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Racial/ethnic-specific differences in the effects of inhaled corticosteroid use on bronchodilator response in patients with asthma

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All authors wrote the manuscript; L.S., S.S.O., T.J.N., and E.G.B. designed the research; S.S., C.E., K.M., E.B.B., M.A.L., H.J.F., D.S., W.R.C., K.B.D., L.N.B., J.R.R., and E.G.B. performed the research; L.S., S.S.O., T.J.N., J.L.E., M.W., T.E., A.M.Z., K.M., E.B.D., R.K., S.T., M.P.Y., L.N.B., and E.G.B. analyzed the data.

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The authors declared no competing interests for this work.

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Abstract

American Thoracic Society guidelines recommend inhaled corticosteroids (ICS) therapy, plus a short-acting bronchodilator, in patients with persistent asthma. However, few prior studies have examined the efficacy of this combination in children of all racial/ethnic groups. We evaluated the association between ICS use and bronchodilator response (BDR) in three pediatric populations with persistent asthma (656 African American, 916 Puerto Rican, and 398 Mexican American children). The association was assessed using multivariable quantile regression. After adjusting for baseline FEV_1 and use of controller medications, ICS use was significantly associated with increased BDR only among Mexican Americans (1.56%, p=0.028), but not African Americans (0.49%, p=0.426) or Puerto Ricans (0.16%, p=0.813). Our results demonstrate that ICS augmentation is disproportionate across racial/ethnic groups, where improved BDR is observed in Mexican Americans only. This study highlights the complexities of treating asthma in children, and reinforces the importance of investigating the influence of race/ethnicity on pharmacological response.

Keywords

Asthma; Inhaled corticosteroids; Precision Medicine; African American; Latino; Ethnicity

INTRODUCTION

Asthma, characterized by recurrent airflow obstruction and bronchospasm, is the leading chronic disease in children.(1–3) In the United States, asthma disproportionately affects minority groups, specifically African American and Hispanic populations.(4, 5) Despite overall improvements in asthma care, therapeutic treatments, and asthma self-management education, disparities in health outcomes among children of racial/ethnic minorities still exist.(6) African Americans and Puerto Ricans not only experience higher asthma morbidity and mortality rates(3, 4) but are less responsive to asthma medications compared to non-Hispanic White Americans.(7, 8) Some of these disparities may be attributed to racial/ethnic-specific differences in drug response due to interactions between genetic and environmental factors.(9, 10)

Inhaled corticosteroids and β_2-agonists (bronchodilators) are the backbone of therapy in the management of chronic asthma.(11, 12) Current guidelines recommend long-term treatment with ICS as first-line therapy for children and adults with persistent asthma. ICS therapy is effective in suppressing airway inflammation, reducing asthma attacks, and reducing asthma-related hospital admissions.(11, 13) Short-acting β_2-agonists (SABA), like albuterol, are prescribed as needed for quick relief of acute asthma symptoms. Corticosteroids are thought to augment the response to β_2-agonists by preventing or reversing β_2-receptor desensitization/downregulation.(14, 15) Prior studies examining the influence of inhaled

corticosteroids on SABA therapy have been limited, only a few have included children(16, 17) and fewer still have included racial/ethnic minorities.(10)

Clinical response to pharmacologic asthma therapy is heterogenous.(18) Many patients with asthma require both β_2-agonists and ICS for disease control, and a proportion of participants are non-responsive to either component of this dual therapy, showing no improvements despite being compliant.(17, 19) Puerto Ricans with asthma, for example, respond significantly less well to albuterol than do Mexican Americans.(7) Moreover, African Americans are more likely to have steroid-insensitive asthma.(19, 20) Observations concerning racial/ethnic differences in drug responses should not be surprising, given that many genetic polymorphisms altering therapeutic efficacy differ in frequency based on race/ethnicity and genetic ancestry. Interventions aimed at treating minority groups may have significant impact on asthma disparities, but limited data are available and further research is needed.(21, 22) The objective of our study was to examine racial/ethnic-specific differences in the effects of ICS use on albuterol bronchodilator response (BDR) in minority children with asthma from distinctracial/ethnic populations.

