declare that they have no relevant conflicts of interest.

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