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: We investigated the association of blood parameters and asthma subtypes with asthma outcomes and examined population-specific eligibility for biologic therapies in minority pediatric populations.

Methods: Using data from 2 asthma case-control studies of pediatric minority populations, we performed case-control (N = 3738) and case-only (N = 2743) logistic regressions to quantify the association of blood parameters and asthma subtypes with asthma outcomes. Heterogeneity of these associations was tested using chi-square tests. Differences in therapeutic eligibility were investigated using chi-square tests. Results: Race/ethnicity modified the association between total IgE and asthma exacerbations. Elevated IgE level 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. Conclusions: 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 racial/ethnic populations. These findings call for more studies in diverse populations for equitable treatment of minority patients with asthma. (J Allergy Clin Immunol 2021;148:3134-41.)

Key words: Asthma, pediatric asthma, biomarker-driven asthma therapeutics, asthma subtypes, peripheral blood parameters, white blood cell count, total IgE, minority pediatric populations

Asthma is a chronic inflammatory obstructive lung disease associated with significant morbidity and mortality for racial/ethnic minority groups. It is the most common and racially/ethnically disparate chronic respiratory disease in children. 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. Asthma mortality is 4-fold higher in Puerto Ricans and African Americans than in Mexican Americans. Populations with the highest asthma prevalence and mortality also tend to be the least responsive to commonly views of, or an endorsement, by the FDA/HHS, or the US government. These comments do not bind or obligate the FDA. Funding for the work was also provided by Genentech Inc, a member of the Roche Group.

Disclosure of potential conflict of interest: The authors whose names are listed above certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers’ bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or nonfinancial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this article.

Received for publication April 1, 2021; revised August 24, 2021; accepted for publication September 1, 2021.

This work was supported in part by the Sandler Family Foundation, the American Asthma Foundation, the RWJF Amos Medical Faculty Development Program, Harry Wm. and Diana V. Hind Distinguished Professor in Pharmaceutical Sciences II, the National Institute of General Medical Sciences (grant no. T32GM007546), the National Institute of Environmental Health Sciences (grant no. RO1ES015794), the National Heart, Lung, and Blood Institute (grant nos. R01HL117004-05 and R01HL155024), the National Heart, Lung, and Blood Institute T0PMed grant (grant no. 1X01HL134589), and the Tobacco-Related Disease Research Program (grant no. 27IR-0030). This publication was supported by the Food and Drug Administration (FDA) of the US Department of Health and Human Services (HHS) as part of a financial assistance award (grant no. U01FD009978) totaling $50,000, with 16% funded by the FDA/HHS, and $245,000 amount, with 80% funded by nongovernment source(s).

The contents are those of the author(s) and do not necessarily represent the official

https://doi.org/10.1016/j.jaci.2021.09.005
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. Briefly, GALA II recruited Hispanics/Latinos from 5 urban study centers across the mainland United States (Chicago, Ill; Bronx, NY; Houston, Tex; and San Francisco Bay Area, Calif) 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 2 years, with no history of other long or chronic nonallergic 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 per 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 Human Research Protection Program Institutional Review Board. Detailed consenting procedures can be found in this article’s Online Repository at www.jacionline.org.

Asthma outcomes

Asthma outcomes were defined as follows: asthma status (yes/no), asthma severity (mild, moderate, or severe), asthma control (uncontrolled, controlled), and at least 1 asthma exacerbation in the year before recruitment (yes/no). Detailed definitions of asthma outcomes are provided in this article’s Online Repository at www.jacionline.org.

Measurement of blood parameters

Serum total 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 third measurement was assayed. White blood cell (WBC) counts were obtained from complete blood cell counts with differentials using commercially available and Clinical Laboratory Improvement Amendments–certified laboratories through Quest Diagnostics in the GALA II data set and through University of California, San Francisco 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. Details on assessment of skin prick positivity can be found in this article’s Online Repository at www.jacionline.org. Eosinophilic asthma was defined as having asthma and an absolute eosinophil count (AEC) greater than or equal to 150 c/µL (≥300 c/µL) separately assessed in this article’s Online Repository at www.jacionline.org. These asthma subtypes were specified as yes or no. Overlap between subtypes was assessed only in African Americans because 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 pretreatment serum total IgE level. The US Food and Drug Administration–approved dosing range for this therapy requires the level of pretreatment serum total IgE to be more than 30 kU/L and either less than 1300 kU/L for children 6 to 11 years old or less than 700 kU/L for those 12 years old. For this eligibility analysis, allergic asthma was defined as having asthma and sensitization to at least 1 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, therapy was assessed using a common clinical threshold for prescribed asthma therapies. Although the etiology of asthma is complex, resulting from the confluence of genetic, environmental, and sociocultural risk factors, the causal basis for these racial/ethnic health disparities remains elusive.

Asthma is a heterogeneous disease composed of multiple, sometimes overlapping, pathological and clinical subtypes. 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 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. 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. Having accurate, population-based information for racial/ethnic minority children is of critical concern given that minorities comprise 50% of children in the United States. Other asthma subtypes such as neutrophilic, late-onset, and obesity-related asthma 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 2 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.

Abbreviations used

AEC: Absolute eosinophil count
GALA II: Genes-environments & Admixture in Latino Americans study
ICS: Inhaled corticosteroid
OR: Odds ratio
SAGE: Study of African Americans, Asthma, Genes, & Environments
SES: Socioeconomic status
WBC: White blood cell
therapeutic use: AEC 150 c/µL. Therefore, participants must have been at least 12 years old, 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 this article’s Online Repository at [www.jacionline.org](http://www.jacionline.org).