RESULTS

CHARACTERISTICS OF STUDY POPULATIONS

Table 1 provides a summary of select demographics and characteristics of the study population, stratified by racial/ethnic groups. A total of 1,970 pediatric participants with persistent asthma were included in our study: 656 African Americans (33.3%), 916 Puerto Ricans (46.5%) and 398 Mexican Americans (20.2%). Compared to their non-ICS counterparts, ICS users were significantly younger in African Americans (13.7 vs 15.2 yr, p=0.003) and Mexican Americans (12.1 vs 13.3 yr, p<0.001). In Puerto Ricans, duration of asthma was significantly shorter in ICS users compared to non-ICS participants (9.8 vs 10.0 yr, p=0.047) and ICS users demonstrated a higher use of oral steroids (27.9% vs 18.0%, p<0.001). ICS users in all racial/ethnic subgroups had a significantly higher IgE level compared to non-ICS participants [African American, (237 vs 158 IU/mL, p=0.006); Puerto Ricans, (340 vs 277 IU/mL, p=0.049; Mexican Americans, (230 vs 150 IU/mL, p=0.043)]. Sex and BMI categories were similar between ICS use groups.

LUNG FUCTION MEASUREMENTS

In African Americans, baseline measurements of forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), FEV_1/FVC ratio and FEV_1 % predicted were similar between ICS and non-ICS groups (Table 1). Puerto Rican ICS users demonstrated a significantly lower baseline FEV_1/FVC (0.84 vs 0.86, p=0.021) and higher baseline FEV_1 % predicted (85.1% vs 82.4%, p=0.021) compared with their non-ICS counterparts. Mexican American ICS users had a significantly lower baseline FEV_1 (2.39L vs 2.74L, p=0.003) and baseline FVC (2.98L vs 3.56L, p=0.007), compared with their non-ICS counterparts.

ASSOCIATION OF ICS USE WITH BRONCHODILATOR RESPONSIVENESS

The association of ICS use with albuterol BDR was examined among different racial/ethnic subgroups. ICS use was evaluated for its crude association with augmented albuterol BDR,

using quantile regression (Model 1, Table 2A). ICS use was significantly associated with increased BDR in Mexican Americans (1.47%, p=0.035), but not in African American (0.72%, p=0.094) or Puerto Rican children (0.20%, p=0.669). After adjusting for baseline FEV_1, and use of controller medication (Model 2), the significant association between ICS use and increased BDR persisted in Mexican Americans (1.56%, p=0.028), but not African Americans (0.49%, p=0.426) or Puerto Ricans (0.16%, p=0.813; Table 2B).

The association of ICS use with albuterol BDR was evaluated by adjusting for relevant covariates: baseline FEV_1 and use of controller meds. Adjusted quantile regression (Model 2) also demonstrated a significant association of ICS use with increased BDR only in Mexican Americans (1.47%, p=0.045) but not African Americans (0.66%, p=0.301) or Puerto Ricans (−0.76%, p=0.278; Table S1 B). Our observations of a significant association with ICS use and increased albuterol BDR in Mexican Americans persisted despite exclusion of LABA users.

Since the combination of a long-acting β_2-agonist (LABA) and an ICS provides greater clinical efficacy(23) and may alter the response to ICS(24), analyses were repeated after exclusion of LABA users. After adjusting for baseline FEV_1, and use of controller medication (Model 2), the significant association between ICS use and increased BDR persisted in Mexican Americans (1.47%, p=0.045), but not African Americans (0.66%, p=0.301) or Puerto Ricans (−0.76%, p=0.278) (Table S1 B).

