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Obesity and Bronchodilator Response in Black and Hispanic Children and Adolescents With Asthma

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BACKGROUND: Obesity is associated with poor asthma control, increased asthma morbidity, and decreased response to inhaled corticosteroids. We hypothesized that obesity would be associated with decreased bronchodilator responsiveness in children and adolescents with asthma. In addition, we hypothesized that subjects who were obese and unresponsive to bronchodilator would have worse asthma control and would require more asthma controller medications.

METHODS: In the Study of African Americans, Asthma, Genes, and Environments (SAGE II) and the Genes-environments and Admixture in Latino Americans (GALA II) study, two identical, parallel, case-control studies of asthma, we examined the association between obesity and bronchodilator response in 2,963 black and Latino subjects enrolled from 2008 to 2013 using multivariable logistic regression. Using bronchodilator responsiveness, we compared asthma symptoms, controller medication usage, and asthma exacerbations between nonobese ($<$ 95th% BMI) and obese ($\geq$ 95th% BMI) subjects.

RESULTS: The odds of being bronchodilator unresponsive were 24% (OR, 1.24; 95% CI, 1.03-1.49) higher among obese children and adolescents compared with their not obese counterparts after adjustment for age, race/ethnicity, sex, recruitment site, baseline lung function (FEV_1/FVC), and controller medication. Bronchodilator-unresponsive obese subjects were more likely to report wheezing (OR, 1.38; 95% CI, 1.13-1.70), being awakened at night (OR, 1.34; 95% CI, 1.09-1.65), using leukotriene receptor inhibitors (OR, 1.33; 95% CI, 1.05-1.70), and using inhaled corticosteroid with long-acting β_2-agonist (OR, 1.37; 95% CI, 1.05-1.78) than were their nonobese counterpart. These associations were not seen in the bronchodilator-responsive group.

CONCLUSIONS: Obesity is associated with bronchodilator unresponsiveness among black and Latino children and adolescents with asthma. The findings on obesity and bronchodilator unresponsiveness represent a unique opportunity to identify factors affecting asthma control in blacks and Latinos.

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ABBREVIATIONS: GALA II = Genes-environments and Admixture in Latino Americans; SAGE II = Study of African Americans, Asthma, Genes, and Environments

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Obesity and asthma are common childhood diseases in the United States that carry significant morbidity. Obesity is at epidemic proportions in the United States; almost one-third of children and adolescents are overweight or obese.[1-3] In obese children, there is an increased incidence of asthma.[4,5] Obesity creates a proinflammatory state, which worsens airway inflammation and subsequently leads to airway hyperreactivity in asthma.[6] Obesity is associated with poor asthma control,[7,8] increased asthma symptoms,[8,9] and a decreased response to asthma controller medications.[10-13]

Asthma is characterized by chronic inflammation of the lower airways, with bronchial hyperreactivity leading to airflow obstruction.[4] This condition is acutely treated with a short-acting β_2-agonist, such as albuterol, which relaxes the smooth muscles in the airways, resulting in bronchodilation and acute relief of asthma symptoms. Depending on the severity of the asthma symptoms and exacerbations, asthma is controlled in a step-up or step-down manner with daily medications such as leukotriene receptor inhibitors, inhaled corticosteroids, and combination inhaled corticosteroids with long-acting β_2-agonist.[14] The bronchodilator response is measured via spirometry and is the change in FEV_1 after albuterol administration. The bronchodilator response is used in the diagnosis of asthma, to assess the degree of airway obstruction reversibility, and to assist with therapeutic decisions. Not every child with asthma responds to albuterol; a child is considered bronchodilator unresponsive if there is a $<12\%$ increase and a <200 mL increase in FVC and/or FEV_1.[14,15] The association between bronchodilator response and obesity has not been studied in minority children.

Because obesity is associated with poor asthma outcomes, we hypothesized that obese children and adolescents would have decreased bronchodilator responsiveness to albuterol compared with nonobese children and adolescents. We then sought to understand whether children and adolescents who were obese and bronchodilator unresponsive had clinical differences in their asthma. We hypothesized that children and adolescents who were obese and bronchodilator unresponsive would have worse asthma control, as measured through asthma symptoms and exacerbations, and would be more likely to be on asthma controller medications.

