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Race is Associated with Differences in Airway Inflammation in Asthma

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Abstract

Background—African-Americans have a greater burden from asthma compared to Caucasians. Whether the pattern of airway inflammation differs between African-Americans and Caucasians is unclear.

Objective—To compare sputum airway inflammatory phenotypes of African-Americans and Caucasians treated or not treated with ICS (ICS+ and ICS-, respectively).

Methods—We performed a secondary analysis of self-identified African-Americans and Caucasians with asthma enrolled in clinical trials conducted by the National Heart, Lung, and Blood Institute-sponsored Asthma Clinical Research Network and AsthmaNet. Demographics, clinical characteristics, and sputum cytology following sputum induction were examined. We utilized a sputum eosinophil 2% cut point to define individuals with either an eosinophilic (≥2%) or non-eosinophilic (<2%) inflammatory phenotype.

Results—Among 1,018 participants, African-Americans (n=264) had a lower FEV_1% predicted (80 vs. 85%, p<0.01), greater total IgE (197 vs. 120, p<0.01) and a greater proportion with uncontrolled asthma (43% vs. 28%, p<0.01) compared to Caucasians (n=754). There were 922 subjects in the ICS+ group (248 African-Americans, 674 Caucasians) and 298 subjects in the ICS− group (49 African-Americans, 249 Caucasians). Eosinophilic airway inflammation was not significantly different between African-Americans and Caucasians in either group (% with eosinophilic phenotype: ICS+ group: 19% vs. 16%, p=0.28; ICS− group: 39% vs. 35%, p=0.65; respectively). However, when adjusted for confounding factors, African-Americans were more likely to exhibit eosinophilic airway inflammation than Caucasians in the ICS+ group (OR:1.58; CI:1.01–2.48; p=0.046), but not in the ICS− group (p=0.984).

Conclusion—African-Americans exhibit greater eosinophilic airway inflammation, which may explain the greater asthma burden in this population.

Keywords

asthma; race; eosinophil; airway inflammation; African-American; body mass index; corticosteroid; induced sputum; clinical trial

INTRODUCTION

African-Americans have a higher prevalence of asthma than Caucasians and a greater burden of morbidity and mortality, with rates of asthma-related emergency department visits, hospitalizations, and death being approximately 2 to 3 times the rates observed in Caucasians [1, 2]. Many factors including asthma severity, differences in access to healthcare and environmental exposures have been implicated as causes of race-related variations in asthma burden [3–8]. Studies that have controlled for these factors have still found higher asthma-related emergency department visits, hospitalizations, and death from asthma among African-Americans [9–11]. Results of some studies suggest that African-Americans may have reduced responsiveness to some asthma therapies, including inhaled corticosteroids (ICS), compared to Caucasians, suggesting biological differences in asthma between these groups [12–15]. The basis for race-related differences in asthma burden and treatment responsiveness is not well understood.

Airway inflammation is a key cornerstone of asthma pathogenesis and is mediated by numerous inflammatory cells that infiltrate the airways including eosinophils, neutrophils, Type 2 lymphocytes, basophils, and mast cells [16]. By counting these inflammatory cells in induced sputum, airway inflammation in asthma has been characterized as either eosinophilic (≥2% eosinophils) or non-eosinophilic (<2% eosinophils)[17–19]. Emerging evidence suggests that differences in airway inflammatory phenotype may affect response to asthma therapies [20–22]. In one study, subjects with non-eosinophilic asthma had an impaired response to treatment with oral and high-dose inhaled corticosteroids compared to those with eosinophilic asthma [20]. Relatively few African-American patients with asthma (21 of 158 patients) were included in this study, so it remains unclear whether differences in airway inflammation could explain at least in part the observed race-related disparities in asthma burden [20].

These considerations led us to ask the question: are there differences in the prevalence of eosinophilic vs. non-eosinophilic airway inflammatory phenotypes in African-American vs. Caucasian patients with asthma? Because use of ICS can improve asthma control and modify the observed airway inflammatory phenotype, we compared the clinical characteristics and airway inflammation phenotypes in African-Americans and Caucasians separately in patients on (ICS+) and off (ICS−) ICS treatment.

METHODS

Study Population

The study population consisted of self-reported African-Americans or Caucasians with asthma enrolled in ten clinical trials conducted by the National Heart, Lung and Blood Institute-sponsored Asthma Clinical Research Network (ACRN) and AsthmaNet (Table E1 and Figure E1 in Online Repository) that included at least one sputum induction as part of the study protocol [23–32]. The data were collected as part of clinical trials that had been reviewed and approved by institutional review boards at all participating ACRN and AsthmaNet centers, and all subjects provided written informed consent. The University of Illinois Institutional Review Board deemed the secondary analyses in this report as exempt from human subjects review.

