Racial differences in biologic predictors of severe asthma: Data from the Severe Asthma Research Program

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Background: Biologic factors are known to contribute to asthma severity. It is unknown whether these factors differentially contribute to asthma severity in black compared with white subjects.
Objective: We sought to assess the extent to which racial disparities between black and white subjects with severe asthma are attributable to physiologic, immunoinflammatory, and sociodemographic variables.
Methods: Black and white asthmatic adults enrolled in a cross-sectional study focused on severe asthma were evaluated. Severe asthma was identified by using the American Thoracic Society definition. After initial univariable analyses, unconditional logistic regression models were used to estimate the probability of having severe asthma for black and white subjects.
Results: Differences in severe asthma in black compared with white subjects were observed. In univariable analysis IgE level was not associated with severe asthma in black or white subjects, whereas in multivariable analysis IgE level was significantly associated with severe asthma for black subjects ($P = .014$) but not for white subjects. The odds of having severe asthma more than doubled for black subjects with 2 or more family members with asthma ($P = .026$), whereas the odds of severe asthma for white participants with a strong family history of asthma decreased by almost half ($P = .05$). Atopy was negatively associated with severe asthma in both races in univariable analysis but remained significant only in black subjects, whereas comorbidities were associated with severe asthma in white subjects.
Conclusion: Biologic factors were distinctly associated with severe asthma only in black subjects. Studies that incorporate comprehensive evaluation of biologic factors associated with asthma might lead to the development of therapies that target biologic abnormalities in black subjects. (J Allergy Clin Immunol 2010;126:1149-56.)

Key words: *Severe asthma, race, IgE, allergic sensitization, immunoinflammatory*

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Although standard treatments can control most asthma, a small number of asthmatic subjects (about 10%) require treatment with the highest level of inhaled corticosteroids, often in combination with other drugs, including systemic corticosteroids.[1,2] Despite these high medication doses, these patients often never achieve adequate disease control and continue to have frequent exacerbations, severe exacerbations, or both; daily symptoms; and bronchodilator use, as well as persistent airway obstruction.[3] Although lower lung function, a history of pneumonia, less atopy, and lower blood basophil numbers have all been shown to be independently associated with the presence of this more severe asthma, much remains to be determined regarding the factors that either associate with or predict its development.[4]

Asthma in black subjects has long been associated with higher morbidity and mortality rates than asthma in white subjects.[5] Black subjects have 4 times the risk of hospitalization and 5 times the risk of mortality than white subjects.[6] Although black subjects have been reported to be more likely to have severe asthma, particularly in relation to asthma exacerbations,[7] concerns have generally focused on contribution from limited access to appropriate medical care, adherence to medications, and related socioeconomic factors to this severe form of disease.[8]

However, in addition to socioeconomic status (SES), biologic factors likely also contribute to asthma severity in both racial groups. Whether there are differences in the contribution of biologic factors to asthma severity in black compared with white subjects has not been specifically addressed. For instance, IgE

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Abbreviations used
BMI: Body mass index
FVC: Forced vital capacity
GERD: Gastroesophageal reflux disease
SARP: Severe Asthma Research Program
SES: Socioeconomic status

levels are well known to be significantly higher in black than white subjects in both asthmatic and nonasthmatic populations.[9-16] In addition to total IgE levels, specific IgE levels also differ by race, with higher levels of grass- and cockroach-specific IgE associated with asthma and more poorly controlled asthma in black subjects.[15,17] Higher total IgE levels have been shown to be associated with lower lung function, with the relationship stronger in some racial and ethnic group than in others.[18] Finally, substantial differences in T_H2-related gene allele frequencies have been described in black compared with white subjects, suggesting that hereditary/genetic differences could explain some of the potential severity differences.[19]

The objective of this article was to determine the extent to which the racial health disparities in asthmatic subjects, particularly those with severe asthma, are attributable to physiologic, immunoinflammatory, and/or sociodemographic variables. We hypothesized that the contribution of immunoinflammatory predictors to asthma severity would differ by race. To address this hypothesis, clinical, immunologic, and physiologic data from the cross-sectional National Heart, Lung, and Blood Institute–sponsored Severe Asthma Research Program (SARP) database were analyzed to determine whether there were differences in the factors associated with severe asthma in black compared with white asthmatic participants.

METHODS

Subjects

The data in this study were obtained from subjects enrolled in SARP, a network established to identify and characterize subjects with severe asthma in relation to subjects with milder asthma to better understand mechanisms for their disease. The baseline characteristics of this population were recently published.[4] SARP initially consisted of 8 funded sites: the University of Pittsburgh, the University of Virginia (subsites at Cleveland and Emory University), Brigham and Women's Hospital, Imperial College, National Jewish Medical and Research Center, Wake Forest University, Washington University, and the University of Wisconsin. The number of sites was reduced to 4 in 2006: the University of Pittsburgh (including National Jewish), the Cleveland Clinics (including the University of Virginia and Emory University), the University of Wisconsin, and Wake Forest University.

From August 2003 until February 2010, 1391 subjects aged 18 to 79 years were recruited and enrolled. Current smokers or persons with 5 or more pack-years of tobacco use were excluded from SARP.[4] The American Thoracic Society's definition was used to determine whether subjects had severe/refractory asthma.[20] Subjects with severe asthma were required to meet one of 2 major criteria (high-dose inhaled or oral corticosteroid use) and at least 2 of 7 minor criteria. All subjects who did not meet the criteria for severe asthma were classified as "not severe." There were no specific requirements for the subjects other than a confirmed diagnosis of asthma based on symptoms, bronchodilator response, or airway hyperresponsiveness.

