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### Authors

Wohlford, Eric M  
Huang, Peter F  
Elhawary, Jennifer R  
[et al.](#)

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## Racial/Ethnic differences in eligibility for asthma biologics among pediatric populations

Eric M. Wohlford, MD, PhD<sup>[a],[b],\*</sup>,

Peter F. Huang, BA<sup>[b],\*</sup>,

Jennifer R. Elhawary, MS<sup>[b],\*,#</sup>,

Lauren A. Millette, PhD<sup>[c]</sup>,

Maria G. Contreras, BS<sup>[b]</sup>,

Jonathan Witonsky, MD<sup>[a],[b]</sup>,

Cécile T.J. Holweg, PhD<sup>[c]</sup>,

Sam S. Oh, PhD, MPH<sup>[b]</sup>,

Christine Lee, PharmD, PhD<sup>[d]</sup>,

Christine Merenda, MPH, RN<sup>[d]</sup>,

Ronald L. Rabin, MD<sup>[e]</sup>,

Richardae Araojo, PharmD, MS<sup>[d]</sup>,

Angel C.Y. Mak, PhD<sup>[b]</sup>,

Celeste S. Eng, BS<sup>[b]</sup>,

Donglei Hu, PhD<sup>[b]</sup>,

Scott Huntsman, MS<sup>[b]</sup>,

Michael A. LeNoir, MD<sup>[f]</sup>,

Jose R. Rodríguez-Santana, MD, FAAP, FCCP<sup>[g]</sup>,

Luisa N. Borrell, DDS, PhD<sup>[h],†</sup>,

Esteban G. Burchard, MD, MPH<sup>[b],[i],†</sup>

<sup>a</sup>Division of Pediatric Allergy and Immunology, University of California San Francisco, San Francisco, CA, United States of America

<sup>b</sup>Department of Medicine, University of California San Francisco, San Francisco, CA, United States of America

<sup>c</sup>Genentech Inc., South San Francisco, CA, United States of America

# **Corresponding Author Information:** Jennifer Elhawary, M.S., Address: Rock Hall, 1550 4<sup>th</sup> Street, Room 582 Box 2911, San Francisco, CA 94158, Phone: 415-514-9931; Fax: 415-514 4365, jennifer.elhawary@ucsf.edu.

\*These authors contributed equally to this work

†These authors share senior authorship

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<sup>d</sup>Office of Minority Health and Health Equity, U.S. Food and Drug Administration, Silver Spring, MD, United States of America

<sup>e</sup>Center for Biologics Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD, United States of America

<sup>f</sup>Bay Area Pediatrics, Oakland, CA, United States of America

<sup>g</sup>Centro de Neumología Pediátrica, Caguas, Puerto Rico, United States of America

<sup>h</sup>Department of Epidemiology & Biostatistics, Graduate School of Public Health & Health Policy, City University of New York, New York, NY, United States of America

<sup>i</sup>Department of Bioengineering and Therapeutic Sciences, University of California San Francisco, San Francisco, CA, United States of America

## Abstract

**Background**—Asthma is a heterogeneous disease. Clinical blood parameters differ by race/ethnicity and are used to distinguish asthma subtypes and inform therapies. Differences in subtypes may explain population-specific trends in asthma outcomes. However, these differences in racial/ethnic minority pediatric populations are unclear.

**Objective**—Investigate the association of blood parameters and asthma subtypes with asthma outcomes and examine population-specific eligibility for biologic therapies in minority pediatric populations.

**Methods**—Using data from two asthma case-control studies of pediatric minority populations, we performed case-control (N=3,738) and case only (N=2,743) logistic regressions to quantify the association of blood parameters and asthma subtypes with asthma outcomes. Heterogeneity of these associations was tested using an interaction term between race/ethnicity and each exposure. Differences in therapeutic eligibility were investigated using chi-square tests.

**Results**—Race/ethnicity modified the association between total immunoglobulin E (IgE) and asthma exacerbations. Elevated IgE was associated with worse asthma outcomes in Puerto Ricans. Allergic asthma was associated with worse outcomes in Mexican Americans whereas eosinophilic asthma was associated with worse outcomes in Puerto Ricans. A lower proportion of Puerto Ricans met dosing criteria for allergic asthma-directed biologic therapy than other groups. A higher proportion of Puerto Ricans qualified for eosinophilic asthma-directed biologic therapy than African Americans.

**Conclusion**—We found population-specific associations between blood parameters and asthma subtypes with asthma outcomes. Our findings suggest that eligibility for asthma biologic therapies differs across pediatric racial/ethnic populations. These findings call for more studies in diverse populations for equitable treatment of minority patients with asthma.