All subjects were age 12 years or older, met the criteria for mild or moderate persistent asthma as defined by the National Asthma Education and Prevention Program Guidelines for the Diagnosis and Management of Asthma, were current non-smokers with a lifetime history of smoking no greater than 10 pack-years, and had not smoked within the past 12 months (Table E1 in the Online Repository) [33]. In addition, all subjects had to have either 1) a positive methacholine challenge with a provocative concentration for a 20% drop in forced expired volume in one second (FEV_1) of less than or equal to 16 mg/ml in ICS+ subjects or less than or equal to 12 mg/ml in ICS− subjects; or 2) a post-bronchodilator increase in FEV_1 of ≥12%. Sputum eosinophils were the chosen inflammatory marker for this study as evidence supports that differences in airway inflammatory phenotype affect asthma exacerbations and response to asthma therapies [20, 21]. Sputum induction data and corresponding clinical data were only included when ICS use or non-use was known and standardized as part of the study protocols. Subjects in the ICS+ group were on ICS

(fluticasone equivalent dose range 80–400 mcg/day) for at least 4 weeks prior to the sputum assessment. Those in the ICS− group had not been treated with ICS for at least 6 weeks prior to the time of sputum assessment. In the ICS− group, patients using a leukotriene modifying agent in the 4 weeks prior to the sputum induction or clarithromycin in the 6 weeks prior to the sputum induction were not included in the analysis due to potential effects on airway inflammation[34–36]. Only unique subjects were included within the ICS+ or ICS− group. Subjects that met criteria for both groups, either at different time points in a study or were participating in a different study were included in the analyses.

The following measures were collected by trained research staff using standardized procedures: self-reported race (African-American or Caucasian), anthropometrics (age, gender, body mass index), atopic status (≥1 positive allergy test), pre-bronchodilator FEV_1, asthma symptom control [Asthma Control Questionnaire (ACQ) or Asthma Control Test score (ACT), depending on the trial protocol], maximum bronchodilator responsiveness (% change in FEV_1 after 4 puffs of albuterol), total blood eosinophils and total serum IgE[37, 38]. We defined uncontrolled asthma as ≥1.5 using the ACQ or ≤19 using the ACT. ACQ or ACT data were not collected in 2 studies (SOCS and SMOG) and maximum bronchodilator responsiveness data were not collected in 2 studies (SOCS and SLIMSIT). Blood eosinophil and total serum IgE were used as secondary markers of inflammation as recent studies have shown an association with asthma severity[39, 40]. Blood eosinophils are also a promising biomarker for eosinophilic airway burden[41]. Blood eosinophil and total serum IgE data were not collected in 4 studies (SMOG, MICE, SOCS, VIDA). Blood eosinophil data were available but not used in 1 study (SLIMSIT), as subjects were not receiving a standardized treatment at the time of blood collection.

Two Induced Sputum Samples

We examined a subgroup of participants who underwent at least 2 sputum inductions (eight studies; Figure E1 in Online Repository) as a previous study found sputum eosinophilia is intermittent [20]. Two sputum samples from 2 different time points when the participant was taking the same treatment regimen for at least 4 weeks in ICS+ group and at least 6 weeks in the ICS− group were analyzed for sputum eosinophilia. Eosinophilia ≥2% occurring on one or both sputum inductions defined eosinophilic airway inflammation.

Sputum Induction and Processing

Sputum was collected using methods validated for consistency and quality control, as previously described [42, 43]. Briefly, subjects had spirometry performed before and 10 minutes after 360 mg of inhaled albuterol to ensure post-bronchodilator FEV_1 greater than 50% predicted. A 12-minute sputum induction was then performed, and cell differentials (eosinophils, neutrophils, macrophages, epithelial cells, and lymphocytes) were calculated as the percent of cells in the whole sputum expectorate. Sputum samples with ≥80% squamous epithelial cells were not included in the analysis. The other cell types in the sputum were calculated as the percentage of non-squamous cells. The presence or absence of eosinophilic inflammation was determined using a 2% cutoff based on published reference values for eosinophils in induced sputum from healthy subjects; subjects with ≥2% sputum eosinophils were classified as having eosinophilic airway inflammation, and subjects with <2% sputum

eosinophils were classified as having non-eosinophilic airway inflammation [17, 18]. The presence of neutrophilic inflammation was determined using a 61% cutoff based on published reference values for neutrophils in induced sputum[44]. Subjects with >61% sputum neutrophils were classified as having neutrophilic airway inflammation and subjects with ≥2% sputum eosinophils AND >61% sputum neutrophils were classified as having mixed eosinophilic/neutrophilic phenotype.