Data collection/measures at interview

All subjects completed multiple (14) allergen skin testing evaluations for atopy, standardized and SARP-specific questionnaires, collection of blood for complete blood counts and differentials, and total IgE level, exhaled nitric oxide, and pulmonary function testing, as previously described.[4] Questionnaires were administered by clinical staff and included information on demographics, medical history, comorbidities, family history, smoking history, and frequency of asthma symptoms, such as wheezing, nocturnal symptoms, and shortness of breath. Medical resource or health care use was assessed by the subject's recollection of emergency department visits, hospital and intensive care unit visits, and asthma ventilation procedures. Baseline prebronchodilator spirometric testing was carried out for each subject. In addition, a maximal bronchodilator response was calculated as the greatest percentage change from the prebronchodilator FEV_1 after 4 to 8 puffs of albuterol. A variety of other procedures were done on subpopulations of SARP subjects (methacholine, sputum induction, and bronchoscopy) but are not included in this study because of incomplete data primarily based on site-specific testing (sputum) or exclusions on the basis of FEV_1 percent predicted (sputum and methacholine) or subject's preference (bronchoscopy).

Statistical analysis

Statistical analyses were conducted with SAS software (SAS Statistical Software, version 9.2; SAS Institute, Inc, Cary, NC) and STATA software (Stata Statistical Software, release 11; StataCorp, College Station, Tex). Categorical variables were examined by using cross-tabulations and frequencies (expressed as numbers with percentages). Fisher exact or χ^2 tests were performed for racial comparisons (white and black [or African racial heritage]) of categorical variables in the severe asthma group. The Wilcoxon-Mann-Whitney test was performed for racial comparisons of continuous variables in the severe asthma group (expressed as medians with 25th-75th percentiles).

Univariable models

Unconditional logistic regression was used to calculate the crude and adjusted odds ratios to estimate the probability of having severe asthma. Race-specific (black and white) models were used for this study. Univariable models were used to determine which variables to include for model selection and exclude during the model-building process, with only the variables with a P value of less than .15 included.

Multivariate models

Variables that had a P value of less than .15 in the univariable models were included for model selection. In addition, variables deemed of clinical significance regardless of statistical significance were included in the full model. The likelihood ratio test P value was used to determine whether variables should remain in the model. Goodness of fit of the model was assessed by using the Pregibon Dbeta and Hosmer and Lemeshow delta-D tests. Models were adjusted for age of enrollment and clinical center.

RESULTS

Baseline demographics

General demographics. For more data on baseline demographics, see Table I. Of the 1391 total enrolled subjects in SARP, 916 met the inclusion criteria for this analysis. This analysis included only adult participants (≥18 years of age). Participants with a racial background classified as nonblack and nonwhite, as well as participants considered healthy (not asthmatic) were excluded (n = 475). There were more white (71%) than black (29%) participants. More female participants were included compared with male participants, and there were slightly more subjects with mild-to-moderate asthma compared with subjects with severe asthma. Forty percent of black subjects and 42% of white subjects were categorized as having severe asthma. The median age at enrollment for black subjects was almost 5 years younger than that for white subjects in the severe asthma group

TABLE I. Baseline characteristics of SARP participants by racial background and phenotype group

	Both races (n= 916)		Black subjects (n = 267 [29.1%])		White subjects (n = 649 [70.9%])	
	Mild-to-moderate asthma (n = 538)	Severe asthma (n = 378)	Mild-to-moderate asthma (n = 159)	Severe asthma (n = 108)	Mild-to-moderate asthma (n = 379)	Severe asthma (n = 270)
Age at diagnosis (y)*	10 (4-21)	12 (3-28)	9 (4-22)	10 (2-27.5)	10 (4-21)	13 (3-30)
Age of enrollment (y)*	33.3 (24.5-42.8)	45.2 (36.1-60.0)	32.7 (25.5-40.6)	42.0 (35.3-49.1)	33.4 (24-44.7)	46.6 (36.2-54.3)
Duration of asthma (y)	19.5 (10.8-28.8)	25.9 (15.6-37.9)	20.3 (11.1-26.7)	25.6 (14.3-37.5)	19.1 (10.7-30.1)	25.9 (16.1-38.3)
BMI (kg/m^2)*	27.2 (23.5-33.0)	30.6 (25.4-35.6)	29.4 (25.8-37.5)	33.1 (29.3-28.9)	26.0 (22.9-31.4)	29.4 (25.0-34.5)
Baseline predrug FEV_1 (L)*	2.76 (2.31-3.37)	1.91 (1.35-2.41)	2.41 (1.93-2.85)	1.74 (1.36-2.19)	2.99 (2.49-3.55)	1.96 (1.33-2.60)
Baseline predrug FEV_1 (% predicted)*	84.5 (74-96)	60.5 (45-77)	81 (70-92)	63.5 (50.5-81)	86 (76-98)	58.5 (44-74)
Baseline predrug FVC (% predicted)*	94 (84-103)	76.4 (64-88)	93 (81-102)	80.4 (69-96.5)	94 (85-104)	74.7 (62.8-86)
FEV_1/FVC ratio*	0.75 (0.68-0.82)	0.65 (0.55-0.74)	0.74 (0.67-0.80)	0.68 (0.57-0.76)	0.76 (0.69-0.82)	0.64 (0.53-0.73)
Maximum FEV_1 reversal (%)	10 (5.5-18.4)	14.5 (6.6-25.9)	14 (6.1-23.8)	15 (6.9-25.9)	9.4 (5.2-15.9)	14.2 (6.0-26.3)
Log IgE (IU/mL)*	2.10 (1.69-2.51)	2.08 (1.59-2.54)	2.24 (1.83-2.68)	2.29 (1.83-2.68)	2.06 (1.60-2.42)	2.01 (1.49-2.46)
Presence of atopy	417 (77.5%)	234 (61.9%)	130 (81.8%)	67 (62%)	287 (75.7%)	167 (61.9%)
≥5 Positive skin test results	186 (34.6%)	84 (22.2%)	72 (45.3%)	31 (28.7%)	114 (30.1%)	53 (19.6%)
Female sex*	362 (67.3%)	242 (64%)	109 (68.6%)	78 (72.2%)	253 (66.8%)	164 (60.7%)
Currently employed*	345 (64.1%)	235 (62.2%)	104 (65.4%)	61 (56.5%)	241 (63.6%)	174 (64.4%)
Diagnosed diabetes	19 (3.5%)	38 (10.1%)	9 (5.7%)	11 (10.2%)	10 (2.6%)	27 (10%)
Diagnosed hypertension	63 (11.7%)	92 (24.3%)	30 (18.9%)	28 (25.9%)	33 (8.7%)	64 (23.7%)
Diagnosed GERD	99 (18.4%)	150 (39.7%)	29 (18.2%)	41 (38.0%)	70 (18.5%)	109 (40.4%)