Study inclusion and exclusion criteria
Of the 5147 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 1710 total SAGE participants, participants whose 4 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 = 1165) were also excluded for an analytical sample of 3738 cases and controls. Analyses for asthma outcomes (severity, control, and exacerbations) included cases only (N = 2743). Analyses investigating the proportion of each population eligible for various biologic therapies were restricted to participants with moderate to severe asthma (N = 1917). A consort diagram is visualized in Fig E1 in this article’s Online Repository at [www.jacionline.org](http://www.jacionline.org). Additional details on analysis-specific inclusions and sample sizes are outlined in Tables E1 and E2 in this article’s Online Repository at [www.jacionline.org](http://www.jacionline.org).

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 (ORs) and 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 because of small sample size (N = 33). Because of the bimodal distribution of basophils in Puerto Ricans (see Fig E2 in this article’s Online Repository at [www.jacionline.org](http://www.jacionline.org)), 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 who would be ineligible for anti-IgE and eosinophilic asthma-directed therapies. We used chi-square 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 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS
Demographic characteristics
Baseline study population characteristics for the total population and stratified by race/ethnicity are presented in Table I. In our population (N = 3738), 1275 self-identified as African American, 967 as Mexican American, and 1496 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 with other racial/ethnic groups (P < .001). In our study population, 2743 (73.4%) participants had asthma. Mexican Americans had the lowest proportion of poor asthma outcomes (P < .05). A higher proportion of Puerto Ricans had eosinophilic asthma compared with African Americans (P < .01), and proportions of those with allergic asthma differed significantly between racial/ethnic groups (P < .05; see Table E3 in this article’s Online Repository at [www.jacionline.org](http://www.jacionline.org)).

Distribution of blood parameters
Total IgE levels were significantly higher in Puerto Ricans compared with African Americans and Mexican Americans (P < .001). Basophil, eosinophil, monocyte, and neutrophil counts differed significantly between African Americans and Puerto Ricans (P < .001), as shown in Fig 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 = .04) as shown in Fig 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 3 racial/ethnic groups: African American (OR, 1.33; 95% CI, 1.21-1.45), Mexican American (OR, 1.35; 95% CI, 1.22-1.50), and Puerto Rican (OR, 1.27; 95% CI, 1.16-1.40). In addition, higher IgE levels were significantly associated with worse asthma severity in African Americans (OR, 1.11; 95% CI, 1.00-1.23) and Puerto Ricans (OR, 1.17; 95% CI, 1.06-1.29), worse asthma control in African Americans (OR, 1.11; 95% CI, 1.00-1.23) and Puerto Ricans (OR, 1.13; 95% CI, 1.03-1.25), and more exacerbations in Puerto Ricans (OR, 1.23; 95% 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; 95% CI, 1.10-2.23, and OR, 1.66; 95% CI, 1.23-2.24, respectively), but associated with exacerbations (OR, 1.67; 95% 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; 95% CI, 1.00-1.10), whereas higher monocyte counts were significantly associated with lower odds of asthma in Puerto Ricans only (OR, 0.84; 95% 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 E4 in this article’s Online Repository at [www.jacionline.org](http://www.jacionline.org).

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 (Fig 2). After controlling for age, sex, obesity status, SES, and ICS use, eosinophilic asthma was associated with worse asthma severity (OR, 1.96; 95% CI, 1.15-3.37), worse asthma control (OR, 1.74; 95% CI, 1.01-3.00), and exacerbations (OR, 1.81; 95% CI, 1.10-2.98) in Puerto Ricans only. Allergic asthma was associated with worse asthma control (OR, 1.49; 95% CI, 1.02-2.19) and exacerbations (OR, 1.82; 95% 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 > .05). All ORs
| Characteristic | Total population (N = 3738) | African American (N = 1275) (34.1%) | Mexican American (N = 967) (25.8%) | Puerto Rican (N = 1496) (40.0%) |
|---------------|-----------------------------|-------------------------------------|------------------------------------|--------------------------------|
| Median age (y) (Q1, Q3) | 13.4 (10.8, 16.8) | 14.8 (11.6, 18.1) | 13.5 (10.7, 16.9) | 12.5 (10.3, 15.3) |
| Sex: female, n (%) | 1833 (49.0) | 642 (50.4) | 362 (37.4) | 440 (29.4) |
| Obese, n (%) | 1191 (31.9) | 389 (30.5) | 636 (65.8) | 1209 (80.8) |
| Asthma, n (%) | 2743 (73.4) | 898 (70.4) | 1209 (80.8) | 1321 (88.3) |
| Moderate to severe asthma, n (%) | 1917 (70.2) | 639 (71.3) | 899 (74.9) | 1321 (88.3) |
| Uncontrolled asthma, n (%) | 1957 (71.3) | 651 (72.5) | 954 (78.9) | 232 (68.4) |
| Exacerbated asthma, n (%) | 1406 (51.3) | 353 (39.3) | 839 (69.4) | 508 (34.0) |
| With total IgE measurement, n (%) | 3554 (95.1) | 1267 (99.4) | 966 (99.9) | 1321 (88.3) |
| Median IgE (kU/L) (Q1, Q3) | 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/µL) (Q1, Q3) | 200 (100, 300) | 110 (60, 210) | — | 200 (100, 400) |
| Eosinophilic asthma, n (%) | 302 (62.1) | 70 (47.6) | — | 232 (68.4) |
| With skin prick data, n (%) | 2470 (66.1) | 1083 (84.9) | 879 (90.9) | 508 (34.0) |
| Allergic asthma, n (%) | 1168 (65.9) | 483 (65.6) | 424 (73.1) | 261 (58.9) |
| SES, n (%) | Low | 1528 (40.9) | 633 (49.6) | 418 (43.2) | 477 (31.9) |
| Medium | 1522 (40.7) | 518 (40.6) | 399 (41.3) | 605 (40.4) |
| High | 688 (18.4) | 124 (9.7) | 150 (15.5) | 414 (27.7) |

P values for between-population comparisons are provided in Table E2.
Q<sub>1</sub>, First quartile; Q<sub>3</sub>, third quartile.
*All values shown are N values and percentages of the population with the exception of age, AEC, and IgE, which represent medians and first and third quartiles.
†Expressed as percentage of population with asthma.
‡Not analyzed because of small sample size.
§Expressed as percentage of asthma cases with measured eosinophil count. Defined as eosinophil count ≥150 c/µL.
∥Expressed as percentage of asthma cases with skin prick measurements. Defined as having positive aeroallergen skin prick test results.