## Capsule Summary:

Blood parameters differ between African American, Mexican American, and Puerto Rican children. More Puerto Rican children may benefit from eosinophil-directed biologic therapies, but fewer met criteria for anti-IgE therapy than other groups.

## Keywords

Asthma; Pediatric asthma; Biomarker-driven asthma therapeutics; Asthma subtypes; Peripheral blood parameters; White blood cell count; Total immunoglobulin E; Minority pediatric populations

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## Introduction

Asthma is a chronic inflammatory obstructive lung disease associated with significant morbidity and mortality for racial/ethnic minority groups.<sup>1</sup> Asthma is the most common and racially/ethnically disparate chronic respiratory disease in children.<sup>2</sup> Lifetime asthma prevalence is greater among Puerto Rican (23.6%) and African American children (18.1%) than among Mexican American (11.5%), and White (9.5%) children.<sup>3</sup> Asthma mortality is 4-fold higher in Puerto Ricans and African Americans than in Mexican Americans.<sup>4</sup> Populations with the highest asthma prevalence and mortality also tend to be the least responsive to commonly prescribed asthma therapies.<sup>5–9</sup> While the etiology of asthma is complex, resulting from the confluence of genetic, environmental, and socio-cultural risk factors the causal basis for these racial/ethnic health disparities remains elusive.

Asthma is a heterogeneous disease composed of multiple, sometimes overlapping, pathobiological and clinical subtypes.<sup>10</sup> Delineating these clinical subtypes is a challenge for clinicians, who must choose between different biologic therapies for their patients. Currently approved asthma biologics in the United States (U.S.) primarily target allergic or eosinophilic asthma. Blood parameters are used to determine eligibility and dosing regimens of these biologics, yet evidence shows that clinical blood profiles differ by race/ethnicity.<sup>11, 12</sup> The lack of population-based information on asthma therapeutic-associated blood parameters in racially/ethnically diverse pediatric populations can leave clinicians uncertain about the choice of biologic therapy for their patients. This is especially true for non-White patients, who have been left out of pulmonary and asthma-related clinical and biomedical research.<sup>13</sup> Having accurate, population-based information for racial/ethnic minority children is of critical concern given that minorities comprise 50% of children in the U.S.<sup>14</sup> Other asthma subtypes such as neutrophilic, late-onset, and obesity-related asthma<sup>10</sup> do not have subtype-directed asthma therapies at this time. Thus, the study of asthma blood profiles may provide insight into population-specific asthma biology and help inform therapeutic management.

We hypothesized that clinical blood profiles and asthma subtypes are differentially associated with asthma outcomes across racial/ethnic populations. We also hypothesized that eligibility for asthma biologic therapies differs across populations. To address these hypotheses, we examined the association of blood parameters and clinical subtypes with asthma outcomes using case-control and case-only analyses in two richly phenotyped pediatric African American and Latino cohorts with and without asthma. In addition, we assessed population-specific eligibility for blood biomarker-informed biologic therapies in those with moderate-to-severe asthma.

## Methods

### Recruitment of Parent Study Population

The Genes-environments & Admixture in Latino Americans study (GALA II) and the Study of African Americans, Asthma, Genes, & Environments (SAGE) are parallel case-control studies using similar protocols and questionnaires, previously described.<sup>15</sup> Briefly, GALA II recruited Hispanics/Latinos from five urban study centers across the mainland U.S. (Chicago, IL; Bronx, NY; Houston, TX; San Francisco Bay Area, CA) and Puerto Rico between 2006 and 2014 using a combination of community and clinic-based recruitment. SAGE recruited African Americans from the San Francisco Bay Area only. In both studies, participants were 8 to 21 years old at recruitment. Cases had physician-diagnosed asthma and asthma symptoms and/or asthma medication use within the last two years, with no history of other lung or chronic non-allergic illnesses. Healthy controls had no history of asthma or allergies, use of allergy medications, or symptoms of wheezing or shortness of breath during their lifetime. Control subjects were 1:1 frequency matched within each recruitment center by age (within 1 year). Case subjects and control subjects were recruited from similar geographic regions. Those in the third trimester of pregnancy, current smokers, and those with at least a 10 pack-year smoking history were ineligible. Parents and grandparents of study participants must have self-identified as Hispanic/Latino or African American. At the time of recruitment detailed clinical measures and biological specimens were collected, along with questionnaire-based information regarding additional social, environmental, and historical risk factors. The study protocols for both GALA II and SAGE were approved by the University of California San Francisco (UCSF) Human Research Protection Program Institutional Review Board (IRB). Detailed consenting procedures can be found in the Online Repository.

### Asthma Outcomes

Asthma outcomes were defined as follows: asthma status (yes/no), asthma severity (moderate-to-severe/mild), asthma control (uncontrolled/controlled), and at least one asthma exacerbation in the year prior to recruitment (yes/no). Detailed definitions of asthma outcomes are provided in the Online Repository.