Continuous variables are presented as medians (25th-75th percentiles), and categorical variables are presented as numbers (percentages).
*$P < .15$, black subjects with severe asthma versus white subjects with severe asthma.

($P = .011$), with 65% of black subjects enrolling in SARP at 45 years of age or less (Fig 1). Although the age that the participants were given their first diagnosis of asthma was not significantly different between black and white subjects with severe asthma, 10% more of the black population compared with the white population were given diagnoses at less than 3 years of age (see Fig E1 in this article's Online Repository at www.jacionline.org). Body mass index (BMI) in black subjects was also higher than that in white subjects.

Socioeconomic factors. White subjects with severe asthma were more likely to be employed compared with their black counterparts. Almost 32% of black subjects with severe asthma were exposed to secondhand smoke compared with 23% of white subjects with severe asthma ($P = .049$). Pet ownership within the severe asthma group was significantly less in black than white subjects, with 22% of black and 47% of white subjects owning pets.

Pulmonary function. When pulmonary function was corrected for race, height, and age, black asthmatic subjects had higher median baseline predrug FEV_1 and forced vital capacity (FVC) percent predicted values compared with white subjects; however, absolute FEV_1 (in liters) values were lower for black compared with white subjects. Bronchodilator reversibility was not significantly different for black and white subjects.

Immunoinflammatory markers. The mean IgE level for subjects with severe asthma was 174 ± 5 IU/mL in black subjects and 85 ± 5 IU/mL in white subjects ($P = .003$). Although there was no difference in the overall prevalence of atopy in the population, black subjects were more likely to have a high number (≥ 5) of positive skin test results compared with white subjects. Blood eosinophil numbers did not differ by race.

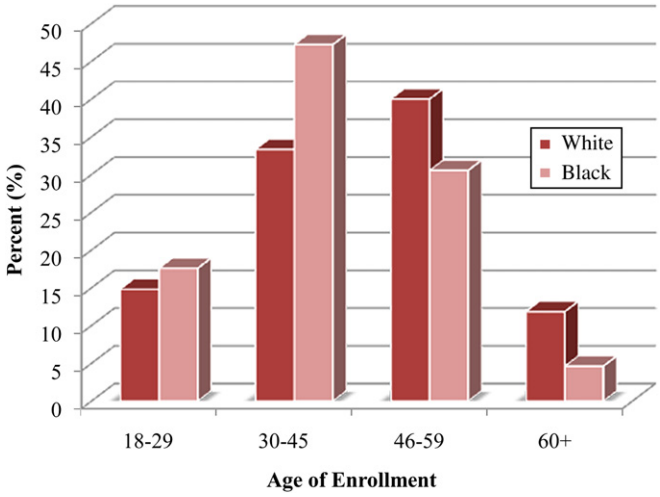


FIG 1. Percentage of black and white participants enrolled into SARP by age at enrollment. Black participants enrolled into SARP at an earlier age compared with white participants ($P = .011$).

Participants younger than 40 years

For more data on participants younger than 40 years, see Table II. Because black subjects had a lower median age at enrollment, a secondary comparison was done between white and black asthmatic subjects enrolled in SARP at older than and younger than 40 years. Even in those younger than 40 years, the mean age at enrollment for black subjects remained slightly (but not significantly) younger compared with that for white subjects (29.6 ± 6.3 and 28.7 ± 6.7, respectively). Similar to the total group, sex did not differ. In contrast to the total dataset, there was no significant difference in employment. Even in the lower age group, BMI remained significantly and substantially higher in black subjects (median, 33.9 kg/m^2; 25th-75th percentile, 30.1-45.0 kg/m^2) than white subjects (median, 27.5 kg/m^2; 25th-75th percentile, 23.8-24.5 kg/m^2). Comorbidities, such as diabetes,

TABLE II. Baseline characteristics of SARP participants who enrolled at less than 40 years of age by racial background and phenotype group