**FIG 1.** Population-specific adjusted ORs for blood parameters on asthma outcomes. ORs adjusted for age, sex, obesity status, SES, and ICS use within 2 weeks of recruitment are plotted with their 95% CI on a log scale. Values shown are associated with a 1-log increase for eosinophils (c/µL) and IgE (kU/L). ORs indicate that the exposure is associated with a poor outcome (asthma/moderate to severe asthma/uncontrolled asthma/exacerbations within the past year). ORs for WBCs in Mexican American children not plotted because of small sample size.
and CIs for this analysis are provided in Table E5 in this article’s Online Repository at www.jacionline.org. Overlap of allergic and eosinophilic asthma in 122 African Americans is presented in Table E6 in this article’s Online Repository at www.jacionline.org.

Eligibility for allergic and eosinophilic asthma biologics across populations

In our study, Puerto Ricans were significantly less likely than other groups to be eligible for anti-IgE therapy, 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 pretreatment 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 12–11 years, >1300 kU/L for ages 6–11 years; Fig 3, A).20 Proportion plots for each pretreatment IgE threshold can be found in Fig E3 in this article’s Online Repository at www.jacionline.org. We found that 51.3% of African Americans and 26.8% of Puerto Ricans age 12 years and older with moderate to severe asthma had AEC less than 150 c/mmL (Fig 3, B) and would not qualify for eosinophilic asthma–directed therapies. A proportion plot for an AEC less than 300 c/mmL cutoff can be found in Fig E4 in this article’s Online Repository at www.jacionline.org. We additionally examined these proportions for those age 6 years and older, as is indicated for the eosinophilic asthma–directed therapy dupilumab,20 and found that the proportions were nearly identical. Significant differences in population eligibility for anti-IgE therapy and eosinophilic asthma–directed therapy for age 12 years and older are presented in Table E7 in this article’s Online Repository at www.jacionline.org.

DISCUSSION

Clinical blood profiles affect asthma outcomes and determine many clinical and therapeutic options. These profiles also differ by race/ethnicity.11,12 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.30 Previous research in children has associated IgE with asthma severity.31,32 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, in whom increased IgE was only associated with severe asthma and poor asthma control, or Mexican Americans, in whom 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.33,34 Although 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 than other racial/ethnic groups from eosinophil-directed biologic therapies. 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. 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. In addition, 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. Although 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 into the therapeutic options available for these 3 populations of children. Overall, we found that a smaller proportion of Puerto Ricans would meet US Food and Drug Administration–approved thresholds for anti-IgE dosing using pretreatment IgE thresholds of less than 700 kU/L or less than 1300 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 pretreatment AEC greater than or equal to 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. 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. Herein, Puerto Ricans had higher average absolute neutrophil counts and elevated eosinophil counts relative to African Americans. On average, Puerto Ricans have lower proportions than African Americans of African ancestry. Relative to Mexican Americans and other Latino populations, the Puerto Rican population has more African admixture and a lower proportion of Native American ancestry. 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.

Although environmental conditions 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, respectively. Although parasitic infections can increase AEC, these infections are now rare in Puerto Rico, consistent with the island’s high human development index and Centers for Disease Control and Prevention traveler guidelines on the safety of drinking water 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. 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 affect 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 whether having 1 or multiple subtypes influence an individual’s risk for poor asthma outcomes or eligibility for asthma biologics. Furthermore, because of 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 oral corticosteroids in the previous 2 weeks had been on chronic versus acute oral corticosteroid therapy, and thus, could not assess the small proportion of patients who could qualify for dupilumab for oral corticosteroid–dependent asthma. Although 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 are reliable, given that these measurements were obtained from Clinical Laboratory Improvement Amendments–certified labs. In addition, there remains a lack of research in minority populations with asthma or lung disease. This precluded us from being able to replicate our findings in an independent data set for these 3 minority populations. Regardless, our analyses included the largest gene-environment study of asthma in minority children to date.

Conclusions

Overall, our findings suggest that peripheral blood parameters are associated with asthma outcomes in African American, Mexican American, and Puerto Rican children. In the United States, available asthma biologic therapies target eosinophilic or allergic asthma. We found that a greater proportion of Puerto Rican participants had eosinophilic asthma compared with 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 whether 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, whereas 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. Although 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.

We acknowledge the families and patients for their participation and thank the numerous health care providers and community clinics for their support and participation in GALAII/SAGEII. In particular, we thank study coordinator Sandra Salazar; the recruiters who obtained the data; Duannya Alva, MD, Gaby Ayala-Rodriguez, Emerita Briginio Buenaventura, Lisa Caine, Elizabeth Castellanos, Jaime Colon, Denise DeJesus, Blanca Lopez, Brenda Lopez, MD, Louis Martos, Kelly Meade, Vivian Medina, Juana Olivo, Mario Peralta, Esther Pomares, MD, Jihan Quraishi, Johanna Rodriguez, Shahdad Saeedi, Dean Soto, and Ana Taveras.