### Measurement of Blood Parameters

Serum total immunoglobulin E (IgE) was measured in our research lab from plasma in duplicate on a Phadia 100 detection system (ThermoFisher Scientific, Uppsala, Sweden). If both measurements were not within 10% concordance, a 3<sup>rd</sup> measurement was assayed. White blood cell (WBC) counts were obtained from complete blood counts with differentials using commercially available and Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories through Quest Diagnostics in the GALA II dataset and through UCSF Clinical Laboratories for SAGE. Serum total IgE and WBC counts were specified as continuous predictors. However, the distributions of serum total IgE, basophils, and eosinophils were highly right-skewed and were log-transformed for analysis purposes.

## Defining Asthma Subtypes

Allergic asthma was defined as having asthma and any sensitization to aeroallergens by skin prick test.<sup>16</sup> Details on assessment of skin prick positivity can be found in the Online Repository. Eosinophilic asthma was defined as having asthma and an absolute eosinophil count (AEC)  $\geq 150$  c/uL ( $\geq 300$  c/uL separately assessed in the Online Repository).<sup>17</sup> These asthma subtypes were specified as yes or no. Overlap between subtypes was only assessed in African Americans as they were the only population in our study with an overlap between skin prick and WBC data.

## Defining Eligibility for Blood Biomarker-Informed Asthma Biologic Therapies

For allergic asthma therapy, dosing of anti-IgE therapy is based on pre-treatment serum total IgE level. The U.S. Food and Drug Administration (FDA)-approved dosing range for this therapy requires the level of pretreatment serum total IgE to be  $>30$  kU/L and either  $<1,300$  kU/L for children 6–11 years old or  $<700$  kU/L for those 12 years or older.<sup>18–22</sup> For this eligibility analysis, allergic asthma was defined as having asthma and sensitization to at least one perennial aeroallergen (dust mite, dog, cat, cockroach, mouse and rat) by skin prick test. Participants with moderate-to-severe, allergic asthma were considered eligible for anti-IgE therapy if they fell within their age-specific limits and ineligible otherwise. For eosinophilic asthma therapy, eligibility was assessed using a common clinical threshold for therapeutic use: AEC  $\geq 150$  c/uL.<sup>17, 23–26</sup> The age indication for most eosinophil directed therapies is 12 years old.<sup>27–29</sup> Therefore, participants must have been at least 12 years of age, and were considered eligible if their AEC was equal to or above the threshold and ineligible otherwise.

## Covariates

Covariates considered for this analysis were age, sex, obesity status, socioeconomic status (SES), and inhaled corticosteroid (ICS) use within 2 weeks of recruitment. Detailed descriptions are provided in the Online Repository.

## Study Inclusion and Exclusion Criteria

Of the 5,147 GALA II participants, those who identified themselves as Hispanic/Latino subgroups other than Mexican American or Puerto Rican or whose grandparents were not identified as the same race/ethnicity were excluded (N=957). Of the 1,710 total SAGE participants, participants whose four grandparents did not all identify as African American were excluded (N=126). After combining both GALA II and SAGE participants, those missing both total IgE data and WBC count data (N=831), those who used oral steroids within 2 weeks of recruitment (N=40), and those missing obesity status (N=1,165) were also excluded for an analytical sample of 3,738 cases and controls. Analyses for asthma outcomes (severity, control, and exacerbations) included cases only (N=2,743). Analyses investigating the proportion of each population that were eligible for various biologic therapies were restricted to participants with moderate-to-severe asthma (N=1,917). A consort diagram is visualized in Figure E1. Additional details on analysis-specific inclusions and sample sizes are outlined in Table E1.

## Statistical Analysis

Descriptive statistics were calculated for both demographic and clinical characteristics for the total population and according to race/ethnicity. We used logistic regressions to test an interaction term of race/ethnicity with each exposure to examine the heterogeneity of their association with asthma outcomes in the total population. We then quantified these associations via odds ratios (OR) and confidence intervals (CI) in each racial/ethnic group (African American, Mexican American and Puerto Rican) adjusting for age, sex, obesity status, SES, and ICS use. Mexican American participants were excluded from WBC count analyses due to small sample size (N=33). Due to the bimodal distribution of basophils in Puerto Ricans (Figure E2), the association of basophils with asthma and asthma outcomes was analyzed only in African Americans. In addition, we examined the proportion of participants from each racial/ethnic group with moderate-to-severe asthma that would be ineligible for anti-IgE and eosinophilic asthma-directed therapies. We used chi-squared tests of independence to examine whether the proportion of those ineligible differed between populations.

All statistical analyses were performed with R v.3.6.2.