Materials and Methods

Study Design

We performed a cross-sectional study of the association of bronchodilator responsiveness in obese compared with nonobese children and adolescents with asthma. The subjects were from the Study of African Americans, Asthma, Genes, and Environments (SAGE II) ($n = 867$) and the Genes-environments and Admixture in Latino Americans (GALA II) study ($n = 2{,}096$), which are two identical, parallel, case-control studies of asthma in black and Latino Americans, respectively. SAGE II recruited black subjects from the San Francisco Bay area. GALA II recruited Latino subjects from Puerto Rico and mainland United States (Bronx, New York; Chicago, Illinois; Houston, Texas; and San Francisco Bay Area, California). We included subjects with asthma who were between 8 and 21 years of age who underwent spirometry and were enrolled from 2008 to 2013. Asthma was defined as physician-diagnosed asthma with two or more asthma symptoms and the use of asthma-related medication during the 2 years before enrollment. Subjects were ineligible if they were pregnant, had other lung disease or chronic illness (other than atopy or allergy-related diseases), were current smokers, or had a >10 pack-year smoking history. Subjects were recruited from medical clinics and the community. Written, age-appropriate informed consent/assent was obtained from all subjects and their legal guardians. This study was conducted in accordance with the amended Declaration of Helsinki and local institutional review boards approved the protocol (Kaiser Northern California: CN-05HFarb-01-H, CN-07EBrig-01-H; Albert Einstein College of Medicine: 2005-032; Baylor College of Medicine: H-22861; Centro de Neumologia Pediatrica: 1073894; Children's Hospital Oakland: 2009-017; Children's Memorial Hospital: 2008-13531; and Northwestern University: CR1_STU00008687).

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BMI Percentile

Weight was measured using a calibrated scale. Height was measured at the study visit with the subject not wearing his or her shoes, with feet together and standing as tall as possible using a calibrated stadiometer. The measurements of weight and height were used to calculate BMI percentiles using sex- and age-specific curves for each participant at the study visit.[16] BMI categories were defined according to the Centers for Disease Control and Prevention Growth Chart as underweight (BMI < fifth percentile), normal weight (BMI between fifth and 85th percentile), overweight (BMI between 85th and 95th percentile), and obese (BMI ≥ 95th percentile). We conducted a sensitivity analysis comparing the CDC categories and found that subjects in the underweight, normal-weight, and overweight groups had the same distribution of bronchodilator responsiveness (P value for $\chi^2 = .9$), and thus, these categories were combined into a nonobese category. Consistent with prior studies, all comparisons were made between the nonobese (BMI < 95th percentile) and obese (BMI ≥ 95th percentile) groups.[17-21]

Bronchodilator Response

Spirometry was performed according to the American Thoracic Society guidelines to measure pulmonary function before albuterol administration and then repeated 15 min after administration of four puffs of albuterol (90 μg per puff).[22] Spirometry was repeated a third time after a second dosage of albuterol (two puffs if < 16 years old or four puffs if ≥ 16 years old). All asthma medications were held for 12 h before spirometry. Predicted pulmonary function was calculated based on Hankinson's formulas.[23] We assessed the maximal bronchodilator response by measuring the percentage change in measured FEV_1 before and after albuterol administration, using the postalbuterol spirometry with the maximal change. A positive bronchodilator response was defined as a ≥ 12% increase and a ≥ 200-mL increase in FEV_1[15]; otherwise, the subject was considered bronchodilator unresponsive.

Data Ascertainment

Trained interviewers fluent in English and Spanish administered questionnaires to subjects and their guardians to collect demographics and medical history. Age was collected as a continuous variable. Sex was specified as male or female. Race/ethnicity was reported for the subject, the parents, and both sets of grandparents and was specified as black, Puerto Rican, Mexican, mixed Latino, and other Latino. In SAGE II, the subject and all parents/grandparents must self-identify as black or African-American. In GALA II, the subject and all parents/grandparents must self-identify as Spanish, Hispanic, or Latino.

Subjects and guardians reported medication use over the past year by either naming their medication or by identifying their asthma medication from pictures. Controller medications were categorized into three classes: leukotriene receptor inhibitors, inhaled corticosteroids, and inhaled corticosteroids with a long-acting β_2-agonist. In addition, controller medications were dichotomized to "any medication use" or "none," regardless of class. Asthma symptoms over the previous week were self-reported as shortness of breath, wheezing, nighttime awakening because of asthma, and activity limitation because of asthma. Asthma exacerbations were self-reported and were classified as oral corticosteroid use in the past year, ED visits in the past year, lifetime hospitalizations, and ICU admissions for status asthmaticus. Controller medications, asthma symptoms, and exacerbation variables were specified as yes/no. Baseline lung function was considered FEV_1/FVC. Additional covariates considered as potential confounders were total serum IgE level (ImmunoCAP 100; Phadia), secondhand smoke exposure, maternal education level, and family income.