We investigated the influence of additional covariates, including: genetically determined measures of African ancestry; tobacco exposure; obesity; and discrimination. Each covariate was added exclusively to Model 2 to generate Model 3 (Table S2a, African ancestry; Table S2b, tobacco exposure; Table S2c, obesity; and Table S2d, discrimination). In African Americans, discrimination was associated with increased BDR (1.34%, p=0.045), but the association between ICS and BDR remained insignificant. In Puerto Ricans, we observed associations between tobacco smoke exposure and decreased BDR (−1.83%, p=0.003), as well as discrimination and decreased BDR (−1.93%, p=0.011), however the association between the ICS and BDR remained insignificant. In both African Americans and Puerto Ricans, African genetic ancestry and obesity were not significantly associated with BDR (Model 3). ICS use remained significantly associated with increased BDR in Mexican Americans with the independent addition of the African ancestry and tobacco exposure variables in Model 3.

ASSOCIATION OF ICS USE ASTHMA SYMPTOMS AND EXACERBATIONS

We found that ICS use was not associated with reduced likelihood of asthma symptoms in any of the racial/ethnic groups, regardless of inclusion or exclusion of LABA users (Table 3). After excluding LABA users, we detected a positive association between asthma exacerbations and ICS use in African Americans (OR = 2.44, 95% CI: 1.57 to 3.78), where participants using ICS had a greater odds of asthma exacerbations. Analyses were suggestive of an association between ICS and increased asthma exacerbations in Mexican Americans, including LABA users (OR = 1.61, CI: 0.98 to 2.64) or excluding LABA users (OR = 1.58, CI: 0.94 to 2.66), however these observations were not significant.

DISCUSSION

Despite the strong racial/ethnic disparities observed in asthma morbidity and mortality, few studies have described the relationship between ICS treatment and BDR among minority pediatric participants.(7, 10, 25) Here we demonstrate that the association between ICS use and augmented albuterol-related BDR differed by race/ethnicity. This study builds on our previous work in minority participants demonstrating racial/ethnic differences in bronchodilator drug response among children with asthma.(10) In efforts to close the knowledge gap, our study may assist in explaining the increased asthma treatment failures observed in racial/ethnic minorities receiving asthma therapies.

In our study of children with persistent asthma, we observed a significant association of increased BDR with ICS use in Mexican American children, but no association in either African American or Puerto Rican children with persistent asthma. Our findings are consistent with a prior study that did not find an association between ICS and augmented albuterol-related BDR in African American children.(10) However, our current results also suggest that ICS use in Puerto Rican children may not impact albuterol related BDR as previously reported. This implies that the role of ICS in African American and Puerto Rican children may be limited. Conversely, ICS may have greater impact on BDR in Mexican American children than previously recognized, and thus, ICS therapy may have a greater utility in the Mexican American population. Disparities in response to ICS among racial/ethnic groups support the need for an improved understanding of racial/ethnic-specific drug-drug interactions and support the movement toward individualized (or precision medicine) approaches to asthma management.

The concomitant use of other asthma therapies may overshadow the influence of ICS, causing differences in drug response to be concealed. A number of studies have indicated that addition of a LABA to existing ICS therapy is clinically more effective than increasing the dose of ICS monotherapy.(26–28) LABAs have been shown to activate and enhance nuclear translocation of the glucocorticoid receptors, substantially mediating the anti-inflammatory actions and resulting in additive synergetic effects to both asthma therapies.(24, 29) In this study, African Americans (23.0%) and Puerto Ricans (18.8%) were less likely than Mexican Americans (25.9%) to use a LABA. This observation may be due to the concerns of serious side effects, reported in the United States in 2005, associated with the LABA component found in the combination inhaler fluticasone propionate-salmeterol xinafoate (Advair) diskus. Individuals using LABA were excluded from our analysis due to the potential for LABA therapy to alter the response to ICS. Nonetheless, significant associations persisted, despite the inclusion or exclusion of LABA users.