## Results

### Demographic Characteristics

Baseline study population characteristics for the total population and stratified by race/ethnicity are presented in Table 1. In our population (N=3,738), 1,275 self-identified as African American, 967 as Mexican American, and 1,496 as Puerto Rican. Almost half of the study population were female (49.0%) and almost a third were classified as obese (31.9%). Mexican Americans were more likely to be obese compared to other racial/ethnic groups ( $p<0.001$ ). In our study population, 2,743 (73.4%) participants had asthma. Mexican Americans had the lowest proportion of poor asthma outcomes ( $p<0.05$ ). A higher proportion of Puerto Ricans had eosinophilic asthma compared to African Americans ( $p<0.01$ ), and proportions of those with allergic asthma differed significantly between racial/ethnic groups ( $p<0.05$ ; Table E2).

### Distribution of Blood Parameters

Total IgE levels were significantly higher in Puerto Ricans compared to African Americans and Mexican Americans ( $p<0.001$ ). Basophil, eosinophil, monocyte, and neutrophil counts differed significantly between African Americans and Puerto Ricans ( $p<0.001$ ), as shown in Figure E2.

### Effect of Blood Parameters on Asthma Outcomes

We observed a significant interaction of race/ethnicity with IgE levels for asthma exacerbations between African Americans and Puerto Ricans ( $p=0.04$ ) as shown in Figure 1. After adjustment for age, sex, obesity status, SES, and ICS use, higher IgE levels were significantly associated with greater odds of asthma in all three racial/ethnic groups: African American (OR=1.33; CI=1.21–1.45), Mexican American (OR=1.35, CI=1.22–1.50), and Puerto Rican (OR=1.27; CI=1.16–1.40). In addition, higher IgE levels were



significantly associated with worse asthma severity in African Americans (OR=1.11; CI=1.00–1.23) and Puerto Ricans (OR=1.17; CI=1.06–1.29), worse asthma control in African Americans (OR=1.11; CI=1.00–1.23) and Puerto Ricans (OR=1.13; CI=1.03–1.25), and more exacerbations in Puerto Ricans (OR=1.23; CI=1.13–1.34). Puerto Ricans were the only group with significant associations between increased IgE and worsening of all asthma outcomes.

Higher eosinophil count was significantly associated with greater odds of asthma in African Americans and Puerto Ricans (OR=1.55; CI=1.10–2.23 and OR=1.66; CI=1.23–2.24, respectively), but associated with exacerbations (OR=1.67; CI=1.18–2.38) in Puerto Ricans only. Higher lymphocyte counts were significantly associated with greater odds of asthma in African Americans only (OR=1.05; CI=1.00–1.10) while higher monocyte counts were significantly associated with lower odds of asthma in Puerto Ricans only (OR=0.84; CI=0.74–0.96). Neutrophils were not associated with asthma or asthma outcomes in African Americans or Puerto Ricans. All ORs and CIs for this analysis are provided in Table E3.

### Effect of Asthma Subtypes on Asthma Outcomes

We observed some associations between asthma subtypes and asthma outcomes in Puerto Ricans and Mexican Americans but not in African Americans (Figure 2). After controlling for age, sex, obesity status, SES, and ICS use, eosinophilic asthma was associated with worse asthma severity (OR=1.96; CI=1.15–3.37), worse asthma control (OR=1.74; CI=1.01–3.00) and exacerbations (OR=1.81; CI=1.10–2.98) in Puerto Ricans only. Allergic asthma was associated with worse asthma control (OR=1.49; CI=1.02–2.19), and exacerbations (OR=1.82; CI=1.19–2.83) only in Mexican Americans. Heterogeneity was not observed for the associations between asthma subtypes and asthma-related outcomes by race/ethnicity ( $p>0.05$ ). All ORs and CIs for this analysis are provided in Table E4. Overlap of allergic and eosinophilic asthma in 122 African Americans is presented in Table E5.

### Eligibility for Allergic and Eosinophilic Asthma Biologics Across Populations

In our study, Puerto Ricans were significantly less likely to be eligible for anti-IgE therapy than other groups, but significantly more likely to qualify for eosinophilic asthma-directed therapies. Specifically, 17.2% of African Americans, 21.2% of Mexican Americans, and 31.4% of Puerto Ricans with moderate-to-severe, allergic asthma had pre-treatment IgE either too low to qualify ( $<30$  kU/L) or too high to recommend a dose for anti-IgE therapy ( $>700$  kU/L for ages 12+,  $>1,300$  kU/L for ages 6–11; Figure 3A).<sup>20</sup> Proportion plots for each pre-treatment IgE threshold can be found in Figure E3. We found that 51.3% of African Americans and 26.8% of Puerto Ricans age 12 and older with moderate-to-severe asthma had AEC  $<150$  c/uL (Figure 3B) and would not qualify for eosinophilic asthma-directed therapies. A proportion plot for an AEC  $<300$  c/uL cutoff can be found in Figure E4. We additionally examined these proportions for those age 6 and older, as is indicated for the eosinophilic asthma-directed therapy duplimab,<sup>29</sup> and found that the proportions were nearly identical. Significant differences in population eligibility for anti-IgE therapy and eosinophilic asthma-directed therapy age 12 and older are presented in Table E6.