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

REFERENCES

1. Institute of Medicine (US) Committee on the Assessment of Asthma and Indoor Air. 3. Patterns of asthma morbidity and mortality. In: Clearing the air: asthma and indoor air exposures. Washington, DC: National Academies Press; 2000.
2. Ferrante G, La Grutta S. The burden of pediatric asthma. Front Pediatr 2018;6:186.
3. Table 2-1 Lifetime asthma prevalence percent by age, United States: National Health Interview Survey, 2018. 2019. Available at: https://www.cdc.gov/asthma/table2-1.htm. Accessed March 18, 2021.
4. Akinbami LJ, Moorman JE, Bailey C, Zahran HS, King M, Johnson CA, et al. Trends in asthma prevalence, health care use, and mortality in the United States, 2001-2010. NCHS Data Brief 2012;1-8.
5. Burchard EG, Avila PC, Nazario S, Casal J, Torres A, Rodriguez-Santana JR, et al. Lower bronchodilator responsiveness in Puerto Rican than in Mexican subjects with asthma. Am J Respir Crit Care Med 2004;169:386-92.
6. Dixon AE. Long-acting beta-agonists and asthma: the saga continues. Am J Respir Crit Care Med 2011;184:1226-1.
7. Naspi M, Thyne S, Choudhry S, Tsai HI, Navarro D, Castro RA, et al. Ethnic-specific differences in bronchodilator responsiveness among African Americans, Puerto Ricans, and Mexicans with asthma. J Asthma 2007;44:639-48.
8. Nelson HS, Weiss ST, Bleckeker ER, Yancey SW, Dorinsky PM, Group SS. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. Chest 2006;129:15-26.
9. Wechsler ME, Castro M, Lehman E, Chinchilli VM, Sutherland ER, Denlinger L, et al. Impact of race on asthma treatment failures in the asthma clinical research network. Am J Respir Crit Care Med 2011;184:1247-53.
10. Kuruvilla ME, Lee FE, Lee GB. Understanding asthma phenotypes, endotypes, and mechanisms of disease. Clin Rev Allergy Immunol 2019;56:219-33.
11. Rappoport N, Paik H, Oskotsky B, Tor R, Ziv E, Zaitlen N, et al. Comparing ethnicity-specific reference intervals for clinical laboratory tests from EHR data. J Appl Lab Med 2018;3:366-77.
12. Finan C, Gauthlon A, Kruger FA, Lumbers RT, Shah T, Engmann J, et al. The drug-gable genome and support for target identification and validation in drug development. Sci Transl Med 2017;9:eaa1166.
13. Burchard EG, Oh SS, Foreman MG, Celedon JC. Moving toward true inclusion of racial/ethnic minorities in federally funded studies. A key step for achieving respiratory health equality in the United States. Am J Respir Crit Care Med 2015;191:514-21.
14. The Annie E. Casey Foundation. Child population by race in the United States. Kids Count Data Center. Available at: https://datacenter.kidscount.org/data/tables/103-child-population-by-race?detailled=1&any=false&1729,57,871,870,573,869,36,868,867,1330,69,67,12,70,66,61,72,123,423,424. Accessed April 1, 2021.
15. Nishimura KK, Galanter JM, Roth LA, Oh SS, Thakur N, Nguyen EA, et al. Early-life air pollution and asthma risk in minority children. The GALA II and SAGE II studies. Am J Respir Crit Care Med 2013;188:309-18.
16. Tschopp JM, Sistek D, Schindler C, Leuenberger P, Perruchoud AP, Wüthrich B, et al. Current allergic asthma and rhinitis: diagnostic efficiency of three commonly used atopic markers (IgE, skin prick tests, and Phadiatop). Results from 8329 randomized adults from the SAPALDIA study. Swiss Study on Air Pollution and Lung Diseases in Adults. Allergy 1998;53:608-13.
17. Kostikas K, Brindicci C, Patalano F. Blood eosinophils as biomarkers to drive treatment choices in asthma and COPD. Curr Drug Targets 2018;19:1882-96.

18. XOLAIR [prescribing information]. Genentech USA, Inc. and Novartis Pharmaceuticals Corporation. 2020. Available at: https://www.gene.com/download/pdf/xolair_prescribing.pdf.

19. Buhl R. Anti-IgE: lessons from clinical trials in patients with severe allergic asthma symptomatic despite optimised therapy. Eur Respir Rev 2007;16:73-7.

20. Busse WW, Morgan WJ, Gergen PJ, Mitchell HE, Gern JE, Liu AH, et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. N Engl J Med 2011;364:1005-15.

21. Chapman KR, Cartier A, Hébert J, McIvor RA, Schellenberg RR. The role of omalizumab in the treatment of severe allergic asthma. Can Respir J 2006;13:1b-9b.

22. Kawakami T, Blank U. From IgE to omalizumab. J Immunol 2016;197:4187-92.

23. Cardet JC, Israel E. Update on reslizumab for eosinophilic asthma. Expert Opin Biol Ther 2015;15:1531-9.

24. Emma R, Morjaria JB, Fuschi V, Polosa R, Caruso M. Mepolizumab in the management of severe eosinophilic asthma in adults: current evidence and practical experience. Ther Adv Respir Dis 2018;12:1753466118804909.

25. FitzGerald JM, Bleeker ER, Nair P, Korn S, Ohta K, Lommatzsch M, et al. Benralizumab, a mono-anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2016;388:2128-41.

26. Wenzel S, Ford L, Pearlman D, Spector S, Sher L, Skobieranda F, et al. Dupilumab in persistent asthma with elevated eosinophil levels. N Engl J Med 2013;368:2455-66.

27. Patient Information DUPIXENT (Du-pix-ent) (dupilimab) injection, for subcutaneous use. 2021. Available at: https://www.regeneron.com/sites/default/files/Dupixent_PI-PIL.pdf. Accessed March 12, 2021.

28. NUCALA (mepolizumab) for injection. 2020. Available at: https://www.gene.com/download/pdf/NUCALA-PI-PIL.pdf. Accessed March 12, 2021.

29. Patient Information FASENRA (fas-en-rah) (benralizumab) injection, for subcutaneous use. 2021. Available at: https://www.gene.com/download/pdf/FASENRA_PI-PIL.pdf. Accessed March 12, 2021.

30. Ahmad Al Obaidi AH, Mohamed Al Samarai AG, Yahya Al Samarai AK, Al Janabi JM. The predictive value of IgE as biomarker in asthma. J Asthma 2008;45:654-63.