	Both races (n = 518)		Black subjects (n = 162 [31.3%])		White subjects (n = 356 [68.7%])	
	Mild-to-moderate asthma (n = 372)	Severe asthma (n = 146)	Mild-to-moderate asthma (n = 114)	Severe asthma (n = 48)	Mild-to-moderate asthma (n = 258)	Severe asthma (n = 98)
Age at diagnosis (y)	8 (4-16)	5 (1-14)	8 (4-18)	4 (1-15.5)	8 (4-15)	5 (1-13)
Duration of asthma (y)	17.3 (10.6-23.3)	22.6 (14.4-29.2)	18.4 (10.9-23.7)	22.5 (14-27.6)	17.1 (10.6-22.9)	22.6 (15.9-29.2)
BMI (kg/m^2)*	25.9 (22.7-32.4)	30.1 (25-36.5)	28.4 (24.6-36.8)	33.9 (30.1-45)	24.9 (22.2-29)	27.5 (23.8-24.5)
Baseline predrug FEV_1 (L)*	2.99 (2.56-3.58)	2.15 (1.54-2.75)	2.57 (2.20-2.94)	1.91 (1.53-2.23)	3.26 (2.74-3.73)	2.28 (1.65-3.00)
Baseline predrug FEV_1 (% predicted)	89 (78-99)	63 (48-81)	83.5 (75-94)	63 (52.5-80)	91 (80-101)	62.5 (48-81)
Baseline predrug FVC (% predicted)	97.3 (89-105)	81.8 (71-95)	96 (86-104)	82.7 (73-90)	98 (89.2-106)	81.4 (68.3-95)
FEV_1/FVC ratio	0.77 (0.71-0.83)	0.68 (0.55-0.78)	0.75 (0.68-0.82)	0.68 (0.55-0.79)	0.78 (0.72-0.83)	0.64 (0.55-0.78)
Max FEV_1 reversal (%)	9.2 (4.9-17.7)	15.3 (6.7-28.9)	14.1 (6-24.6)	14.6 (6.8-26.8)	8.1 (4.3-14.1)	16.2 (6.5-29.5)
Log IgE (IU/mL)	2.18 (1.79-2.55)	2.18 (1.78-2.59)	2.25 (1.84-2.71)	2.31 (1.74-2.68)	2.12 (1.74-2.49)	2.11 (1.79-2.52)
Atopy	295 (79.3%)	98 (67.1%)	97 (85.1%)	33 (68.8%)	198 (76.7%)	65 (66.3%)
≥5 Positive skin test results	142 (38.2%)	44 (30.1%)	56 (49.1%)	19 (39.6%)	86 (33.3%)	25 (25.5%)
Female sex	255 (68.5%)	94 (64.4%)	79 (69.3%)	34 (70.8%)	176 (68.2%)	60 (61.2%)
Currently employed	220 (59.1%)	91 (62.3%)	74 (64.9%)	28 (58.3%)	146 (56.6%)	63 (64.3%)
Diagnosed diabetes	7 (1.9%)	7 (4.8%)	6 (5.3%)	2 (4.2%)	1 (0.4%)	5 (5.1%)
Diagnosed hypertension	26 (7.0%)	20 (13.7%)	17 (14.9%)	9 (18.8%)	9 (3.5%)	11 (11.2%)
Diagnosed GERD	50 (13.4%)	52 (35.6%)	17 (14.9%)	21 (43.8%)	33 (14%)	31 (31.6%)

Continuous variables are presented as medians (25th-75th percentiles), and categorical variables are presented as numbers (percentages). Mean age: 28.99 ± 6.62 years.
*$P < .15$, black subjects with severe asthma versus white subjects with severe asthma.

hypertension, and gastroesophageal reflux disease (GERD), were not significantly different between races, and most participants were atopic. The median IgE level in black asthmatic subjects was higher compared with that seen in white subjects, but the levels did not differ in the severe asthma subgroup. By using percent predicted values, FEV_1 did not differ across the races; however, the absolute FEV_1 (in liters) was significantly and markedly lower in black subjects (median, 1.91 L; 25th-75th percentile, 1.53-2.23 L) compared with that seen in white subjects (median, 2.28 L; 25th-75th percentile, 1.65-3.00 L), despite black subjects being younger in this subset. There was no difference in bronchodilator reversibility.

Participants 40 years and older

For more information on participants 40 years and older, see Table III. Among older asthmatic subjects, black subjects with severe asthma were both significantly younger and younger at diagnosis than white subjects with severe asthma. Greater than 10% more black subjects with severe asthma were female than white subjects ($P = .07$). Current employment again did not differ among the races. White asthmatic subjects were more likely to report a diagnosis of GERD than black subjects (45% and 33%, respectively), despite the higher BMI in the older black subjects with severe asthma. There were no differences in atopic/allergic markers across the 2 races.

Similar to the younger age group, baseline predrug FEV_1 and FVC percent predicted values and the FEV_1/FVC ratio were significantly higher in black compared with white subjects. The absolute FEV_1 (in liters) did not differ between black and white subjects in this age group but was likely confounded by the higher percentage of female subjects and the lower overall age in the black participants. Bronchodilator reversibility did not differ between the races.

Univariable models

Black participants. In the univariable models for black participants (Table IV), current age and pulmonary function (baseline predrug FEV_1 in liters and baseline predrug FEV_1 percent predicted) were highly associated with asthma severity. BMI, GERD, and current employment were also associated with severe asthma, but no other comorbidity was associated, including exposure to secondhand smoke. Interestingly, the presence (yes/no) and degree (percentages of participants with ≥5 positive allergen skin test results) of atopy were negatively associated with severe asthma, whereas the presence of 2 or more family members with asthma was positively associated. In the univariable analysis IgE levels were not associated with severe asthma in black subjects.

White participants. The results from the white univariable models (Table V) differed substantially from those from the black univariable models. Although current age, BMI, GERD, and pulmonary function (baseline predrug FEV_1 in liters and percent predicted) were statistically significant in these models, in white subjects other comorbidities, such as diabetes and hypertension, were highly associated with asthma severity. However, similar to black subjects, secondhand smoke exposure was not associated. In contrast to black subjects, older age when first given a diagnosis of asthma and increasing degree of bronchodilator responsiveness were also highly associated with asthma severity. Similar to black subjects, the presence and degree of atopy were also negatively predictive of severe asthma. Unlike black subjects, owning a pet was marginally associated with decreased odds for severe asthma in white subjects. Family history of asthma was not associated with asthma severity in white subjects.