## Discussion

Clinical blood profiles affect asthma outcomes and determine many clinical and therapeutic options. These profiles also differ by race/ethnicity.<sup>11, 12</sup> We found that increased levels of serum total IgE were highly associated with asthma status across African American, Mexican American, and Puerto Rican children. Serum total IgE is a biomarker and biologic therapeutic target associated with allergic asthma and with decreased lung function in patients with asthma.<sup>30</sup> Previous research in children has associated IgE with asthma severity.<sup>31, 32</sup> Within our Puerto Rican population, increased IgE levels were significantly associated with severe asthma, worse asthma control, and a history of asthma exacerbations. We did not observe the same pattern among African Americans, where increased IgE was only associated with severe asthma and poor asthma control, or Mexican Americans, where increased IgE was not associated with any of these outcomes.

Our findings of racial/ethnic-specific blood profiles and associations with asthma outcomes may suggest different asthma pathobiology or environmental effects in the populations studied. It has been previously shown that peripheral blood eosinophil counts are associated with eosinophilic asthma, as measured by airway eosinophils and asthma outcomes.<sup>33, 34</sup> While eosinophil count was significantly associated with asthma in both African American and Puerto Rican groups, only in our Puerto Rican population was higher eosinophil count associated with a history of asthma exacerbations. It is possible that Puerto Ricans and African Americans may have a different pathobiological basis for poor asthma outcomes, and that Puerto Ricans may benefit more from eosinophil-directed biologic therapies than other racial/ethnic groups. We note that baseline AEC was elevated in Puerto Ricans relative to African Americans regardless of asthma status. It has been reported that elevated baseline AEC is a predictor of treatment response to mepolizumab therapy for asthma.<sup>35</sup> Whether or not elevated baseline AEC predisposes the Puerto Rican population to eosinophilic disease is yet unknown.

The associations between clinically significant predictors and disease outcomes produced surprising results. Specifically, Mexican Americans were the only population studied with any significant associations between allergic asthma and worse asthma outcomes. Additionally, eosinophilic asthma was significantly associated with worse asthma severity, control, and exacerbations in Puerto Ricans only, which suggests that eosinophil-directed biologic therapies may benefit Puerto Ricans more than other populations. While these findings may be due to population-specific differences in social and environmental exposures or genetic ancestry proportions, further studies are needed to fully understand the effect that race/ethnicity has on allergic asthma outcomes.

Our study of children with moderate-to-severe asthma from different racial/ethnic groups provide novel insights on the therapeutic options available for these three populations of children. Overall, we found that a smaller proportion of Puerto Ricans would meet FDA-approved thresholds for anti-IgE dosing using pre-treatment IgE thresholds of <700 kU/L or <1,300 kU/L, compared with African Americans or Mexican Americans. In contrast, for eosinophilic asthma, a smaller proportion of African Americans qualified for eosinophilic asthma-directed therapies based on pre-treatment AEC  $\geq 150$ , when compared with Puerto

Ricans. These differences highlight the need for future study of asthma biologic therapies in racially/ethnically diverse populations, which may identify clinical subgroups that would benefit most from targeted biologic therapies.

The underlying basis for the differences in peripheral blood parameters and racial/ethnic groups is likely multifactorial.<sup>11</sup> WBC counts are known to be affected by genetic ancestry, with African ancestry being associated with lower neutrophil counts and some elevations in eosinophil and other WBC counts, due to variation at the Duffy locus.<sup>36,37</sup> Herein, Puerto Ricans had a higher average absolute neutrophil counts and elevated eosinophil counts relative to African Americans. On average, Puerto Ricans have lower proportions of African ancestry than African Americans.<sup>38</sup> Relative to Mexican Americans and other Latino populations, the Puerto Rican population has more African admixture and a lower proportion of Native American ancestry.<sup>39</sup> More broadly, the expressed blood parameters of various global populations may be influenced by their particular genetic background; related to history, geography, and other factors. An expanding list of genetic variants is known to play a role in WBC count differentials, which varies by race/ethnicity across studies.<sup>37,40,41</sup> While environmental conditions<sup>42</sup> may affect eosinophil counts, and could relate to the observed differences between Puerto Ricans and African Americans, participants were enrolled in urban settings for both GALA II and SAGE studies, respectively. Although parasitic infections can increase absolute eosinophil count, these infections are now rare in Puerto Rico, consistent with the island's high human development index and Center for Disease Control and Prevention (CDC) traveler guidelines on the safety of drinking water<sup>43, 44</sup> in urban areas, where all patients were enrolled. None of the populations in our study had testing for parasitic infections, and we cannot evaluate whether this could have affected AEC values. Environmental and hereditary factors have been previously associated with serum total IgE levels.<sup>45, 46</sup> There are likely yet unknown genetic and environmental factors affecting the peripheral blood counts and IgE levels we observed, which may be clarified by future studies in racially/ethnically diverse populations.