31. Borish L, Chibbs B, Deniz Y, Gugrathi S, Zheng B, Dolan CM. Total serum IgE levels in a large cohort of patients with severe or difficult-to-treat asthma. Ann Allergy Asthma Immunol 2005;95:247-53.

32. Davila I, Valera A, Estreras LM, Valveny N, Herrera L. Relationship between serum total IgE and disease severity in patients with allergic asthma in Spain. J Investig Allergol Clin Immunol 2015;25:120-7.

33. Casciano J, Krishnan JA, Small MB, Buck PO, Gopalun G, Li C, et al. Value of peripheral blood eosinophil markers to predict severity of asthma. BMC Pulm Med 2016;16:109.

34. Zhang XY, Simpson JL, Powell H, Yang IA, Upham JW, Reynolds PN, et al. Full blood count parameters for the detection of asthma inflammatory phenotypes. Clin Exp Allergy 2014;44:1137-45.

35. Katz LE, Gleich GF, Hartley BF, Yancey SW, Ortega HG. Blood eosinophil count is a useful biomarker to identify patients with severe eosinophilic asthma. Ann Am Thorac Soc 2014;11:531-6.

36. Reich D, Nalls MA, Kao WH, Akyebekova EL, Tandon A, Patterson N, et al. Reduced neutrophil count in people of African descent is due to a regulatory variant in the Duffy antigen receptor for chemokines gene. PLoS Genet 2009;5:e1000360.

37. Crosslin DR, McDavid A, Weston N, Nelson SC, Zheng X, Hart E, et al. Genetic variants associated with the white blood cell count in 13,923 subjects in the eMERGE Network. Hum Genet 2012;131:639-52.

38. Bryan K, Durand EY, Macpherson JM, Reich D, Mountain JL. The genetic ancestry of African Americans, Latinos, and European Americans across the United States. Am J Hum Genet 2015;96:37-53.

39. Peralta CA, Li Y, Wissell C, Choudhry S, Palmas W, Seldin MF, et al. Differences in albuminuria between Hispanics and whites: an evaluation by genetic ancestry and country of origin: the multi-ethnic study of atherosclerosis. Circ Cardiovasc Genet 2010;3:240-7.

40. Astle WJ, Elding H, Jiang T, Allen D, Ruklisa D, Mann AL, et al. The allelic landscape of human blood cell trait variation and links to common complex disease. Cell 2016;167:1415-29.

41. Jain D, Hodonsky CJ, Schick UM, Morrison JV, Minnerath S, Brown L, et al. Genome-wide association of white blood cell counts in Hispanic/Latino Americans: the Hispanic Community Health Study/Study of Latinos. Hum Mol Genet 2017;26:1193-204.

42. Messinga TT, Schouten JP, Rijkken B, Weiss SW, van der Lende R. Host factors and environmental determinants associated with skin test reactivity and eosinophilia in a community-based population study. Ann Epidemiol 1994;4:382-92.

43. Puerto Rico (U.S.) Clinician View. 2020. Available at: https://wwwnc.cdc.gov/travel/destinations/clinician/none/puerto-rico. Accessed April 1, 2021.

44. Painter JE, Guragano JW, Collier SA, Yoder JS. Giardiasis surveillance—United States, 2011-2012. Morb Mortal Wkly Rep MMWR 2015;64(SS03):15-25.

45. Fundora-Hernández H, Venero-Fernández SJ, Suárez-Medina R, Mora-Faife Ede L, García-García G, del Valle-Infante I, et al. What are the main environmental exposures associated with elevated IgE in Cuban infants? A population-based study. Trop Med Int Health 2014;19:545-54.

46. Palmer LJ, Burton PR, Faux JA, James AL, Musk AW, Cookson WO. Independent inheritance of serum immunoglobulin E concentrations and airway responsiveness. Am J Respir Crit Care Med 2000;161:1836-43.
METHODS
Consenting procedures
Questionnaires were administered to adult participants and parents of minors. All participants provided written consent to be in the study. Consent was obtained from all adult participants and parent/legal guardians of minor participants. The study protocols for both GALA II and SAGE were approved by the University of California, San Francisco Human Research Protection Program Institutional Review Board, and all institutions participating in recruitment obtained the appropriate approvals from their institutional review boards for recruitment-related activity.

Definition of asthma outcomes
Asthma status was recorded on the basis of a history of physician diagnosis and asthma symptoms, asthma medication use within the last 2 years, with no history of other lung or chronic nonallergic illnesses.

Report 3 of the National Asthma Education and Prevention Program (NAEPP) Guidelines5,6 assesses asthma control and severity by both impairment and risk. Impairment is determined by the individuals’ recall from the previous 2 to 4 weeks of symptoms, use of rescue medication, and in the case of asthma severity, also spirometry. Risk is broadly determined as exacerbations requiring oral steroids. We leveraged the validated Childhood Asthma Control Test7 and the Asthma Control Questionnaire8,9 to assess symptoms of impairment for both asthma control severity scores as outlined in the NAEPP guidelines. Asthma control was scored as controlled, not well controlled, or very poorly controlled on the basis of impairment or risk feature that displayed the worse control. For analysis, asthma control was dichotomized into controlled and uncontrolled (not well controlled or very poorly controlled).

Scoring severity was not as straightforward as asthma control because the NAEPP guidelines for assessing severity are outlined for individuals not currently taking control medication. Because most of our participants were on control medication, severity was instead assessed across impairment and treatment. Specifically, impairment features were categorized as mild persistent, moderate persistent, and severe persistent while treatment was categorized as mild intermittent, mild persistent, moderate persistent, and severe persistent on the basis of (1) the use of a short beta-agonist, (2) one of an inhaled steroid, leukotriene inhibitor, or theophylline tablet, (3) more than or a combination of an inhaled steroid, leukotriene inhibitor, or theophylline tablet, or (4) oral steroid use in the last week, respectively. The final severity score was determined to be the treatment score. However, if the participant had not well controlled or poorly controlled asthma but was scored as mild intermittent for treatment, their highest severity impairment feature score was used. In addition, if treatment was scored as mild or moderate persistent, yet the participant had not well controlled or poorly controlled asthma, their severity score was bumped to moderate and severe persistent, respectively. This bump-up of severity from asthma control is consistent with the NAEPP stepwise approach for managing asthma. For analysis, severity was dichotomized into mild (mild intermittent or mild persistent) and severe (moderate or severe persistent).