Recognizing racial/ethnic-specific differences in drug response may also have an impact on reducing asthma symptoms and exacerbations. African Americans experience more severe asthma symptoms, have a mortality rate ten times that of non-Hispanic White children, and are four times more likely to be admitted to the hospital for asthma, as compared to non-Hispanic White children.(30, 31) However, asthma morbidity and mortality are higher in Puerto Ricans than in any other racial or ethnic groups.(32) Given the existing disparities in asthma morbidity by race/ethnicity and the importance of ICS therapy in asthma control, it is

important to elucidate the factors associated with ICS responsiveness among African American and Puerto Rican patients with asthma, as this knowledge may improve the tailoring of asthma controller therapy. Our results suggest that ICS use may be less effective in reducing asthma symptoms or exacerbations in certain minority children. However, we remain cautious in our interpretations. Further study may yield insight into the complex relationship between ICS and management of acute asthma symptoms and/or exacerbations as well as a more defined role and clinical efficacy of ICS use in minority children with asthma.

Our study addresses the unmet, critical need in understanding the existing inequalities in asthma morbidity and mortality as well as the importance of elucidating the factors associated with response to asthma therapy among African American and Latino children with asthma. Our results provide an opportunity to examine an association between ICS use and augmented albuterol-related BDR, while addressing an important clinical research question: Is the ICS and bronchodilator combination equivalently effective across all racial/ethnic groups? A significant number of children with asthma in the United States are racial/ethnic minorities. However, there is limited data addressing disparities in asthma-related outcomes. A key strength of our investigation was the use of a large, diverse, pediatric population that is, in part, representative of the current pediatric patient population.

Our study is not without limitations. Our analyses lack information on ICS dosing and duration, precluding the determination whether higher ICS doses would elicit an association with BDR in African American and Puerto Rican children with persistent asthma. Some of our observations may have been influenced by unknown confounders, including medication dosing, duration of use, and adherence as well sub-classifications of persistent asthma. Patients with persistent asthma require pharmacologic therapy beyond that recommended for mild asthma, and potentially exhibit varying degrees of response based on their sub-classification. The generalizability of this study is limited by the characteristics of the study participants, where results may not apply to other racial/ethnic groups in the U.S. While the selection bias was inadvertent, in order to gain more information in minority health disparities, it was also unavoidable. Additionally, there is the potential of bias due to misclassification of exposures, covariates and outcomes. However, outcome misclassification within our study is unlikely because we followed thorough, established spirometry and BDR protocols. Our study is reinforced by the use of detailed measures of social, environmental and pharmacological exposures by means of a comprehensive questionnaire.

CONCLUSIONS

We individualize approaches to asthma therapeutic targets to apply therapies to patients who are most likely to respond to them. This is of particular importance when considering therapies such as ICS, which has potentially significant side effects. Our results suggest that ICS may not augment albuterol-related BDR among African American and Puerto Rican children with asthma to the extent previously reported. This is particularly notable given that these two ethnic groups have disproportionately high asthma morbidity and mortality rates. Conversely, our results suggest that ICS may be more efficacious in Mexican-American

children than previously recognized. Unraveling the racial/ethnic-specific differences of ICS response in patients with persistent asthma has great potential to help clinicians provide effective, individualized approaches to asthma pharmacotherapeutics. This, in turn, has the potential to contribute to overall reduction of asthma-related health disparities in disproportionally afflicted populations.