Analyses

Continuous variables are presented as means and standard deviations (SDs) or medians and interquartile ranges, as appropriate. Categorical variables are reported using frequencies and percentages. Differences between groups were assessed using two-sample t-tests, Wilcoxon rank sum tests, Fisher exact tests or chi-squared tests, as appropriate. In the subgroup of participants who underwent a second sputum induction, we calculated the intraclass correlation coefficient to assess the within-individual reliability of % eosinophils in separate sputum inductions in unique subjects. We used multivariable logistic regression models to assess the adjusted association between race and eosinophilic airway inflammation, after accounting for potential confounders, separately in the ICS+ and ICS− groups. The variables for the multivariable logistic regression model were selected if they were significantly different between African Americans and Caucasians. To avoid collinearity in the regression models, we did not include total serum IgE (related to atopy) and sputum neutrophilia (related to BMI). Analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC) and Systat version 11 (San Jose, CA) statistical software. A 2-tailed p-value <0.05 was used to denote statistically significant differences.

RESULTS

Subject Characteristics

Of the 1,018 subjects, 264 (26%) self-identified as African-Americans. Compared to Caucasians (n=754, 74%), African-American subjects were significantly older, had a higher BMI, a lower FEV_1% predicted, were more likely to have uncontrolled asthma and higher total IgE level (Table 1). In the large majority of both African-American and Caucasian subjects, the age at asthma onset was before the age of 40 years (Table 1).

ICS+ Subjects

Of 922 ICS+ subjects, 248 (27%) were African-Americans (Table 2). African-Americans were older, less atopic, had a higher BMI, lower FEV_1 % predicted, higher total serum IgE and were more likely to have uncontrolled asthma compared to Caucasians. There was no significant difference in the age at asthma onset, total blood eosinophils or percentage of sputum eosinophils/neutrophils in African-American and Caucasian subjects (Table 2). Only 17% of ICS+ subjects had eosinophilic airway inflammation. There were no significant differences between African-American and Caucasian subgroups (19 vs. 16%, p=0.28; Figure 1) even when stratified by age, age of asthma onset, atopy and presence or absence of uncontrolled asthma (Table E2 in online repository). When stratified by BMI, the proportion with eosinophilic airway inflammation was similar in African-Americans and Caucasians except for those with BMI ≥30 kg/m^2 (Table E2 in online repository). In the subgroup with

BMI≥30 kg/m^2, African-Americans were more likely to have eosinophilic airway inflammation than Caucasians (16% vs. 8%). Of those subjects with eosinophilic airway inflammation, there was no difference in the percent sputum eosinophils in African-Americans vs. Caucasians (6.8% vs 5.9%, p=0.95, respectively). African-Americans with eosinophilic airway inflammation were twice as likely to have a mixed granulocytic airway inflammation (≥2% eosinophils and >61% neutrophils) compared to Caucasians (7% vs. 3%; p=0.02). In non-eosinophilic subjects, almost three-quarters had neutrophilic airway inflammation (>61% neutrophils). African-Americans were less likely to exhibit this airway inflammatory pattern (71% vs. 75%, p=0.02).

ICS− Subjects

Of ICS− subjects, 16% (n=49) were African-American (Table 3). African-Americans had a higher BMI. As in the ICS+ group, there was no difference in the percentage of sputum eosinophils/neutrophils in African-American and Caucasian subjects (Table 3). Only 36% of ICS− subjects had eosinophilic airway inflammation, with no significant difference between African-American and Caucasian subgroups (39% vs. 35%, p=0.65; Figure 1) even when stratified by BMI, age, age of asthma onset, atopy and uncontrolled asthma (Table E3 in online repository). In contrast to ICS+ subjects, ICS− eosinophilic subjects showed a trend towards lower percent sputum eosinophils in African-Americans compared to Caucasians (5.4% vs. 9.4%, p=0.07, respectively). African-Americans with eosinophilic airway inflammation were four times as likely to have mixed granulocytic airway inflammation compared to Caucasians (14% vs. 3%; p=0.003). African-Americans with non-eosinophilic airway inflammation, were twice as likely to exhibit neutrophilic inflammation (>61% neutrophils; 35% vs. 17%, p=0.004).

Multivariable logistic regression

A multivariable logistic regression analysis was performed in the ICS+ and ICS− subgroups to investigate if race was associated with eosinophilic airway inflammation, after accounting for potential confounders (age, gender, atopic status, BMI, FEV_1 % predicted, and uncontrolled asthma; Table E4 in online repository). Interestingly, race was associated with eosinophilic airway inflammation in the ICS+ group only. African-Americans had a 58% greater odds of eosinophilic airway inflammation than Caucasians (OR: 1.58; CI: 1.01–2.48; n= 757; p=0.046; Figure 2). There were no race-related differences in eosinophilic airway inflammation in the ICS− stratum, though there were fewer individuals in this stratum and the confidence intervals were wide.

