

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Reply to Non and Chang

From the Authors:

We read the letter from Drs. Non and Chang with interest and recognize the critical need for discussions around race/ethnicity and ancestry in pulmonary arterial hypertension (PAH), especially because these terms are often conflated in studies of genetic association. Because of the rare nature of the disease, a paucity of PAH studies incorporate sufficient representation of diverse populations. The issue was directly recognized by the *Journal* (1) calling for more research efforts to address health disparities in PAH. In response to these challenges, we assembled five multiinstitutional cohorts, all including Hispanic patients, and attempted to address part of this gap (2). To our knowledge, our primary finding was the first to evaluate and report a reproducible survival benefit in Hispanic patients across clinical settings using

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self-reported race/ethnicity. Drs. Non and Chang primarily raise concerns related to sensitivity analyses within the supplement and accounting for the roles of environmental factors and socioeconomic status (SES). We agree that these factors are critical to consider when studying effects of race/ethnicity, as demonstrated by prior reports from our team (3). However, we maintain that our methods/conclusions already address many of their concerns.

First, the survival advantage in Hispanic patients remained significant after rigorously adjusted analyses, including accounting for age and prostacyclin use. These adjusted findings suggest that the survival benefit is not solely based on younger age. They also directly address published data on prostacyclin that report both its influence on survival (4) as well as its reduced use in Hispanic patients (5). We acknowledged that our findings support the broadly observed Hispanic paradox, recognizing possible roles of SES and genetic factors. In addition, the prevalence of PAH subtypes is different across races/ethnicities (5), which could influence survival outcomes. However, we observed a consistent survival advantage in patients with idiopathic PAH from the PAH Biobank and across broader group 1 PAH populations in our meta-analysis.

Second, we acknowledged that although genetic variability specific to Native American (NA) populations *may* provide a survival advantage to Hispanic patients, our observations *may also* reflect the various SES factors captured by self-report of Hispanic ethnicity. However, registries in PAH, like many diseases, not only lack adequate representation of people of color but also all variables (clinical, genetic, and SES) that can influence survival. Despite this limitation, we respectfully disagree with the claim that genetically based conclusions cannot be derived without accounting for any SES and/or environmental influences. Rather, we believe that the survival advantage in Hispanic patients demands further study of this disparity and its contributing factors, including both genetics and sociocultural factors. Genetic analyses can be especially valuable when presented in synchrony with results related to self-reported race and in the context of possible SES influences.

Third, for consistency in definitions of race/ethnicity, our primary analyses *only* used self-identified race/ethnicity. We acknowledged that although self-reported race/ethnicity may introduce misclassification from a genetic standpoint, it has the potential to capture a host of SES and/or environmental information such as diet, lifestyle choices, and healthcare practices. Our ancillary analyses involved identifying race/ethnicity based on genetics and were performed to assess the robustness of our primary results with self-reported race/ethnicity, observing consistent findings using both approaches. Using only genetically derived ancestry to define Hispanic patients in these supplementary analyses would have been insufficient and unreliable. The mosaic-like ancestry (admixed with genomes of European, African, and NA ancestors) (6), combined with unique SES factors, limits ancestry-based definitions of discrete race/ethnic groups in Hispanic individuals. This limitation was a major driver for our

decision to base our primarily analysis on self-reported race/ethnicity alone.

Finally, we agree that the survival observation may be due largely to increased NA ancestry in self-reported Hispanic patients (and not NA ancestry itself). However, we also observed that NA patients were significantly protected from poor outcomes in our inpatient analyses of the National Inpatient Sample database. We believe that our conclusions were appropriately objective, stating that “Our results reinforce the presence of racial/ethnic disparities in PAH and suggest that these disparities are due *in part* to genetic differences between race/ethnic groups.” Moreover, we were fully transparent in our inability to distinguish between NA and East Asian ancestry based on resolution of global ancestral proportion estimates and the lack of availability of reference panels in NA populations, citing prior studies. We have also rerun STRUCTURE, replacing our East Asian panel with an NA panel (7). Survival analysis using new NA ancestry estimates indicated a stronger effect than that previously observed (random effects meta-analysis hazard ratio, 0.40 [0.18–0.90]; $P=0.03$). This result may again reflect increased NA ancestry in self-reported Hispanic individuals (and not NA ancestry itself). Despite well-known barriers in studying NA populations, we hope our results will encourage research to identify NA-specific variants important in PAH.

To our knowledge, our cohorts represent the largest populations of diverse patients with PAH yet analyzed with both genetic and clinical data. Clearly, our intent is not to harm patients by deemphasizing SES, and we have acknowledged the potential influence of SES and appropriately tempered observations around ancestral contributions. We appreciate the efforts of Drs. Non and Chang to highlight the importance of SES and/or environmental factors in analyses of ancestry and hope our study encourages their evaluation in future prospective PAH studies. In an era in which addressing the underrepresentation of people of color in medical research is at the forefront, we strongly believe our findings promote clinical PAH studies to increase diversity/equity while simultaneously promoting deeper investigations into both genetic and SES contributors to PAH outcomes. Given that medically underserved populations are significantly underrepresented in PAH studies, more research in these vulnerable populations is critical to ensuring equitable benefits of genetic research and combating the pervasive and lamentable racial disparities that plague the genomic medicine literature. ■

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Erratum: Epithelial Damage in Children with Sleep-disordered Breathing



There are errors in the editorial by Horne (1), published in the December 1, 2020 issue of the *Journal*. The word *epithelial* was inadvertently substituted for *endothelial* in the title and in several places throughout the text of the editorial. The *Journal* has replaced the online version with a corrected version. ■

Reference

1. Horne RSC. Endothelial damage in children with sleep-disordered breathing. *Am J Respir Crit Care Med* 2020;202:1497–1499. (editorial).

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