METHODS

STUDY POPULATION

Participants were recruited from two parent studies: the Study of African Americans, Asthma, Genes and Environments (SAGE) and the Genes-environments and Admixture in Latino Americans study (GALA II), two identical, parallel, case-control studies of asthma in African American and Latino American children, respectively. Study protocols and inclusion/exclusion criteria have been described in detail elsewhere.(7, 33, 34) Briefly, participants included children and youth ages 8–21 with and without asthma who were recruited from community clinics and hospitals. Recruitment was standardized across all sites; GALA II participants were recruited from Houston, Chicago, San Francisco Bay Area, New York City, and Puerto Rico during the years 2006–2018 and SAGE participants were recruited from San Francisco Bay Area during years 2006–2015. Participants in both parent studies were excluded if they reported any of the following: (1) any smoking within one year of the recruitment date; (2) 10 or more pack-years of smoking; (3) pregnancy in the third trimester; (4) history of lung diseases other than asthma (cases only) or chronic illness (cases and controls). Local institutional review boards approved both studies, and all participants or, for participants 17 or younger, their parents, provided written informed consent.

SUBJECT SELECTION

To be considered eligible in the current study, participants had physician-diagnosed asthma(11), the same self-reported race/ethnicity as their biological parents and grandparents, and were characterized as having persistent asthma. Persistent asthma was determined by the degree of asthma severity and history asthma exacerbations, as defined by the National Asthma Education and Prevention Program (NAEPP).(11) Briefly, baseline spirometry and standardized questionnaires were used to assess report of asthma symptoms occurring during the year preceding recruitment. Asthma symptoms included wheezing, coughing, nocturnal wakening and limited activity. Participants who reported having ever experienced oral steroid use, asthma-related emergency department (ED) visits, hospitalizations, or intensive care unit (ICU) admissions were considered to have had asthma exacerbations. Based on these criteria, participants whose asthma severity status corresponded to the “mild persistent”, “moderate persistent”, or “severe persistent” NAEPP classifications were considered to have persistent asthma.(11)

OUTCOME MEASURES: BRONCHODILATOR RESPONSIVENESS

The primary outcome for this study was the effect of ICS use on BDR, evaluated by comparing FEV_1 of patients using an ICS with that of those not using an ICS. ICS use was defined as any reported use of an inhaled steroid medication in 12 months prior to recruitment. Lung function was evaluated using spirometry performed according to

American Thoracic Society standards.(35) Spirometry was performed before and 15 minutes after] administration of four puffs of albuterol (90μg per puff) through a 5-cm plastic mouthpiece from a standard metered-dose inhaler. Spirometry was performed for a third time following an age-dependent dose of albuterol, given approximately 15 min after the first dose: 2 puffs (180μg) were administered for participants aged <16 years and 4 puffs (360μg) for participants ≥ 16 years. Before testing, participants withheld short-acting bronchodilators for at least 8 hours, long-acting bronchodilators for at least 48 hours and xanthines (including caffeine, theophylline, and aminophylline) for at least 12 hours.

Maximal BDR was calculated by measuring the relative change in forced expiratory volume in one second (FEV_1, measured in liters) before and after albuterol administration: 100% x (post-FEV_1 – pre-FEV_1) / (pre-FEV_1). Generally, a positive BDR is defined as ≥ 12% increase in FEV_1 and ≥ 200mL absolute change in FEV_1. However, there is no reference for positive BDR among children, and a 200mL absolute change represents a much larger relative volume in a small child than in an adult.(36, 37) Therefore, we only assessed the % change in FEV_1, where BDR was evaluated as a continuous variable. Baseline pulmonary function parameters included for study were FEV_1, FVC, FEV_1/FVC and FEV_1 % predicted. FEV_1 values were determined by Hankinson equations(38) derived from African American and Mexican nonsmokers. Spirometry reference values for Puerto Ricans were derived using the prediction equation for Mexican Americans, as there are currently no Puerto Rican-specific reference equations. Although some participants' spirometry values were statistical outliers (three times the interquartile range), their spirometry flow-volume loops were considered to be clinically plausible after evaluation by a pulmonologist, and therefore included in our analyses.