Analyses of two induced sputum samples

Four hundred seventy-seven (477) subjects (47%) had at least two induced sputum samples that were included in the analysis. The interval between the sputum inductions varied from 2–53 weeks (Figure E2 in online repository). African-Americans that had at least two induced sputum samples were younger (ICS− group only), and had a higher BMI and lower FEV_1 % predicted (ICS+ group only; Tables E5 and E6 in online repository). When compared to subjects with one induced sputum sample, subjects with two induced sputum samples were older, had a higher BMI, lower FEV_1 % predicted, and greater bronchodilator reversibility (Table E7 in online repository). When results from two induced sputum samples

were used, the percentage of subjects (ICS+ and ICS− group) with eosinophilic airway inflammation increased, supporting the intermittent nature of the eosinophilia that occurs in the asthmatic airway (Figure 3A/B). There were no significant race-related differences in the proportion of subjects with eosinophilic airway inflammation when results of two induced sputum samples from the same subject were used (within the ICS+ and ICS− groups, p= 0.29 and p=0.78, respectively; Figure 3A/B). The induced sputum pattern of inflammation within an individual remained eosinophilic or non-eosinophilic in 80.1% of unique subjects (339/423) when sputum induction was repeated; the intraclass correlation coefficient for % sputum eosinophils between two induced sputa was 0.31 in ICS+ group (fair agreement) and 0.68 in the ICS− group (moderate agreement).

DISCUSSION

The principal findings from this study were: 1) Only a minority of subjects with mild or moderate persistent asthma had eosinophilic sputum airway inflammatory phenotype; and 2) there are race-related differences in eosinophilic airway inflammation in asthma subjects treated with ICS.

The current report significantly contributes to the current body of literature on the influence of race on airway inflammatory patterns in asthma. A previous study, which included only small numbers of African-Americans (25 patients), suggested potential variations in airway inflammation based on race[45]. In this previous study, African-Americans with asthma had a greater number of sputum neutrophils, but the analysis did not take into account ICS use [45]. The current study includes a ten-fold higher number of African-Americans (n=264) with asthma and examined eosinophilic and non-eosinophilic airway inflammation separately in patients treated with or without ICS.

We did not observe race-related differences in eosinophilic and non-eosinophilic airway inflammation until we accounted for potential confounders. After accounting for baseline differences in age, gender, atopic status, BMI, FEV_1 % predicted, and uncontrolled asthma, we observed an increased odds of eosinophilic airway inflammation in African-American subjects taking ICS. Significant race differences in neutrophilic and mixed granulocytic airway inflammation were also found. Neutrophilic airway inflammation is commonly seen in patients with severe disease[46]. In our population of mild to moderate asthma patients, it was frequently seen both in African-Americans and Caucasians in the ICS+ group likely due to use of ICS. However, in the ICS− group, African-Americans were twice as likely to have neutrophilic inflammation, which may identify a group of patients that may be less responsive to ICS treatment [47]. Mixed granulocytic airway inflammation is associated with poorer asthma control, greater asthma symptoms and health care utilization and lower lung function. Our findings of higher numbers of African-Americans with this inflammatory pattern in both the ICS+ and ICS− group suggests a mechanism that may account for more severe and difficult to control asthma in African-Americans. Further cluster analyses in African-Americans with asthma may identify whether the mixed granulocytic inflammatory pattern identifies patients with severe asthma, as has been reported previously in a predominantly Caucasian population [48].

We identified a number of race-related differences in clinical characteristics. African-Americans had lower lung function (FEV_1 %), a higher BMI and total serum IgE level and they were more likely to have uncontrolled asthma. These findings are consistent with previous reports indicating lower lung function and elevated total serum IgE are associated with a greater burden of asthma among African-Americans compared to Caucasians [13, 39, 48, 49].

Our study suggests that differences in eosinophilic airway inflammation may contribute to race-related differences in asthma burden. This increased risk of eosinophilic airway inflammation in African-Americans on ICS may be due to higher rates of corticosteroid insensitivity and reduced cellular sensitivity to corticosteroids in African-Americans with asthma [14, 50, 51]. The biologic mechanisms for steroid insensitivity, however, are unclear and may include a decreased number of steroid receptors, reduced steroid receptor binding, increased nuclear transcription factor levels or other pharmacogenomic effects [15, 52–54]. Although, differential adherence may account for differences in patterns of airway inflammation, a previous study examining race effects on treatment failures in Asthma Clinical Research Network (ACRN) trials showed similar medication adherence in African-Americans and Caucasians (87.5% vs. 91%, respectively)[13]. Therefore, differential adherence likely does not impact the findings of this current study. In this analysis, we found that the BMI among African-Americans was about 6 kg/m^2 higher than among Caucasians (ICS+ and ICS− groups combined). Some studies suggest that obesity is associated with more difficult to control asthma and a poor response to asthma treatment or corticosteroid insensitivity [52, 55]. Whether the combination of African-American race and obesity leads to greater corticosteroid insensitivity is yet to be determined. Obesity (BMI 30 kg/m^2) in this study was found to be associated with an eosinophilic phenotype only in African-Americans taking ICS. This may indicate a race interaction in airway inflammation, though larger studies that adjust for the higher rates of obesity in this particular subgroup of asthma patients are needed to confirm our finding. Since obesity is associated with worse asthma control, efforts directed at obesity prevention and weight loss may help reduce race-related asthma disparities [56–58].