Multivariate models

Black participants. For more information on multivariate models in black participants, see Table VI. For every 10%

TABLE III. Baseline characteristics of SARP participants who enrolled at 40 years and older by racial background and phenotype group

	Both races (n = 398)		Black subjects (n = 105 [26.4%])		White subjects (n = 293 [73.4%])	
	Mild-to-moderate asthma (n = 166)	Severe asthma (n = 232)	Mild-to-moderate asthma (n = 45)	Severe asthma (n = 60)	Mild-to-moderate asthma (n = 121)	Severe asthma (n = 172)
Age at diagnosis (y)*	18 (5-36)	20 (5.5-35)	18 (5-35)	13 (3.5-33.5)	18 (6-38)	21 (6.5-35)
Duration of asthma (y)	31.6 (11.2-42.3)	29.9 (15.8-45.3)	25.9 (11.2-39.6)	31.9 (15.3-43.5)	32 (11.2-42.7)	29.4 (16.5-46.4)
BMI (kg/m^2)*	29.1 (25.8-34.9)	30.8 (26-35.2)	32.9 (28.3-38.2)	32.9 (26.9-36.9)	28.4 (24.6-32.9)	30 (25.8-34.3)
Baseline predrug FEV_1 (L)	2.31 (1.81-2.73)	1.74 (1.26-2.26)	1.84 (1.69-2.31)	1.71 (1.30-2.18)	2.45 (2.00-2.89)	1.77 (1.24-2.34)
Baseline predrug FEV_1 (% predicted)*	78 (66-87)	57 (44-75)	73 (57-86)	64.5 (48.5-85.5)	79 (66-88)	56 (42-71)
Baseline predrug FVC (% predicted)*	85 (76-94)	73.6 (60-84)	83 (72.3-91)	79 (66.8-97)	86 (77-94)	72 (58-82)
FEV_1/FVC ratio*	0.73 (0.65-0.78)	0.65 (0.54-0.72)	0.73 (0.64-0.76)	0.67 (0.3-0.72)	0.72 (0.66-0.78)	0.63 (0.53-0.72)
Max FEV_1 reversal (%)	11.5 (7.1-20.2)	13.8 (6.3-24.5)	13.1 (6.8-20.7)	15.4 (7.5-25.7)	11 (7.1-19.4)	13.7 (6-24)
Log IgE (IU/mL)*	1.94 (1.46-2.36)	2.00 (1.44-2.49)	2.14 (1.73-2.64)	2.29 (1.83-2.72)	1.90 (1.43-2.31)	1.93 (1.34-2.36)
Atopy	122 (73.5%)	136 (58.6%)	33 (73.3%)	34 (56.7%)	89 (73.6%)	102 (59.3%)
≥5 Positive skin test results	44 (26.5%)	40 (17.2%)	16 (35.6%)	12 (20%)	28 (23.1%)	28 (16.3%)
Female sex*	107 (64.5%)	148 (63.8%)	30 (66.7%)	44 (73.3%)	77 (63.6%)	104 (60.5%)
Currently employed	125 (75.3%)	144 (62.1%)	30 (66.7%)	33 (55%)	95 (78.5%)	111 (64.5%)
Diagnosed diabetes	12 (7.2%)	31 (13.4%)	3 (6.7%)	9 (15%)	9 (15%)	22 (12.8%)
Diagnosed hypertension	37 (22.3%)	72 (31%)	13 (28.9%)	19 (31.7%)	19 (31.7%)	53 (30.8%)
Diagnosed GERD*	49 (29.5%)	98 (42.4%)	12 (26.7%)	20 (33.3%)	37 (30.6%)	78 (45.3%)

Continuous variables are presented as medians (25th-75th percentiles), and categorical variables are presented as numbers (percentages). Mean age: 51.3 ± 7.86 years.
*$P < .15$, black subjects with severe asthma versus white subjects with severe asthma.

decrease in baseline FEV_1 percent predicted, the odds of having severe asthma increased 40% ($P < .0001$). Although bronchodilator responsiveness was of borderline significance ($P = .058$), the odds for severe asthma decreased by 2%, with an increase of 1% in reversibility after bronchodilator use, suggesting that those black asthmatic subjects with more fixed airflow limitation were at the highest risk of severe asthma.

In contrast to the univariable analysis, IgE was strongly associated with severe asthma in black subjects ($P = .014$). For every $\log_{10}$ increase in IgE level, the risk of severe asthma more than doubled. The odds of having severe asthma also more than doubled for black subjects who had 2 or more family members with diagnoses of asthma ($P = .026$). Despite the association with total IgE levels and family history, having 5 or more positive skin test results to allergens was negatively associated with severe asthma ($P = .05$).

Black subjects with GERD have more than 3 times the odds of having severe asthma compared with black subjects without GERD ($P = .002$). Although employment was marginally associated with severe asthma in the univariable models, it was not significant in the multivariate analyses ($P = .366$).

After adjusting for confounders, baseline predrug FEV_1 percent predicted, GERD, total IgE level, and having 2 or more family members with asthma remained significantly associated with asthma severity. Given the relatively smaller sample size of black participants, lower bronchodilator responsiveness and having less than 5 positive skin test results might also be considered significant in this model.

White participants. For more information on multivariable models in white participants, see Table VII. Similar to black subjects, baseline FEV_1 percent predicted was highly associated with severe asthma, with every 10% decrease in baseline FEV_1 increasing the odds of having severe asthma by 60% ($P < .0001$). Additionally, GERD remained highly associated with severe asthma (doubling the odds of severe asthma, $P = .009$), whereas in contrast to black subjects, diabetes remained marginally associated with asthma severity ($P = .114$).

Current pet ownership decreased the odds of severe asthma by 35% ($P = .05$). In contrast to black subjects with severe asthma, the odds of severe asthma for white participants who had 2 or more family members with diagnoses of asthma decreased by almost half ($P = .05$), and IgE levels (and measures of atopy) did not enter the final model. The final model for white subjects after adjusting for age and site included baseline FEV_1 percent predicted, GERD, lack of current pet ownership, and having no or a weak family history of asthma as positive predictors of asthma severity.