We also examined the relationship between ICS use and other asthma-related health outcomes as a secondary analysis. Assessed asthma-related health outcomes included asthma exacerbations and asthma symptoms occurring during the year preceding recruitment. Symptoms included self-reported shortness of breath, wheezing, coughing, and nocturnal awakening due to shortness of breath, coughing or wheezing. Asthma-related exacerbation was defined as any self-reported hospitalization, ER visit, ICU admission or use of oral steroid for respiratory symptoms.

COVARIATES

Answers to a detailed clinical questionnaire, which included the child's age, sex, maternal education level, family income, family history of atopic diseases, body mass index (BMI), age at asthma diagnosis, duration of asthma and controller medication therapy (including leukotriene modifiers, and oral steroids), were provided by the subject (if ≥18 years of age) or the subject's parent/guardian. Information was also collected on environmental factors (e.g., pet ownership, home environment, and tobacco smoke exposure) as well as prenatal and postnatal information (maternal smoking during pregnancy and breastfeeding). Peripheral blood samples were collected during enrollment for measurement of relevant biomarkers, including immunoglobulin E (IgE) levels.

Previous studies have shown that genetic African ancestry(39), tobacco exposure(40), obesity(41), and discrimination(42), may have important roles in asthma and drug response.

Therefore, we included these variables in our data analyses. Genetic ancestry proportions for participants were determined using the ADMIXTURE software package and modeled assuming three ancestral populations (African, Native American, and European).(43, 44) The criterion for secondhand tobacco smoke exposure was whether the subject was living in a home where a smoker currently lived, at time of recruitment. Body mass index (BMI) was calculated as weight(kg) / ((height(m)^2) and child's BMI category (underweight, normal weight, overweight, obese) was determined using an age- and sex-specific percentile for BMI. Psychosocial stress, including racial discrimination, has also been shown to influence BDR.(45, 46) Self-reported discrimination was defined as any report of discrimination either at school, a public setting, or soliciting service in a store/restaurant, or medical facility.(42)

Analysis was limited to study participants with complete age, ICS use, and lung function data. Participants with persistent asthma were stratified by race/ethnicity and included: 656 African American, 916 Puerto Rican, and 398 Mexican American pediatric participants.

STATISTICAL ANALYSES

Descriptive statistics for selected characteristics were presented for each racial/ethnic group and the total population. The Shapiro–Wilk test was used to evaluate the normality of distribution of the continuous variables. Student's t-test or the Kruskal-Wallis test was used to compare continuous variables by ICS use, depending on normality of distribution. Categorical variables were compared by ICS use with the chi-squared test.

The distribution of BDR was not normal. Therefore, quantile (median) regression was utilized. This method is valuable in understanding outcomes that have nonlinear relationships with predictor variables, in that regression estimates are more robust against outliers.(47) We estimated the effects of ICS use (the exposure of interest) on BDR (the primary outcome) via three models:

1. BDR ~ ICS use
2. BDR ~ ICS use + covariates
3. BDR ~ ICS use + covariates + 1 exploratory covariate

A bivariate regression analysis was used to determine the crude association between ICS use and BDR (Model 1). Covariates for multivariable regression analysis were first investigated for association with BDR using Kruskal-Wallis tests, and evaluated for clinical relevance. Significant predictors (based on a p-value <0.1) were included in the multivariable model. Covariates in the multivariable quantile regression model were baseline FEV_1 in liters (continuous) and use of asthma controller medication (dichotomous; "yes or no"), including leukotriene modifiers, and oral steroids (Model 2). Leukotriene modifiers block proinflammatory activities, thereby preventing airway bronchoconstriction and improving lung function.(48, 49) The independent influence of additional covariates, previously shown to influence respiratory health, was explored: African genetic ancestry (continuous), secondhand tobacco smoke exposure (dichotomous; "yes or no"), obesity (categorical), and discrimination (dichotomous; "yes or no").(40, 45) Each exploratory covariate was added exclusively and independently to Model 2 to generate Model 3 (Model 2 + 1 exploratory covariate) to assess its association with BDR. The effect of ICS use on BDR was also further

analyzed in a population excluding 426 LABA users since LABA therapy may alter the response to ICS.