The major strengths of this study include the large number of African-American and Caucasian patients with asthma enrolled into these clinical trials conducted across the United States, and the analysis of data from multiple studies using standardized protocols and quality controls for sputum induction and cytology measurements. There are, however, a number of potential limitations to the study. Notably, our study was conducted among clinical trial participants with mild or moderate persistent asthma. It is not known if our findings are generalizable to patients with intermittent or severe persistent asthma. Results of studies in clinical trial participants may not apply to all patients with asthma, since only a minority of patients with asthma are eligible and enroll in clinical trials. Moreover, we used self-reported race in this study; further studies using genetic ancestry markers to classify patients' race are recommended. Use of genetic ancestry markers will provide the opportunity to examine the extent to which the airway inflammatory phenotype varies with the percentage of African ancestry (rather than a dichotomous "race" variable)[59]. We assessed two broad phenotypes of airway inflammation: eosinophilic and non-eosinophilic. We recognize that other inflammatory phenotypes exist: neutrophilic and pauci-granulocytic.

The relationship of these inflammatory phenotypes with a clinical phenotype is not clearly defined and is an area for further research. Furthermore, our analysis relied mostly on a single assessment of airway inflammation using induced sputum. While induced sputum is a direct and non-invasive measure of airway inflammation, other measures, including blood eosinophils, exhaled nitric oxide and total serum IgE, have been associated with greater asthma severity, yet have not consistently been shown to predict ICS treatment responsiveness to the same degree as sputum eosinophils have [60–62]. Blood eosinophils and total serum IgE were measured in a subset of patients in this analysis. No difference was found in blood eosinophils, although African-Americans had significantly higher total serum IgE levels compared to Caucasians. Larger studies examining additional measures of airway inflammation such as blood eosinophils, activated airway eosinophils, exhaled nitric oxide and total serum IgE should be pursued to fully address airway inflammatory differences that may exist in African-Americans and Caucasians with asthma. The analyses we conducted in the subset of patients with two induced sputum samples demonstrated no significant race-related differences in the proportion of patients with eosinophilic (or non-eosinophilic) asthma. These analyses included sputum samples with highly variable time periods between the two induced sputa (up to 53 weeks, depending on the study). Additionally, subjects included may not be representative of the entire sample, as we reported differences in the clinical characteristics of subjects with one vs. two induced sputum samples. These differences are likely due to variations in eligibility criteria used in the different study protocols (some of which included two induced sputa).

The findings from our study have important clinical implications. In both African-Americans and Caucasians with mild to moderate asthma, we found that non-eosinophilic airway inflammation was the predominant pattern. Patients with non-eosinophilic airway inflammation may not benefit from treatment intensification that focuses on targeting eosinophils, such as ICS. Other treatments such as the addition of beta-agonists and/or anti-muscarinic agents should be considered [20, 21]. In a recent post-hoc analysis, African-Americans without atopic inflammation (history of eczema, elevated blood eosinophils and total serum IgE) had a better response to adding a long-acting beta-agonist compared to increasing the dose of the ICS or adding a leukotriene modifier [63]. Another important finding from this study is that African-American subjects taking ICS were more likely to have eosinophilic airway inflammation. There are multiple factors that may account for this novel finding including greater disease severity, uncontrolled asthma, obesity and glucocorticoid resistance in African-American subjects in the ICS+ group[14, 50, 51]. Though we did not see a race difference in those not taking ICS, this may be due to the small sample size in the ICS− group. Additional studies in African-American adults need to be performed to determine if race and atopic status impact the response to therapy in those on and off ICS. There is an ongoing AsthmaNet study evaluating the most efficacious add-on treatment options in African-Americans with asthma that will begin to address our knowledge gaps in this field [22].

In summary, in our study of over 1,000 patients with asthma (a quarter of whom were African-American), we found evidence of worse asthma impairment (lower lung function, higher total serum IgE, worse symptom control) among African-Americans compared to Caucasians, and a greater risk of eosinophilic airway inflammation in African-Americans on

ICS treatment. We conclude that differences in eosinophilic airway inflammatory phenotype in the context of ICS use may contribute to the greater burden of asthma in African-Americans compared to Caucasians. Additional studies are needed to address the mechanisms underlying this novel finding, particularly the role of ICS in this patient population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of Abbreviations

ACQ	Asthma Control Questionnaire
ACRN	Asthma Clinical Research Network
ACT	Asthma Control Test
BMI	Body Mass Index
ICS	inhaled corticosteroids

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Clinical Implications

African-Americans with asthma carry a greater disease burden than Caucasians. Race-related differences in eosinophilic airway inflammation may contribute to the disparities in adults with asthma on inhaled corticosteroids.