DISCUSSION

In this cross-sectional analysis of more than 900 black and white asthmatic subjects, striking differences were found in the factors associated with severe asthma. Although baseline FEV_1 percent predicted and GERD were important factors for both racial groups, biologic factors, including IgE levels, skin test reactivity, and family history, were distinctly associated with severe asthma in black subjects. Although socioeconomic factors almost certainly affect the high health care use and associated morbidity of asthma in black subjects, the results from this analysis suggest biologic/genetic factors related to atopy/allergy are also of substantial, if not even greater, importance. These results underline the importance of understanding differences in pathobiologic mechanisms driving asthma and its severity in different racial groups.

Asthma has often been described as an atopic disease, with atopy defined as the development of specific IgE in response to environmental allergens. However, the association of allergies with asthma severity has been more difficult to confirm. Indeed, in the initial SARP demographic study, the presence of atopy was a strong negative predictor for severe asthma.[4] Therefore the finding that increasing IgE levels were strongly predictive of severe asthma in black subjects (and not at all in white subjects) was surprising. Although IgE level was not a significant predictor of severity in the univariable model for black subjects ($P = .717$), it became a strong predictor of severity in the multivariate model, suggesting that when numerous confounding factors were

TABLE IV. Univariable logistic regression models for black participants in SARP (n = 267)

Variable	Coefficient	SE	OR	95% CI	G	*P* value
Age of onset	0.006	0.0090	1.01	0.99-1.02	0.45	.503
Age	0.057	0.0119	1.06	1.03-1.08	22.63	<.0001
Female sex	0.176	0.2745	1.19	0.70-2.04	0.41	.521
Center	−0.112	0.0462	0.89	0.82-0.98	5.83	.016
BMI	0.033	0.0142	1.03	1.01-1.06	5.36	.021
Employed	−0.376	0.2559	0.69	0.42-1.13	2.16	.141
Secondhand smoke	−0.205	0.2660	0.82	0.48-1.37	0.59	.442
Pets	0.042	0.3008	1.04	0.58-1.88	0.02	.889
GERD	0.977	0.2865	2.66	1.52-4.66	11.63	.001
Diabetes	0.647	0.4681	1.91	0.76-4.78	1.91	.167
HTN	0.409	0.2988	1.51	0.84-2.70	1.87	.171
FEV_1 (% predicted)	−0.031	0.0066	0.97	0.96-0.98	22.07	<.0001
FEV_1 (L)	−1.397	0.2312	0.25	0.16-0.39	36.54	<.0001
Eosinophils (%)	0.007	0.0351	1.01	0.94-1.08	0.04	.849
Reversal	0.0067	0.0061	1.01	0.995-1.02	1.18	.277
IgE	0.075	0.2077	1.08	0.72-1.62	0.13	.717
≥5 Skin test results	−0.486	0.2843	0.62	0.35-1.07	2.92	.088
Atopy	−1.009	0.2855	0.37	0.21-0.64	12.50	.0004
1 Fam Hx	−0.065	0.3090	0.94	0.51-1.72	0.04	.834
≥2 Fam Hx	0.511	0.3166	1.67	0.90-3.10	2.61	.106

IgE was entered as a continuous log-transformed variable in the model.
OR, Odds ratio; *Age of onset*, age when first given a diagnosis of asthma; *Age*, age when enrolled into SARP; *Center*, clinical center site; *Secondhand smoke*, exposure to secondhand smoke during the day; *Pets*, owns any pets; *HTN*, hypertension diagnosis; *Eosinophils*, eosinophils in the blood; *Reversal*, maximum FEV_1 reversal; *≥5 Skin tests*, 5 or more positive skin test results; *1 Fam Hx*, 1 family member with asthma; *≥2 Fam Hx*, 2 or more family members with asthma.

TABLE V. Univariable logistic regression models for white participants in SARP (n = 649)

Variable	Coefficient	SE	OR	95% CI	G	*P* value
Age of onset	0.015	0.0054	1.02	1.00-1.03	7.61	.006
Age	0.057	0.0067	1.06	1.05-1.07	72.70	<.0001
Female sex	−0.261	0.1656	0.77	0.56-1.07	2.48	.115
Center	−0.138	0.0289	0.87	0.82-0.92	22.68	<.0001
BMI	0.044	0.0115	1.05	1.02-1.07	14.64	.0001
Employed	0.037	0.1660	1.04	0.75-1.44	0.05	.823
Secondhand smoke	0.106	0.1930	1.11	0.76-1.62	0.30	.584
Pets	−0.309	0.1621	0.73	0.53-1.01	3.63	.057
GERD	1.116	0.1827	3.05	2.13-4.37	37.30	<.0001
Diabetes	1.420	0.3793	4.14	1.97-8.70	14.02	.0002
HTN	1.198	0.2319	3.31	2.10-5.22	26.67	<.0001
FEV_1 (% predicted)	−0.066	0.0055	0.94	0.93-0.95	145.77	<.0001
FEV_1 (L)	−1.399	0.1264	0.25	0.19-0.32	122.56	<.0001
Eosinophils (%)	−0.010	0.0304	0.99	0.93-1.05	0.10	.748
Reversal	0.029	0.0055	1.03	1.02-1.04	27.14	<.0001
IgE	−0.124	0.1399	0.88	0.67-1.16	0.79	.374
≥5 Skin test results	−0.488	0.1962	0.61	0.42-0.90	6.17	.013
Atopy	−0.654	0.1734	0.52	0.37-0.73	14.25	.0002
1 Fam Hx	−0.246	0.1874	0.78	0.54-1.13	1.72	.190
≥2 Fam Hx	−0.096	0.2103	0.91	0.60-1.37	0.21	.648

IgE was entered as a continuous log-transformed variable in the model.
OR, Odds ratio; *Age of onset*, age when first given a diagnosis of asthma; *Age*, age when enrolled into SARP; *Center*, clinical center site; *Secondhand smoke*, exposure to secondhand smoke during the day; *Pets*, owns any pets; *HTN*, hypertension diagnosis; *Eosinophils*, eosinophils in the blood; *Reversal*, maximum FEV_1 reversal; *≥5 Skin tests*, 5 or more positive skin test results; *1 Fam Hx*, 1 family member with asthma; *≥2 Fam Hx*, 2 or more family members with asthma.