Asthma exacerbations were scored on the basis of definition set by the American Thoracic Society and European Respiratory Society. Briefly, we assigned points for each reported hospitalization (1), emergency department visit (1), and oral steroid use (1 point was given if the participant used oral steroids in the 12 months before recruitment). Points were summed to derive a composite score. To avoid double counting for oral steroid prescriptions, a point was given to those who used any oral steroid in the last 12 months only among those participants who did not report a history of emergency visits or hospitalizations for asthma. For analysis, exacerbations were dichotomized into none or at least 1 exacerbation in the last 12 months.

Detailed description of covariate data
Age at time of recruitment was calculated using the difference between recruitment date and the participants’ birth date.

Sex was self-reported.
Body mass index (BMI) values were quantified using standardized methodologies with a clinical scale and a stadiometer. For participants younger than 20 years, BMI percentiles were calculated using the recommended Centers for Disease Control and Prevention sex-age curves. Conversely, for participants older than 20 years, BMI was calculated using the standard formula, height (kg)/weight (m²). Raw BMI and BMI percentiles were used to specify the following categories: underweight, normal, overweight, and obese using the Centers for Disease Control and Prevention guidelines. BMI categories were then collapsed into obese and nonobese for analysis.

SES was derived from a combination of mother’s education level, insurance status, and household income weighted by region of recruitment. Each component of the SES was scored on a 3-point scale, with 1 being lowest and 3 being the highest. Mother’s education was broken down by less than high school (1), high school diploma or equivalent (2), and greater than high school (3). Income status was broken down by no insurance (1), insurance through the government (2), and insurance through self, a family member, or an employer (3). Household income was split into tertiles, with recruitment region acting as a weight for income level. The 3 components were then averaged and partitioned into a 3-level categorical variable (high, medium, low) using tertile cutoff points. SES was adjusted for in our models as a 3-level ordinal variable.

ICS use was defined as use of at least 1 of the following inhaled steroid or combo medications within the 2 weeks before recruitment: Intal (cromolyn), Aerobid, Intal Solution (nebulized), Flovent, Tilade, Pulmicort (budesonide), Vanceril, Beclovent, Qvar, Azmacort, Pulmicort Respules, Symbicort, and Advair. ICS use was dichotomized into yes and no for analysis.

Assessment of aeroallergen sensitization
Skin testing was performed on the volar aspect of the forearm, using the Multi-Test II Device (Lincoln Diagnostics, Decatur, Ill) for a panel of 14 aeroallergens including dust mites (Dermatophagoides pteronyssinus and Dermatophagoides farinae), pets (dog and cat), pests (mix of German and American cockroach, mouse epithelium, and rat epithelium), trees (oak and olive/elm), grasses (perennial ryegrass/timothy and short ragweed), and molds (Alternaria tenuis, Hormodendrum cladospiroides, and Aspergillus mix).

Any allergen with a mean wheal diameter of at least 3 mm greater than the mean wheal diameter of the saline control and that had a flare greater than the wheal was considered positive. In addition, subjects with tests considered invalid (having the mean wheal diameter of the histamine <3 mm greater than the mean wheal diameter of the saline control) were removed from the study. A score of 1 or 0 was given depending on whether the individual experienced at least 1 positive allergen test result or none.

REFERENCES
E1. National Asthma Education and Prevention Program. Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma Update on Selected Topics—2002. J Allergy Clin Immunol 2002;110:S141-219.
E2. Liu AH, Zeiger R, Sorkness C, Mahr T, Ostrom N, Burgess S, et al. Development and cross-sectional validation of the Childhood Asthma Control Test. J Allergy Clin Immunol 2007;119:817-25.
E3. Juniper EF, O’Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J 1999;14:902-7.
E4. Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med 2009;180:59-99.
E5. A SAS Program for the 2000 CDC Growth Charts (ages 0 to <20 years). Available at: https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm. Accessed March 3, 2021.
FIG E1. Exclusion consort diagram. Consort diagram demonstrating the derivation of our study population for analyses. *GP, Grandparent; OCS, oral corticosteroid; tIgE, total serum IgE; w/in, within.
FIG E2. Blood parameter distributions in African American, Mexican American, and Puerto Rican children. Distribution of total IgE (A), basophils (B), eosinophils (C), lymphocytes (D), monocytes (E), and neutrophils (F). Total IgE plotted on a log scale. Comparison between populations calculated using Wilcoxon test. Significant differences ($P < .05$) are in boldface.
FIG E3. Proportion of African American, Mexican American, and Puerto Rican children who do not meet individual dosing criteria for IgE-targeted therapy. Proportion of populations with moderate to severe perennial allergic asthma with total IgE levels less than 30 kU/L in all ages (A), more than 1300 kU/L in children aged 6 to 11 years (B), and more than 700 kU/L in children older than 12 years (C).
FIG E4. Proportion of African American and Puerto Rican children who do not meet greater than or equal to 300 c/μL criteria for eosinophilic asthma–directed therapies. Proportion of participants eligible (teal) or ineligible (salmon) for eosinophilic asthma–directed therapies with the 300 c/μL cutoff.
### TABLE E1. Inclusion criteria and stratified sample sizes for each association analysis

| Outcome                          | Exposure | Inclusion criteria | Population (N) |
|----------------------------------|----------|--------------------|----------------|
|                                  |          |                    | African American | Mexican American | Puerto Rican | Total |
| Asthma status*                   | Total IgE| 1                  | 1267            | 966             | 1321         | 3554  |
|                                  | WBCs     | 2                  | 251             | —               | 471          | 722   |
| Asthma outcomes†‡§               | Total IgE| 1, 3               | 891             | 636             | 1092         | 2619  |
|                                  | WBCs     | 2, 3               | 147             | —               | 339          | 486   |
|                                  | Eosinophilic asthma | 2, 3            | 147             | —               | 339          | 486   |
|                                  | Allergic asthma | 3, 4            | 736             | 580             | 443          | 1759  |