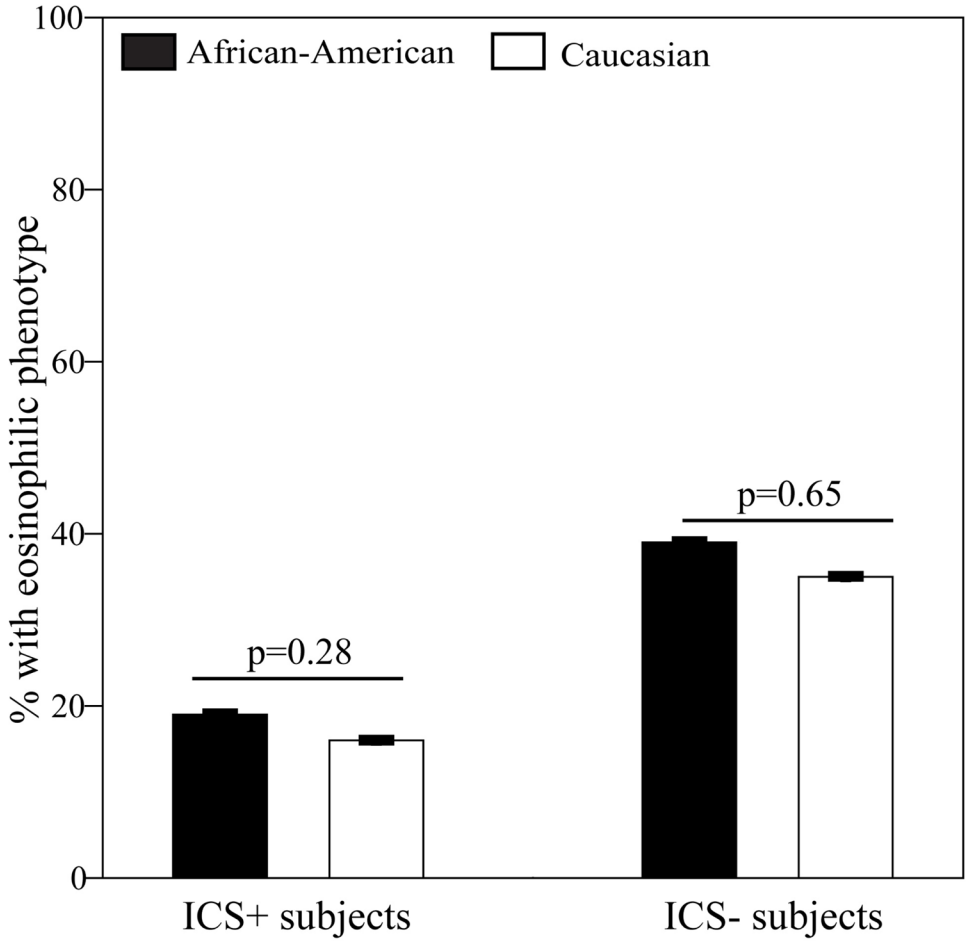

Figure 1. Distribution of eosinophilic airway inflammation (≥2% eosinophils) in ICS+ and ICS− African-Americans (black bars) and Caucasians (white bars) with asthma

Similar distribution of inflammatory phenotype in African-Americans and Caucasians with asthma. ICS+ group: 248 African-Americans, 674 Caucasians; ICS− group: 49 African-Americans, 249 Caucasians.

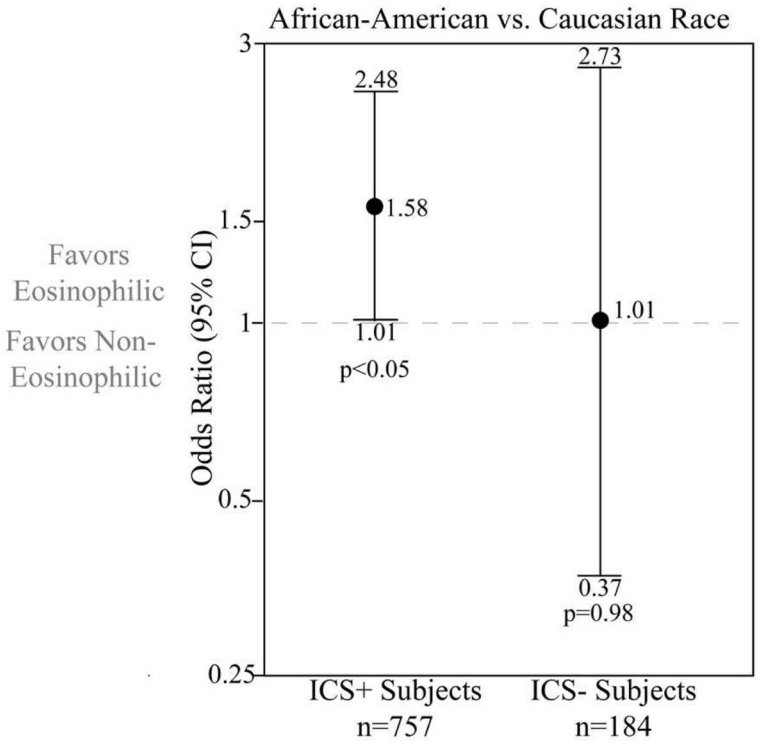

Figure 2. Odds ratio estimates and confidence intervals for eosinophilic airway inflammation (≥2% eosinophils) in African-Americans vs. Caucasians, stratified by ICS status