controlled, IgE remained a predictive variable ($P = .016$). Black asthmatic subjects were again confirmed to have a much higher total IgE level compared with white asthmatic subjects, irrespective of severity. These results extend the findings of Naqvi et al,[18] who demonstrated that higher IgE levels were associated with more severe asthma in black, Mexican, and Puerto Rican patients. However, unlike the study by Naqvi et al, SARP used a rigidly predefined and validated definition of severity that supports the relevance of this biologic difference to disease severity.[4] Naqvi et al used the frequency of symptoms and FEV_1 percent predicted scores to categorize a participant as having moderate-to-severe asthma, whereas SARP requires that a participant be continuously using an oral or high-dose inhaled corticosteroid.

Although IgE level was a significant positive predictor of asthma severity in black subjects, having 5 or more positive skin test results was a significant negative predictor of severe asthma. It is still unclear why 2 measures of atopy have apparently opposing effects on asthma severity within the black SARP population. The serum IgE level, which is a sum of all the circulating systemic IgE, would appear to be measuring something additional to the presence or absence of the 14 specific IgEs measured by means of skin testing in SARP. Interestingly, a subsequent *post hoc* univariate model also did not find a positive skin test result for cockroaches to be associated with severe asthma in black subjects ($P = .60$). Although further pathobiologic studies of this relationship are needed, the data suggest that it might not be the number of positive skin test results but rather the amount of specific IgE made to each or any allergen or the presence of a specific yet unidentified IgE. In future studies the total wheal size to each allergen can also be included in the analyses. Additionally, robust measures of allergen exposure were not included in these studies, which could also contribute to these differences.

A well-known risk factor for asthma is having a first-degree relative with asthma.[21] Atopy and allergy are also known to be contributed to by hereditary/genetic factors. Therefore although it might be expected that family history would be predictive for asthma, studies on the hereditary relationship to severity in specific racial groups (as opposed to presence) have been limited. Perhaps more surprisingly, a reasonably strong family history of asthma in white participants was negatively associated with severe asthma. Given the generally later age of onset in the white participants (especially in those >40 years old), these results suggest that severe asthma in white subjects specifically includes a different nonatopic/allergic, late-onset disease subset/phenotype with less genetic elements, as has been previously identified.[22] This specific subtype/phenotype of severe asthma is not being identified in black subjects either because it is less likely to occur or possibly for socioeconomic related reasons. In any case, studies of black asthmatic populations might be more likely to produce genetic links to severity compared with studies of white populations.

Numerous studies have pointed to the critical role that socioeconomic factors and health disparities play in asthma in the black community. In the current study factors related to SES, including current employment and pet ownership, were not related to severe asthma in black subjects. However, this lack of relationship to SES might be related to the limited data collected in SARP related to SES. As SARP expands, the questionnaires

TABLE VI. Final model with for black participants in SARP (n = 267)

Variable	OR	95% CI	*P* value > |z|
Age	1.06	1.02-1.09	.002
Center	0.93	0.81-1.07	.318
Employed	0.72	0.35-1.48	.366
1 Family history	1.50	0.62-3.60	.367
≥2 Family history	2.79	1.13-6.87	.026
GERD	3.59	1.62-7.97	.002
Baseline FEV_1 (% predicted)	0.96	0.94-0.98	<.0001
Max FEV_1 reversal	0.98	0.96-1.00	.058
IgE	2.12	1.16-3.87	.014
≥5 Positive skin test results	0.46	0.21-1.01	.053

IgE was entered as a continuous log-transformed variable in the model. Values were adjusted for current age (age of SARP enrollment) and clinical center.
OR, Odds ratio; *Age*, age when enrolled into SARP; *Center*, clinical center site; *1 Family history*, 1 family member with asthma; *≥2 Family history*, 2 or more family members with asthma.

TABLE VII. Final model with for white participants in SARP (n = 649)

Variable	OR	95% CI	*P* value > |z|
Age	1.02	1.00-1.04	.046
Center	0.88	0.81-0.95	.001
BMI	1.00	0.98-1.03	.790
Age of onset	1.00	0.99-1.02	.866
1 Family history	0.67	0.42-1.09	.108
2+ Family history	0.57	0.32-1.00	.051
Pets	0.65	0.42-1.00	.051
GERD	1.92	1.18-3.13	.009
Diabetes	2.27	0.82-6.29	.114
Baseline FEV_1 (% predicted)	0.94	0.93-0.95	<.0001

IgE was entered as a continuous log-transformed variable in the model. Values were adjusted for current age (age of SARP enrollment) and clinical center.
OR, odds ratio; *Age*, age when enrolled into SARP; *Center*, clinical center site; *Age of onset*, age when first given a diagnosis of asthma; *1 Family history*, 1 family member with asthma; *≥2 Family history*, 2 or more family members with asthma; *Pets*, own any pets.

have added educational, marital status, and zip code, which should improve the ability to assess the role of SES in the severity of asthma. Interestingly, although employment status was not associated with severity in either black or white subjects, as has been noted previously, pet ownership was associated with protection from severe asthma in white subjects.[23] Black participants in SARP, in general, had significantly lower pet ownership than white subjects in SARP. It is unclear whether increasing pet ownership would improve asthma outcomes in black subjects (as seen in white subjects), even without substantial changes in SES, but this requires further study.