A total of 3,134 subjects with asthma were included from the SAGE II and GALA II study; 171 subjects were excluded because their spirometry did not meet the quality control standards. The final study sample consisted of 2,963 subjects.

Statistical Analysis

Descriptive statistics were calculated for all covariates according to obesity using χ^2 analysis for categorical covariates and the Student t test or Mann-Whitney test for continuous covariates. Multivariable logistic regression models were used to quantify the association between obesity and bronchodilator response with the bronchodilator-unresponsive group as the referent group. The following covariates were included in our model as confounders: age, sex, race/ethnicity, and site of recruitment. We examined additional covariates as potential confounders: baseline lung function (FEV_1/FVC), any asthma controller medication use, specific classes of asthma medications, total serum IgE level, secondhand smoke exposure, maternal education level, and family income. However, only baseline lung function (FEV_1/FVC) and use of any asthma controller medication resulted in a ≥ 10% change in the OR, and thus, were included in the analysis. For the analysis of medication use, symptoms, and exacerbations, obese and nonobese groups were compared using multivariable logistic regression stratified by bronchodilator responsiveness, with the nonobese group as the referent group. We adjusted for the same covariates as mentioned previously. A two-tailed P value < .05 was considered statistically significant. Data analysis was performed using Stata version 12.1 (StataCorp LP).

Results

Characteristics of Study Population

In our study, 36% of the subjects were obese, with a slightly lower prevalence of obesity in girls than in boys (35.0% vs 36.8%) (Table 1). Obese and nonobese subjects had a similar median age of 12.6 (interquartile range, 5.8) and 12.7 (interquartile range, 5.3) years old, respectively. Obesity was more common in Mexicans and mixed/other Latinos, whereas blacks and Puerto Ricans had the lowest prevalence of obesity. Subjects recruited from New York, Texas, and Chicago were more likely to be obese than were those from San Francisco Bay Area and Puerto Rico. Obese and nonobese subjects had normal mean lung function (FVC, FEV_1, and FEV_1/FVC) although means were higher among obese subjects. In analyses not shown, bronchodilator-responsive subjects (31.9%) had a mean FEV_1/FVC of 0.80, which was lower than that of bronchodilator-unresponsive subjects (68.1%), who had a mean FEV_1/FVC of 0.87. In addition, bronchodilator-responsive subjects had a higher maximal bronchodilator response (19.0%) than did bronchodilator-unresponsive subjects (6.3%).

Bronchodilator Response and Obesity

In the unadjusted analysis, obesity was not associated with bronchodilator response (OR, 1.03; 95% CI, 0.87-1.21) (Table 2). However, after adjustment for age, sex, race/ethnicity, site of recruitment, baseline lung function (FEV_1/FVC), and use of controller asthma medication, we found that the odds of being bronchodilator unresponsive were 24% (OR, 1.24; 95% CI, 1.03-1.49) greater among obese children and adolescents than among their nonobese counterparts.

TABLE 1] Characteristics of Subjects by Obesity Status Among Children and Adolescents Enrolled in the GALA II Study and SAGE II: 2008-2013

Characteristic	Nonobese (BMI < 95th Percentile)	Obese (BMI ≥ 95th Percentile)	*P* Value[a]
Number	1,897 (64.0)	1,066 (36.0)	…
Age, median (interquartile range), y	12.7 (5.8)	12.6 (5.3)	.09
Sex			.3
Male	999 (63.2)	582 (36.8)	
Female	898 (65.0)	484 (35.0)	
Race/ethnicity			< .001
Black	573 (66.1)	294 (33.9)	
Mexican	399 (58.1)	288 (41.9)	
Puerto Rican	678 (69.6)	296 (30.4)	
Mixed/other Latino	247 (56.8)	188 (43.2)	
Center of recruitment			< .001
Chicago	188 (60.3)	124 (39.7)	
New York	153 (51.2)	146 (48.8)	
Puerto Rico	609 (71.5)	243 (28.5)	
San Francisco	827 (64.1)	463 (35.9)	
Texas	120 (57.1)	90 (42.9)	
Spirometry, mean (SD)			
FVC % predicted	95.8 (15.0)	102.1 (16.4)	< .001
FEV_1% predicted	92.5 (14.9)	96.4 (16.7)	< .001
FEV_1/FVC	0.881 (0.016)	0.879 (0.015)	.02
Maximal bronchodilator response	10.5 (8.4)	10.2 (9.0)	.5
Controller medication	1,076 (62.6)	673 (37.4)	.001
Total IgE > 100 IU/mL	1,143 (65.4)	646 (34.6)	.5