In secondary analyses, the effect of ICS use on asthma symptoms and asthma exacerbations was investigated in separate models. We utilized logistic regression models, adjusting for age, baseline FEV_1, and controller medication. Asthma symptoms and asthma exacerbations were analyzed as dichotomous variables (present or absent).

Significance was determined at an alpha level of 0.05. All analyses were conducted with STATA version 15.1 software (StataCorp LP) and R version 3.5.1.(50)

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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STUDY HIGHLIGHTS:

What is the current knowledge on the topic?

In the United States, African Americans and Puerto Ricans experience a higher burden of asthma and are less responsive to asthma medications compared to Whites and Mexican Americans. The high degree of heterogeneity in asthma burden and drug response among minorities is complex. Despite established clinical guidelines, there is considerable racial/ethnic variability in inhaled corticosteroid (ICS) response and bronchodilator response (BDR).

What question did this study address?

Our objective was to characterize racial/ethnic-specific differences in the effect of ICS on BDR in African American and Latino youth with persistent asthma.

What does this study add to our knowledge?

Our results suggest that ICS may not improve bronchodilator drug response among African American and Puerto Rican children with asthma to the extent previously believed, but that ICS use in Mexican-American children may be more efficacious than previously recognized.

How might this change clinical pharmacology or translational science?

Our understanding of racial/ethnic-specific drug-drug interactions, particularly in groups experiencing the highest burden of asthma morbidity and mortality, is limited. More studies, like this one, are necessary to identify patients unlikely to benefit from treatment, which in turn, will provide clinicians with tools designed improve the selection of therapy.

Table 1.

Characteristics of Subjects with Persistent Asthma, in SAGE study, 2006–2015 and GALA II study, 2006–2018.

	Comparison by Race/Ethnicity[#]								
	African Americans			Puerto Ricans			Mexican Americans		
Characteristics[*]	Non ICS n=196	ICS Use n=460	*p*-value[^]	Non ICS n=532	ICS Use n=384	*p*-value[^]	Non ICS n=134	ICS Use n=264	*p*-value[^]
Age, yr	15.2 (11.9–18.7)	13.7 (11.0–11.7)	0.003	11.8 (9.9–14.6)	11.4 (9.8–14.5)	0.347	13.3 (10.9–16.8)	12.1 (9.9–14.1)	<0.001
Sex, %male	47.4	53.7	0.168	53.8	54.7	0.833	46.9	59.1	0.105
Asthma duration, yr	10.3 (7.6–14.1)	10.1 (7.3–13.5)	0.582	10.0 (8.2–13.0)	9.8 (7.6–12.5)	0.047	8.0 (4.6–12.5)	7.5 (5.1–9.8)	0.133
Serum IgE, IU/mL	158 (38–380)	237 (82–497)	0.006	277 (85–725)	340 (115–822)	0.049	150 (35–412)	230 (54–649)	0.043
BMI									
Normal, %	48.5	43.3		45.9	48.7		32.8	35.2	
Overweight, %	22.4	17.2	0.658	15.6	15.6	0.144	15.7	18.9	0.930
Obese, %	29.1	38.0		30.4	32.0		50.8	44.7	
Underweight, %	0.0	1.1		8.1	3.7		0.7	1.2	
Controller Medication Use									
Long-acting beta-agonist, %	1.0	32.4	<0.001	1.3	43.0	<0.001	0.0	39.0	<0.001
Leukotriene modifiers, %	5.1	12.8	0.003	21.1	44.3	<0.001	14.9	33.0	<0.001
Oral steroids, %	0.5	0.0	0.123	18.0	27.9	<0.001	1.5	0.4	0.225
Spirometry									
Baseline FEV_1, L	2.61 (2.10–3.11)	2.45 (1.94–3.01)	0.077	2.13 (1.72–2.65)	2.10 (1.69–2.64)	0.813	2.74 (2.15–3.29)	2.39 (1.88–3.07)	0.003
Baseline FVC, L	3.23 (2.52–3.77)	3.01 (2.36–3.75)	0.192	2.46 (2.00–3.19)	2.51 (2.01–3.17)	0.628	3.56 (2.71–3.91)	2.98 (2.26–3.78)	0.007
Baseline FEV_1/FVC	0.83 (0.78–0.89)	0.83 (0.76–0.88)	0.170	0.86 (0.80–0.91)	0.84 (0.79–0.90)	0.021	0.82 (0.78–0.86)	0.82 (0.77–0.87)	0.708
Baseline FEV_1 %predicted	95.2 (86.3–106.5)	96.7 (88.3–105.4)	0.641	82.4 (73.6–92.2)	85.1 (74.2–95.4)	0.021	96.7 (87.7–106.5)	95.0 (87.3–103.7)	0.205