One limitation of our study was that none of the participants were on biologic therapy for asthma, limiting our ability to make conclusions about blood profiles and associations with biologic therapeutic response. In this study, few participants had both skin prick and WBC data, which prevented us from assessing how overlapping subtypes affects asthma. In the real-world, asthma subgroups are not mutually exclusive; patients can have both allergic and eosinophilic asthma. Further research is needed to examine if having one or multiple subtypes influence an individual's risk for poor asthma outcomes or eligibility for asthma biologics. Furthermore, due to small samples sizes in some analyses as the result of unmeasured WBC count data, we cannot make definitive conclusions about racial/ethnic group-level differences in WBC counts and eligibility for eosinophilic-asthma directed therapy. We were also not able to determine which of the 40 patients taking OCS in the prior two weeks had been on chronic versus acute OCS therapy, and thus, could not assess the small proportion of patients who could qualify for dupilumab for OCS-dependent asthma. While research has suggested that differences in gut microbiomes may affect asthma outcomes, we were not able to assess the impact of microbiome differences in this study. Our study was also limited by the fact that we did not have a White population for comparison purposes. In addition, the blood profiles in our populations were measured

from a single point in time, which meant we could not analyze how longitudinal changes in blood profiles may impact disease outcomes or eligibility for biologics. However, our WBC data is reliable, given that these measurements were obtained from CLIA-certified labs. Additionally, there remains a lack of research in minority populations with asthma or lung disease.<sup>13</sup> This precluded us from being able to replicate our findings in an independent dataset for these three minority populations. Regardless, our analyses included the largest gene-environment study of asthma in minority children to date.

Overall, our findings suggest that peripheral blood parameters are associated with asthma outcomes in African American, Mexican American, and Puerto Rican children. In the U.S., available asthma biologic therapies target eosinophilic or allergic asthma. We found a greater proportion of Puerto Rican participants had eosinophilic asthma compared to African Americans. Unlike Puerto Ricans, African Americans did not have associations between increased eosinophil counts and poor asthma outcomes including more severe asthma or asthma exacerbations. Further research is needed to determine if these observed differences relate to differential treatment responses between racial/ethnic groups. Mexican Americans had the highest frequency of allergic asthma, which was uniquely associated with worse asthma control and exacerbations. Of participants with moderate-to-severe asthma, a higher proportion of African American and Mexican American participants than Puerto Rican participants met dosing criteria for treatment with anti-IgE therapy for allergic asthma, while a higher proportion of Puerto Rican than African American participants met criteria for eosinophilic asthma therapies. Selecting the correct biologic asthma therapy for a given patient remains a struggle for clinicians, which may be compounded in racial/ethnic minorities given the lack of clinical and biomedical research in these populations. While biologic therapies represent a new dawn in asthma care, that dawn has not yet risen for all patients of different racial/ethnic backgrounds. It is critical that current and future biomarker-driven asthma therapeutics are studied in patients of diverse backgrounds to bring maximal benefits to all patients.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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### Abbreviations/Acronyms:

<b>AEC</b>	absolute eosinophil count
<b>CDC</b>	Center for Disease Control and Prevention
<b>CI</b>	confidence interval
<b>CLIA</b>	Clinical Laboratory Improvement Amendments
<b>FDA</b>	U.S. Food and Drug Administration
<b>GALA II</b>	the Genes-environments & Admixture in Latino Americans study
<b>ICS</b>	inhaled corticosteroids
<b>IgE</b>	immunoglobulin E
<b>IRB</b>	institutional review board
<b>OR</b>	odds ratios
<b>SAGE</b>	the Study of African Americans, Asthma, Genes, & Environments
<b>SES</b>	socioeconomic status
<b>UCSF</b>	University of California, San Francisco
<b>WBC</b>	white blood cell count