Data are presented as No. (%) unless indicated otherwise. GALA II = Genes-environments and Admixture in Latino Americans; SAGE II = Study of African Americans, Asthma, Genes, and Environments.
[a]For χ^2 statistics (categorical variables) and Student *t* tests or Mann-Whitney *U* tests (continuous variables).

Asthma Controller Medication Prescriptions

We examined how asthma controller medication use differed between obese and nonobese subjects when stratified by bronchodilator responsiveness (Table 3). After controlling for age, sex, race/ethnicity, recruitment site, and baseline lung function, obese subjects were 33% (OR, 1.33; 95% CI, 1.05-1.70) more likely to be prescribed leukotriene receptor inhibitors than were nonobese subjects in the bronchodilator-unresponsive group. Obese subjects were 37% (OR, 1.37; 95% CI, 1.05-1.78) more likely to be on an inhaled corticosteroid with long-acting β_2-agonist than were nonobese subjects in the bronchodilator-unresponsive group. There was no statistically significant association between inhaled corticosteroid prescriptions and obesity status in the bronchodilator-unresponsive group. No statistically significant association was observed between controller medication prescriptions and obesity status in the bronchodilator-responsive group.

Asthma Symptoms and Exacerbations

To determine whether there was a difference in asthma control, we examined the association of asthma symptoms and exacerbations with obesity status stratified according to bronchodilator responsiveness (Table 3). Obese subjects were 38% (OR, 1.38; 95% CI, 1.13-1.70) more likely to report wheezing than were nonobese subjects in the bronchodilator-unresponsive group after controlling for age, sex, race/ethnicity, baseline lung function, recruitment site, and controller medications. In addition, obese subjects were 34% (OR, 1.34; 95% CI, 1.09-1.65) more likely to report being awakened at night by their asthma symptoms than were nonobese subjects in the bronchodilator-unresponsive group. There was no statistically significant association between asthma symptoms and obesity status in the bronchodilator-responsive group. Moreover, there was no statistically significant association between asthma exacerbations (oral corticosteroid use, ED visits, hospitalizations, or

TABLE 2] Adjusted OR for the Association Between Bronchodilator Response and Obesity, Including the Covariates Included in the Model, Among Children and Adolescents Enrolled in the GALA II Study and SAGE II: 2008-2013

Characteristic	OR (95% CI)	*P* Value
Obese (vs nonobese)	1.24 (1.03-1.50)	.025
Covariates		
Sex	1.38 (1.13-1.63)	.001
Age	1.08 (1.05-1.11)	< .001
Baseline lung function	1.16 (1.14-1.17)	< .001
Race/ethnicity		
Mexican	1.00	…
Puerto Rican	0.63 (0.39-1.03)	.06
Mixed/other Latino	0.63 (0.45-0.89)	.008
Black	0.71 (0.50-0.99)	.04
Controller medication	0.84 (0.70-1.02)	.08
Recruitment site		
Texas	1.00	…
Illinois	1.62 (1.03-2.52)	.04
New York	1.48 (0.92-2.38)	.1
Puerto Rico	0.45 (0.25-0.80)	.007
California	1.61 (1.06-2.45)	.03

Adjusted for age, sex, race/ethnicity, recruitment site, baseline lung function, and controller medication use. See Table 1 legend for expansion of abbreviations.

ICU admissions) and obesity status regardless of bronchodilator responsive status.

Discussion

In this large cross-sectional study of minority children and adolescents with asthma, we found that, after adjusting for other factors that influence bronchodilator response, obese subjects were less likely to respond to bronchodilators than were nonobese subjects. We also found that among the bronchodilator-unresponsive group, obese subjects had worse asthma control and increased asthma morbidity than did nonobese subjects: they were more likely to report wheezing and being awakened at night from their asthma and more likely to be prescribed leukotriene receptor inhibitors and inhaled corticosteroids with long-acting β_2-agonists. However, these associations were not observed in the bronchodilator-responsive subjects.