Univariable models revealed that comorbidities were highly associated ($P < .0001$) with asthma severity in white subjects. This association was much less in black subjects, except for GERD, which, as previously shown in SARP, continued to be a positive predictor of severity for both black and white subjects. In contrast, hypertension and diabetes were highly significant predictors for white but not black subjects, despite their higher prevalence in black compared with white subjects in the general population. It can be hypothesized that asthma itself might be affecting black subjects much more than white subjects, such that the severity of the asthma could be masking the effects of other diseases. Black subjects might be focusing on the most severe ailments, whereas other diseases might not yet be diagnosed. Black subjects might have received diagnoses of asthma at younger ages because of a better pediatric medical safety net or because black babies with asthma are substantially sicker than white babies with asthma. As they age, black subjects might not be going to the doctor regularly to get full checkups, which would allow diagnosis of comorbidities, such as diabetes. In support of this, black subjects with severe asthma reported lower percentages of diagnosed diabetes and hypertension compared with white subjects, whereas black subjects with mild-to-moderate asthma reported diabetes and hypertension twice as often as their white counterparts. Exposure to tobacco smoke has also been shown to increase the prevalence and severity of asthma. In a cohort of adult nonsmoking asthmatic subjects, adults exposed to secondhand smoke at baseline had higher asthma severity scores compared with those without tobacco smoke exposure.[24] However, in SARP secondhand smoke was not a significant predictor of asthma severity for either race and was therefore not included within the final predictor model for both races.

A lower baseline predrug FEV_1 value is well recognized as a predictor of severe asthma.[3,20,25] In this study the odds of severe asthma increased by 40% and 60% for black and white subjects, respectively, for every 10% decrease in FEV_1 percent predicted. Although we used FEV_1 percent predicted in the models, there are also striking differences in the absolute FEV_1 (in liters) in black compared with white subjects, which are "corrected" by the Hankinson equations used in SARP lung function testing. When racially corrected (and age/sex corrected), the mean/median FEV_1 percent predicted is higher in black compared with white subjects. However, the absolute FEV_1 is significantly lower compared with that seen in white subjects, despite the younger age of the black asthmatic subjects. Hankinson equations for FEV_1 percentages were built on disproportionate sample sizes among black compared with white subjects. White participants are equally distributed throughout the age groups, whereas after the age of 50 years, the number of black participants drastically decreases compared with the number of younger black participants.[25] As a black participant ages beyond the age of 50 years, the accuracy of the Hankinson equations might not be as valid as they are for the younger black participants. Furthermore, recent genetic studies suggest that being identified as "black" in America is accompanied by a wide range of genetic racial admixture, ranging from 100% African ancestry to 10% or less, such that predictive equations for "black" subjects might not apply to all "black" participants.[26] In any case measuring lung function by FEV_1 percent predicted could easily overestimate the lung capacity of many black patients and lead to underrecognition of the severity of the disease.

In addition to FEV_1 percent predicted, maximum bronchodilator responsiveness was marginally associated with asthma severity in black subjects. However, for every percentage increase in bronchodilator responsiveness, the odds for severe asthma decreased by 2%. The reasons for this inverse relationship are not clear but suggest that as asthma worsens in black subjects, the airways might stiffen/remodel such that the most commonly used treatment for asthma (β-agonists) becomes less effective. Whether these findings suggest a mechanism for the recent findings regarding increased severe asthma exacerbations and deaths in black subjects taking long-acting β-agonists remains to be determined.[27]

This study is not without limitations, certainly the biggest of which is the cross-sectional study design. It is difficult to

confirm a temporal relationship in regard to severity and the variables of interest. Another limitation is the sample size differences for each race. The white SARP population consisted of more than 70% of the data in this analysis, whereas less than 30% of the data are from the black SARP population. Having populations of similar sizes would aid in confirming the results from this study and possibly reveal stronger associations between predictors and severe asthma. Although the SARP database is one of the most extensive databases of asthmatic subjects from numerous geographic sites and includes the collection of lung inflammatory markers, such as sputum eosinophil numbers, sputum induction was only performed on about 50% of the population. Therefore sputum measures could not be used. However, genome-wide association data and longitudinal participant information are being added to the database, enabling even more complete studies on asthma severity in the future.

In conclusion, distinctly different factors appear to be associated with rigidly defined severity of asthma in black compared with white subjects with allergic markers and strong family history, much stronger positive predictors of severity for black subjects than for white subjects. Thus in addition to socioeconomic factors, studies that incorporate comprehensive evaluation of biologic and genetic factors of relevance to asthma in black subjects in particular might lead to the development of targeted therapies that improve overall asthma outcomes in the black population.

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Key message

- **Severe asthma in black subjects is strongly associated with traditional markers of allergic and genetic patterns of disease. These same patterns are not seen in white subjects.**

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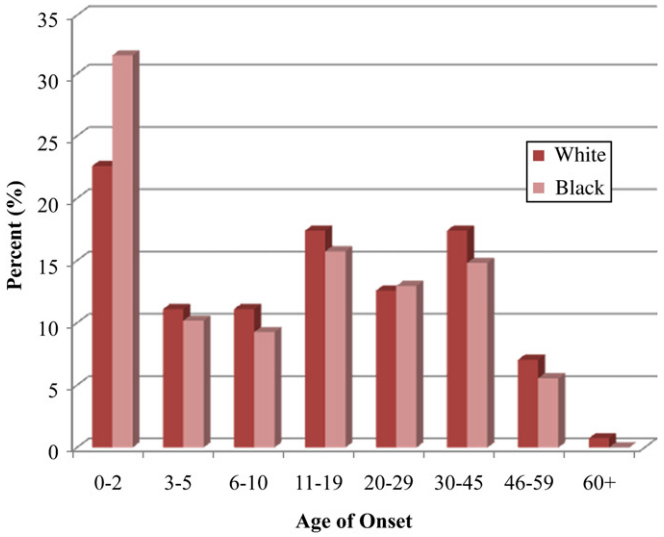


FIG E1. Percentage of the black and white population given a diagnosis of asthma. Black participants are given diagnoses of asthma at a younger age compared with white participants.