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**Clinical Implications:**

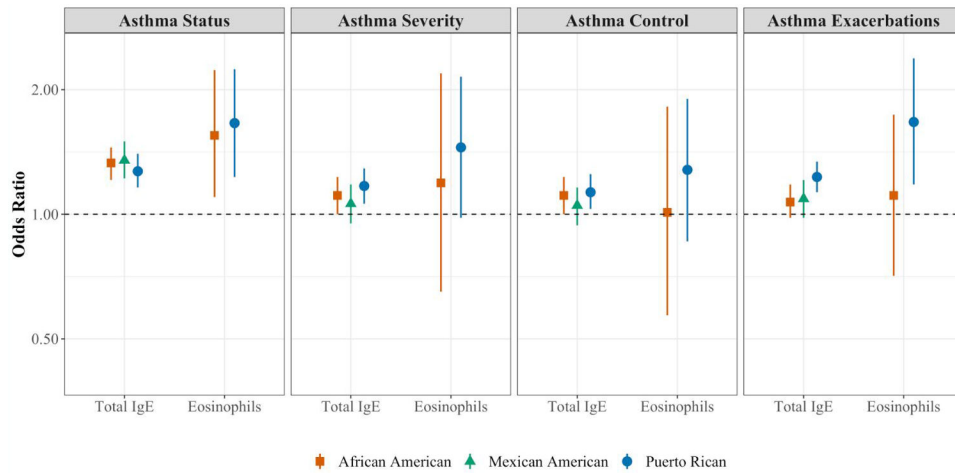
There are racial/ethnic-specific differences in eligibility for asthma biologics among pediatric populations based on commonly used blood parameter thresholds.

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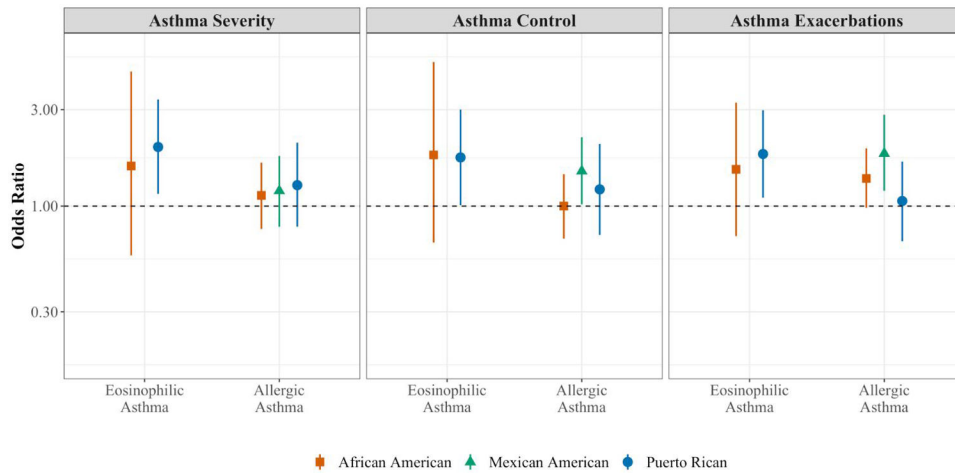
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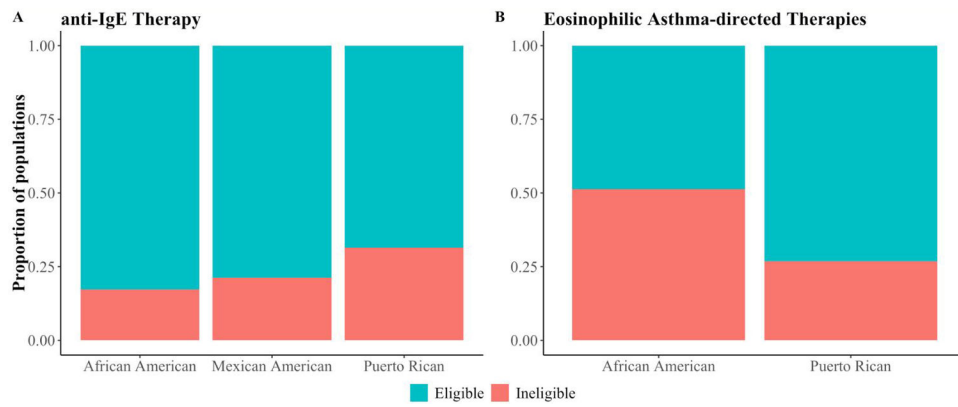
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**Figure 1. Population-specific adjusted odds ratios for blood parameters on asthma outcomes.** Odds ratios adjusted for age, sex, obesity status, socioeconomic status, and inhaled corticosteroid use within two weeks of recruitment are plotted with their 95% confidence intervals on a log scale. Values shown are associated with a 1-log increase for eosinophils (c/uL) and IgE (kU/L). Odds ratios indicate that the exposure is associated with a poor outcome (asthma/moderate-to-severe asthma/uncontrolled asthma/exacerbations within the past year). Odds ratios for white blood cells in Mexican American children not plotted due to small sample size.