Abbreviations: IgE, Immunoglobulin E; BMI, body mass index; ICS, inhaled corticosteroid; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity

[#]GALA II participants were recruited from Houston, Chicago, San Francisco Bay Area, New York City, and Puerto Rico during the years 2006–2018 and SAGE participants were recruited from San Francisco Bay Area during years 2006–2015.

[*]Data given as median (25th-75th percentile), unless otherwise indicated

[^]P-values obtained using Kruskal-Wallis test for continuous nonnormally distributed variables, or chi-squared test for categorical variables.

Table 2.

Regression Analysis: *Association of inhaled corticosteroid (ICS) use with bronchodilator responsiveness, in SAGE study, 2006–2015 and GALA II study, 2006–2018.*

Variable	African Americans (n = 656)		Puerto Ricans (n= 916)		Mexican Americans (n = 398)	
	β	*p*-value	β	*p*-value	β	*p*-value
A. Bivariate Regression						
ICS use	0.72	0.094	0.20	0.669	1.47	0.035
B. Multivariable Quantile Regression						
ICS use	0.49	0.426	0.16	0.813	1.56	0.028
Covariates						
Baseline FEV_1	−1.91	<0.001	−1.85	<0.001	−2.30	<0.001
Controller medication	−0.75	0.26	0.16	0.801	−0.94	0.269

Abbreviations: ICS, inhaled corticosteroid; FEV_1, forced expiratory volume in 1 second

β coefficients represent percentage difference in FEV_1 between nonICS and ICS use groups

Table 3.

Adjusted Odds Ratios for the Association between ICS Use and Asthma Symptoms/Exacerbations, in SAGE study, 2006–2015 and GALA II study, 2006–2018.

	Asthma Symptoms[+]	Asthma Exacerbations[^]
	OR (95% CI)	**OR (95% CI)**
Entire Study Population		
African Americans (n = 656)	1.32 (0.91–1.91)	1.18 (0.71–1.94)
Puerto Ricans (n= 916)	1.05 (0.75–1.49)	0.75 (0.40–1.41)
Mexican Americans (n= 398)	0.91 (0.50–1.66)	1.61 (0.98–2.64)
After exclusion of LABA users		
African Americans (n = 505)	1.26 (0.86–1.84)	2.44 (1.57–3.78)
Puerto Ricans (n= 744)	0.84 (0.58–1.21)	0.77 (0.39–1.50)
Mexican Americans (n= 295)	0.94 (0.51–1.73)	1.58 (0.94–2.66)

Adjusted for age, baseline FEV_1 and controller medication.

[+]Symptoms includes wheezing not associated with a cold, coughing, reduced activity, nocturnal wakening, and shortness of breath, during the year preceding recruitment.

[^]Exacerbations include use of steroids, ER admission, hospital admission, or ICU visit, during the year preceding recruitment.