Estimated Odds Ratio (OR) with 95% Confidence Intervals (CI) are shown for eosinophilic airway inflammation after adjusting for age, gender, atopy, BMI, FEV_1% predicted, and uncontrolled asthma. In the ICS+ group, African-Americans were significantly more likely to have eosinophilic airway inflammation (p=0.046) compared to Caucasians. In the ICS− group, no significant race-related differences in eosinophilic airway inflammation were observed, though the confidence intervals were wide and the number of subjects in the ICS− stratum was approximately 25% of the number of individuals in the ICS+ stratum. Depending on the protocol in the parent clinical trials, some individuals contributed to the ICS+ and ICS− strata at different points in the trial (n=89 individuals); a total of 852 unique individuals contributed to the analyses. See Table E4 in the online repository for adjusted ORs for other covariates in the analyses.

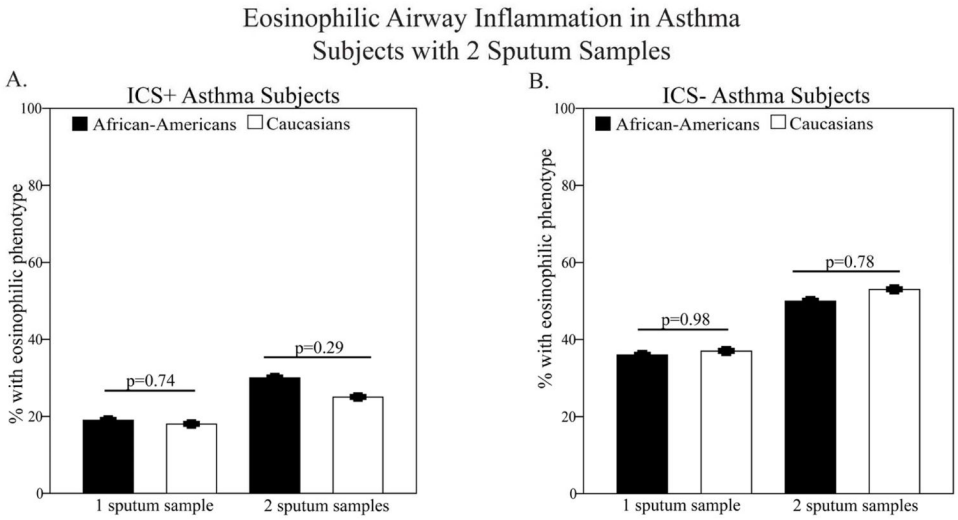

Figure 3. Frequency of eosinophilic airway inflammation (≥2% eosinophils on one or both sputum inductions) in subjects with two sputum samples

A: Sputum inflammatory cell profile assessed by the first versus two sputum samples in African-Americans (black bars; n=99) and Caucasians (white bars; n=266) in the ICS+ subgroup with two sputa analyzed. B: Sputum inflammatory cell profile assessed by the first versus two sputum samples in African-Americans (black bars; n=22) and Caucasians (white bars; n=90) in the ICS− subgroup with two sputa analyzed. Overall, there were no significant differences by race observed in each ICS stratum.

Table 1

Subject Characteristics, All subjects

	African American N=264	Caucasian N=754	p-value
Age, years	38±12	35±12	<0.01
Female, n (%)	186 (70)	478 (63)	0.04
Age at asthma onset, n (%)			
<40 years old	248 (94)	699 (94)	0.67
≥40 years old	15 (6)	48 (6)	
Atopy[a]	226 (87)	674 (91)	0.03
BMI, kg/m^2	34±10	28±7	<0.01
Pre-bronchodilator FEV$_1$% predicted	80±13	85±14	<0.01
Bronchodilator responsiveness, % change in FEV$_1$	14±12	13±9	0.21
Uncontrolled asthma, n (%)[b,c]	102 (43)	180 (28)	<0.01
Sputum eosinophils, (%), median (IQR)	0.4 (0.0, 1.3)	0.4 (0.0, 1.4)	0.56
Sputum neutrophils, (%), median (IQR)	43 (23, 68)	40 (24, 57)	0.07
Blood eosinophils, /mm^3, median (IQR)[d]	169 (100–291)	200 (108–300)	0.20
Total serum IgE, IU/mL, median (IQR)[e]	197 (111– 497)	120(48–282)	<0.01

Values above represent mean±SD unless otherwise indicated; BMI: Body Mass Index; FEV1: Forced Expiratory Volume in 1 second; IQR: Interquartile range.