Sample sizes for logistic regression models stratified by race/ethnicity. Inclusion criteria key: (1) measured IgE, (2) measured WBCs, (3) asthma, (4) a valid aeroallergen skin prick test, (5) sensitization to at least 1 perennial aeroallergen by skin prick test, (6) moderate to severe asthma, (7) age ≥ 12 y, and (8) age 6-11 y.

*Case-control analysis.

†Case-only analysis.

‡Outcomes: asthma severity, asthma control, and history of exacerbations.

§A total of 12 participants with asthma were missing asthma severity data.
TABLE E2. Inclusion criteria and stratified sample sizes for biologic asthma therapy eligibility analyses

| Ineligibility analysis | Ineligible threshold | Inclusion criteria | African American | Mexican American | Puerto Rican | Total |
|------------------------|----------------------|--------------------|------------------|------------------|--------------|-------|
| Anti-IgE therapy*      | <30 kU/L             | 1, 4, 5, 6         | 232              | 231              | 191          | 654   |
|                        | >700 kU/L            | 1, 4, 5, 6, 7      | 167              | 131              | 91           | 389   |
|                        | >1300 kU/L           | 1, 4, 5, 6, 8      | 65               | 100              | 100          | 265   |
| Eosinophil-targeted therapy* | <150 c/µL     | 2, 6, 7 | 78               | —                | 142          | 220   |
|                        | <300 c/µL            | 2, 6, 7            | 78               | —                | 142          | 220   |

Sample sizes for ineligibility analyses stratified by race/ethnicity. Inclusion criteria key: (1) measured IgE, (2) measured WBCs, (3) asthma, (4) a valid aeroallergen skin prick test, (5) sensitization to at least 1 perennial aeroallergen by skin prick test, (6) moderate to severe asthma, (7) age ≥ 12 y, and (8) age 6-11 y.

*Case-only analysis.
**TABLE E3. Population comparison of demographic and clinical characteristics**

| Characteristic                        | P value          |
|---------------------------------------|------------------|
|                                       | AA v MX | AA v PR | MX v PR |
| Median age (y)                        | <.001    | <.001   | <.001   |
| Sex: female                           | .81      | .14     | .29     |
| Obese                                 | <.001    | .56     | <.001   |
| Asthma                                | .02      | <.001   | <.001   |
| Moderate to severe asthma             | <.001    | .07     | <.001   |
| Uncontrolled asthma                   | <.001    | <.001   | <.001   |
| Exacerbated asthma                    | <.001    | <.001   | <.001   |
| Median IgE (kU/L)                     | .25      | <.001   | <.001   |
| Median AEC (c/mL)                     | —*       | <.001   | —*      |
| Eosinophilic asthma (150 c/mL)       | —*       | <.001   | —*      |
| Allergic asthma                       | .004     | .02     | <.001   |
| SES                                   | <.001    | <.001   | <.001   |
| Steroid usage, past 2 wk              | .046     | <.001   | <.001   |

Paired population comparisons of demographic and clinical characteristics. χ² and Wilcoxon rank-sum tests were used to compare categorical and continuous variables between populations, respectively. Significant differences (P < .05) are denoted in boldface.

AA, African American; MX, Mexican American; PR, Puerto Rican.

*Not analyzed because of small sample size.
## TABLE E4. Asthma outcome ORs from blood parameters in African American, Mexican American, and Puerto Rican children

| Population       | Blood parameter | Asthma status | Severe asthma | Uncontrolled asthma | Exacerbated asthma |
|------------------|-----------------|---------------|---------------|---------------------|-------------------|
| African American | Total IgE *     | 1.33 (1.21-1.45) | 1.11 (1.00-1.23) | 1.11 (1.00-1.23) | 1.07 (0.98-1.18) |
|                  | Basophils †     | 1.05 (0.61-1.80) | 1.88 (0.80-4.78) | 2.15 (0.91-5.51) | 0.82 (0.43-1.51) |
|                  | Eosinophils ‡   | 1.55 (1.10-2.23) | 1.19 (0.65-2.19) | 1.01 (0.57-1.82) | 1.11 (0.71-1.74) |
|                  | Lymphocytes §   | 1.05 (1.00-1.10) | 1.02 (0.94-1.10) | 1.03 (0.96-1.11) | 1.01 (0.96-1.06) |
|                  | Monocytes ¶     | 1.00 (0.84-1.20) | 0.84 (0.64-1.09) | 0.85 (0.67-1.10) | 1.01 (0.80-1.24) |
|                  | Neutrophils ‡   | 0.99 (0.97-1.01) | 1.02 (0.99-1.06) | 1.00 (0.97-1.04) | 1.00 (0.98-1.03) |
| Mexican American | Total IgE *     | 1.35 (1.22-1.50) | 1.06 (0.95-1.18) | 1.05 (0.94-1.16) | 1.09 (0.98-1.21) |
| Puerto Rican     | Total IgE *     | 1.27 (1.16-1.40) | 1.17 (1.06-1.29) | 1.13 (1.03-1.25) | 1.23 (1.13-1.34) |
|                  | Eosinophils ‡   | 1.66 (1.23-2.24) | 1.45 (0.98-2.15) | 1.28 (0.86-1.90) | 1.67 (1.18-2.38) |
|                  | Lymphocytes §   | 1.01 (0.98-1.04) | 1.02 (0.99-1.07) | 1.03 (0.99-1.08) | 0.99 (0.96-1.02) |
|                  | Monocytes ¶     | 0.84 (0.74-0.96) | 1.15 (0.96-1.38) | 1.10 (0.92-1.32) | 1.06 (0.91-1.24) |
|                  | Neutrophils ‡   | 1.00 (0.98-1.01) | 1.01 (0.99-1.03) | 1.00 (0.98-1.02) | 1.00 (0.98-1.02) |