**Figure 2. Population-specific adjusted odds ratio for asthma subtypes on asthma outcomes.** Odds ratios adjusted for age, sex, obesity status, socioeconomic status, and inhaled corticosteroid use within two weeks of recruitment are plotted with their 95% confidence intervals on a log scale. Eosinophilic asthma defined as eosinophil count  $\geq 150$  c/uL. Allergic asthma was defined as having any sensitization to aeroallergens by skin prick test. Values represent odds of the outcome for a given asthma subtype. Odds ratios indicate that the exposure is associated with a poor outcome (moderate-to-severe asthma/uncontrolled asthma/exacerbations within the past year).



**Figure 3. Proportion of study populations that do not meet dosing criteria for IgE targeted therapy or 150 c/uL criteria for eosinophilic asthma-directed therapies.** Proportion of participants eligible (teal) or ineligible (salmon) for anti-IgE therapy (A) or eosinophilic asthma-directed therapies with the 150 c/uL cutoff (B).

Distribution of demographic and clinical characteristics for African American, Mexican American and Puerto Rican participants in GALA II and SAGE: 2006–2014

Table 1.

Characteristic*	Total Population (N=3,738)	African American (N=1,275) (34.1%)	Mexican American (N=967) (25.8%)	Puerto Rican (N=1,496) (40.0%)
Median age, yrs (Q <sub>1</sub> , Q <sub>3</sub> )	13.4 (10.8, 16.8)	14.8 (11.6, 18.1)	13.5 (10.7, 16.9)	12.5 (10.3, 15.3)
Female (n, %)	1,833 (49.0)	642 (50.4)	481 (49.7)	710 (47.5)
Obese (n, %)	1,191 (31.9)	389 (30.5)	362 (37.4)	440 (29.4)
Asthma (n, %)	2,743 (73.4)	898 (70.4)	636 (65.8)	1,209 (80.8)
Moderate-to-Severe asthma <sup>†</sup> (n, %)	1,917 (70.2)	639 (71.3)	379 (59.7)	899 (74.9)
Uncontrolled asthma <sup>†</sup> (n, %)	1,957 (71.3)	651 (72.5)	352 (55.3)	954 (78.9)
Exacerbated asthma <sup>†</sup> (n, %)	1,406 (51.3)	353 (39.3)	214 (33.6)	839 (69.4)
With total IgE measurement (n, %)	3,554 (95.1)	1,267 (99.4)	966 (99.9)	1,321 (88.3)
Median IgE, kU/L (Q <sub>1</sub> , Q <sub>3</sub> )	169.3 (46.8, 482.8)	138.9 (37.0, 388.6)	121.2 (35.3, 369.2)	271.6 (80.4, 683.6)
With WBC measurements (n, %)	755 (20.2)	251 (19.7)	33 (3.4)	471 (31.5)
Median AEC, c/uL (Q <sub>1</sub> , Q <sub>3</sub> )	200 (100, 300)	110 (60, 210)	<sup>‡</sup>	200 (100, 400)
Eosinophilic asthma <sup>§</sup> (n, %)	302 (62.1)	70 (47.6)	<sup>‡</sup>	232 (68.4)
With skin prick data (n, %)	2,470 (66.1)	1,083 (84.9)	879 (90.9)	508 (34.0)
Allergic asthma <sup>  </sup> (n, %)	1,168 (65.9)	483 (65.6)	424 (73.1)	261 (58.9)
SES				
Low (n, %)	1,528 (40.9)	633 (49.6)	418 (43.2)	477 (31.9)
Medium (n, %)	1,522 (40.7)	518 (40.6)	399 (41.3)	605 (40.4)
High (n, %)	688 (18.4)	124 (9.7)	150 (15.5)	414 (27.7)
ICS use within 2 weeks of recruitment (n, %)	719 (19.2)	327 (25.6)	212 (21.9)	180 (12.0)

Abbreviations: Q<sub>1</sub>, 1<sup>st</sup> quartile; Q<sub>3</sub>, 3<sup>rd</sup> quartile; IgE, immunoglobulin E; WBC, white blood cell; AEC, absolute eosinophil count; SES, socioeconomic status; ICS, inhaled corticosteroid

P-values for between population comparisons are provided in Table E2.

\* All values shown are N values and percentages of the population with the exception of age, AEC, IgE which represent medians and 1<sup>st</sup> and 3<sup>rd</sup> quartiles.

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<sup>‡</sup>Expressed as percentage of population with asthma.

<sup>‡</sup>Not analyzed due to small sample size.

<sup>§</sup>Expressed as percentage of asthma cases with measured eosinophil count. Defined as eosinophil count  $\geq$  150 c/uL.

<sup>||</sup>Expressed as percentage of asthma cases with skin prick measurements. Defined as having positive aeroallergen skin prick test.