[a] ≥1 positive skin test

[b] Uncontrolled asthma=ACT Score ≤19 or ACQ Score ≥1.5.

[c] Asthma control data available in 869 subjects: 235 African-Americans and 634 Caucasians.

[d] Blood eosinophil data available in 463 subjects: 97 African-Americans and 366 Caucasians.

[e] Total serum IgE data available in 543 subjects: 115 African-Americans and 428 Caucasians.

Table 2

Subject Characteristics, ICS+ group

	African-American N=248	Caucasian N=674	p-value
Age, years	38±12	36±12	<0.01
Female, n (%)	177 (71)	434 (64)	0.05
Age at asthma onset, n (%)			
<40 years old	234 (94)	626 (93)	0.56
≥40 years old	14 (6)	45 (7)	
Atopy[a]	211 (86)	601 (91)	0.03
BMI, kg/m^2	34±10	28±7	<0.01
Pre-bronchodilator FEV$_1$% predicted	80±13	86±14	<0.01
Bronchodilator responsiveness, % change in FEV$_1$	14±11	13±9	0.10
Uncontrolled asthma, n (%)[b,c]	100 (45)	147 (27)	<0.01
ICS dose, mcg/day, median (IQR)	320 (80–400)	176 (80–400)	0.04
Sputum eosinophils, (%), median (IQR)	0.4 (0.0, 1.2)	0.3 (0.0, 1.1)	0.45
Sputum neutrophils, (%), median (IQR)	42 (23, 65)	40 (24, 59)	0.26
Blood eosinophils, /mm^3, median (IQR)[d]	190 (100–228)	182 (100–260)	0.75
Total serum IgE, IU/mL, median (IQR)[e]	197 (103–497)	120 (48–293)	<0.01

Values above represent mean±SD unless otherwise indicated; BMI: Body Mass Index; FEV1: Forced Expiratory Volume in 1 second; IQR: Interquartile range;The total number of patients in Table 2 and 3 do not equal the total number of unique patients shown in Table 1 as 203 patients (20%) met criteria to be included (at different times) for both the ICS+ and ICS− group. Patients were treated with ICS for at least 4 weeks to be in the ICS+ group.

[a] ≥1 positive skin test

[b] Uncontrolled asthma=ACT Score ≤19 or ACQ Score ≥1.5.

[c] Asthma control data available in 775 subjects: 222 African-Americans, and 553 Caucasians.

[d] Blood eosinophil data available in 378 subjects: 85 African-Americans and 293 Caucasians.

[e] Total serum IgE data available in 466 subjects: 104 African-Americans and 362 Caucasians.

Table 3

Subject characteristics, ICS− group

	African-American N=49	Caucasian N=249	p-value
Age, years	31±10	32±10	0.32
Female, n (%)	31 (63)	145 (58)	0.51
Age at asthma onset, n (%)			
<40 years old	46 (96)	236 (97)	0.65
≥40 years old	2 (4)	7 (3)	
Atopy[a]	45 (92)	235 (95)	0.50
BMI, kg/m^2	30±9	26±5	<0.01
Pre-bronchodilator FEV$_1$% predicted	83±14	86±13	0.14
Bronchodilator responsiveness, % change in FEV$_1$	11±13	12±9	0.55
Uncontrolled asthma, n (%)[b,c]	6 (21)	44 (28)	0.47
Sputum eosinophils, (%), median (IQR)	0.7 (0.2, 3.1)	1.1 (0.2, 3.9)	0.50
Sputum neutrophils, (%), median (IQR)	43 (24, 73)	37 (22, 60)	0.12
Blood eosinophils, /mm^3, median (IQR)[d]	140 (80–300)	200 (130–300)	0.11
Total serum IgE, IU/mL, median (IQR)[e]	178 (78–464)	128 (64–258)	0.13

Values above represent mean±SD unless otherwise indicated; BMI: Body Mass Index; FEV1: Forced Expiratory Volume in 1 second; IQR: Interquartile range; The total number of subjects in Table 2 and 3 do not equal the total number of unique subjects shown in Table 1 as 203 subjects (20%) met criteria to be included (at different times) for both the ICS+ and ICS− group. Patients were off ICS for at least 6 weeks to be in the ICS− group.

[a] ≥1 positive skin test

[b] Uncontrolled asthma=ACT Score 19 or ACQ Score 1.5.

[c] Asthma control data available in 185 subjects: 28 African Americans, and 157 Caucasians.

[d] Blood eosinophil data available in 156 subjects: 23 African-Americans and 133 Caucasians.

[e] Total serum IgE data available in 146 subjects: 21 African-Americans and 125 Caucasians.