Adjusted ORs (95% CIs) of the association between blood parameters and asthma and asthma outcomes in pediatric African Americans, Mexican Americans, and Puerto Ricans. Basophils were not modeled in Puerto Ricans because of their bimodal distribution. Blood cell counts were not modeled in Mexican Americans because of small sample size. ORs indicate that the exposure is associated with a poor outcome (asthma/moderate to severe asthma/uncontrolled asthma/exacerbations within the past year). Significant associations (P < .05) are denoted in boldface. Associations approaching significance (.05 < P < .01) are denoted in italics.

*ORs interpreted as a 1-log kU/L increase.
†ORs interpreted as a 1-log c/µL increase.
‡ORs interpreted as a 100 c/µL increase.
§ORs interpreted as a 1-log c/mL increase.
### TABLE E5. Asthma outcome ORs from asthma subtypes in African American, Mexican American, and Puerto Rican children

| Population       | Asthma subtype | Severe asthma (OR (95% CI)) | Uncontrolled asthma (OR (95% CI)) | Exacerbated asthma (OR (95% CI)) |
|------------------|----------------|-----------------------------|----------------------------------|----------------------------------|
| **African American** |                |                             |                                  |                                  |
|                  | Eosinophilic (300) | 1.70 (0.43-8.94)            | 1.01 (0.29-4.19)                | 1.52 (0.71-3.25)                |
|                  | Eosinophilic (150) | 1.58 (0.57-4.63)            | 1.79 (0.66-5.16)                | 1.47 (0.70-3.10)                |
|                  | Allergic        | 1.13 (0.77-1.64)            | 1.00 (0.69-1.44)                | 1.37 (0.98-1.93)                |
| **Mexican American** |                |                             |                                  |                                  |
|                  | Allergic        | 1.19 (0.79-1.77)            | **1.49 (1.02-2.19)**            | **1.82 (1.19-2.83)**            |
| **Puerto Rican**  |                |                             |                                  |                                  |
|                  | Eosinophilic (300) | 1.53 (0.91-2.60)            | 1.42 (0.84-2.43)                | 1.83 (1.15-2.95)                |
|                  | Eosinophilic (150) | **1.96 (1.15-3.37)**        | **1.74 (1.01-3.00)**            | **1.81 (1.10-2.98)**            |
|                  | Allergic        | 1.27 (0.79-2.06)            | 1.21 (0.72-2.03)                | 1.06 (0.67-1.66)                |

Adjusted ORs (95% CI) of the association between commonly used asthma subtypes and asthma outcomes in pediatric African Americans, Mexican Americans, and Puerto Ricans. Eosinophilic asthma untested in Mexican Americans because of small sample size (n = 11). Eosinophilic asthma defined as eosinophil count ≥150 c/μL and separately as eosinophil count ≥300 c/μL. Allergic asthma was defined as having any sensitization to allergens by skin prick test. ORs indicate that the exposure is associated with a poor outcome (asthma/moderate to severe asthma/uncontrolled asthma/exacerbations within the past year). Significant associations (P < .05) are denoted in boldface. Associations approaching significance (.05 < P < .01) are denoted in italics.
TABLE E6. Allergic and eosinophilic asthma overlap in African American children

| Asthma subtype, n (%) | 150 c/µL cutoff | 300 c/µL cutoff |
|-----------------------|-----------------|-----------------|
| Noneosinophilic, nonallergic | 33 (27.0)       | 39 (32.0)       |
| Noneosinophilic, allergic      | 32 (26.2)       | 62 (50.8)       |
| Eosinophilic, nonallergic     | 8 (6.6)         | 2 (1.6)         |
| Eosinophilic, allergic        | 49 (40.2)       | 19 (15.6)       |

Overlap of allergic and eosinophilic asthma in 122 African Americans. Eosinophilic asthma defined as eosinophil count \( \geq 150 \) c/µL and separately as eosinophil count \( \geq 300 \) c/µL. Allergic asthma was defined as having any sensitization aeroallergens by skin prick test. Overlap not assessed in Mexican Americans or Puerto Ricans due to lack of skin prick and WBC count data overlap.
TABLE E7. Comparisons for asthma biologics ineligibility between African American, Mexican American, and Puerto Rican children

| Criteria tested                  | AA v MX | AA v PR | MX v PR | Age restriction |
|----------------------------------|---------|---------|---------|-----------------|
| Combined anti-IgE*               | .33     | .001    | .02     | 6 y and older   |
| IgE <30 kU/L                     | .06     | .20     | .75     | 6 y and older   |
| IgE >1300 kU/L                   | .57     | .13     | .01     | 6-11 y          |
| IgE >700 kU/L                    | .29     | .003    | .09     | 12 y and older  |
| Eosinophil count <300 c/μL       | —†      | <.001   | —†      | 12 y and older  |
| Eosinophil count <150 c/μL       | —†      | <.001   | —†      | 12 y and older  |

χ² comparisons for biologic eligibility across populations. Participants had moderate to severe asthma. Sensitization to at least 1 perennial allergen (dust mite, dog, cat, cockroach, mouse, and rat) by skin prick test was required for inclusion in anti-IgE analyses. Significant differences (P < .05) are denoted in boldface.

AA, African American; MX, Mexican American; PR, Puerto Rican.

*Combined anti-IgE compared ineligibility across all age groups considering both the lower bound (30 kU/L) and the upper bound (1300 kU/L for ages 6-11 y, 700 kU/L for ages 12 y and older).

†Not analyzed because of small sample size.