This is the first study, to our knowledge, to show a negative association between obesity and bronchodilator responsiveness in minority children and adolescents. Our finding is consistent with that of a previous study that showed decreased bronchodilator response with increased BMI in a primarily non-Hispanic white population.[24] Similarly, other studies have shown that obese children have a decreased drug response to inhaled corticosteroids.[10-13] The finding that obese children and adolescents who are bronchodilator unresponsive have worse asthma control and increased asthma morbidity is also consistent with the findings of prior studies showing that obese children have worse asthma control,[7,8] are more symptomatic,[8,9] and have increased asthma severity[1] than do nonobese children.

There is limited understanding of why some subjects with asthma are bronchodilator responsive and others are not. Patients with well-controlled asthma will have a decreased bronchodilator response and can be bronchodilator unresponsive. However, in this study, bronchodilator-unresponsive, obese subjects were less likely to have well-controlled asthma than were their nonobese counterparts, despite being more likely to be on asthma controller medications. Patients who are given a misdiagnosis of asthma may be bronchodilator unresponsive; however, obese and nonobese patients are equally likely to be given a misdiagnosis.[25] In addition, bronchodilator response is partially dependent on the amount of airway inflammation present.[26] Obesity has been associated with elevated inflammatory biomarkers such as IL-6, IL-1β, and transforming growth factor-β1.[27,28] These same inflammatory biomarkers are also increased in asthma.[29] Hence, it is possible that the airways in obese patients have increased inflammation, reducing their response to β-agonists, although further studies are needed to prove this relationship.

This study was a cross-sectional analysis of cases from two case-control studies. Therefore, it cannot establish a causal relationship between obesity and bronchodilator unresponsiveness. However, to the best of our knowledge, this study is the first, to our knowledge, to describe an association between obesity and bronchodilator response in minority children and adolescents. Further longitudinal interventional studies and analyses will be needed to determine causality and biologic mechanisms. Because of the design of the study, we cannot determine if some subjects were over- or undertreated for their asthma. In this study, medication adherence was not measured; we relied on self-report of medication usage, asthma symptoms, and exacerbations, which may introduce recall bias. Overreporting of asthma symptoms, medication usage, and exacerbations would bias the results toward the null. This may explain why no difference in asthma exacerbations was detected.

TABLE 3] Adjusted ORs for the Association of Obesity (Obese vs Nonobese) With Asthma Controller Medication, Asthma Symptoms, and Asthma Exacerbations According to Bronchodilator-Responsive Status Among Children and Adolescents Enrolled in the GALA II Study and SAGE II: 2008-2013

	Bronchodilator Responsive		Bronchodilator Unresponsive	
Characteristic	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Controller medications[a]				
Inhaled corticosteroid	1.21 (0.90-1.62)	.2	1.14 (0.93-1.39)	.2
Leukotriene receptor inhibitor	1.18 (0.86-1.61)	.3	1.33 (1.05-1.70)	.02
Inhaled corticosteroid/long-acting β_2-agonist	1.27 (0.86-1.76)	.3	1.37 (1.05-1.78)	.02
Asthma symptoms[b]				
Wheezing	1.16 (0.87-1.54)	.3	1.38 (1.13-1.70)	.002
Short of breath	1.07 (0.81-1.42)	.6	1.11 (0.91-1.35)	.3
Limited activity	1.14 (0.85-1.52)	.4	1.14 (0.85-1.52)	.4
Awakened	1.14 (0.85-1.51)	.4	1.34 (1.09-1.65)	.005
Asthma exacerbations[b]				
Oral corticosteroids	1.14 (0.69-1.89)	.6	1.23 (0.79-1.91)	.4
ED	1.09 (0.81-1.47)	.6	0.93 (0.76-1.14)	.5
Hospitalizations	0.83 (0.63-1.20)	.2	1.03 (0.84-1.25)	.8
ICU admission	0.72 (0.46-1.10)	.1	1.30 (0.93-1.81)	.1

See Table 1 legend for expansion of abbreviations.
[a]Adjusted for sex, age, race/ethnicity, recruitment site, and baseline lung function.
[b]Adjusted for sex, age, race/ethnicity, recruitment site, baseline lung function, and controller medication use.

Some of the reports of nighttime awakening may have been from OSA; however, information about OSA was not collected.

Despite these limitations, the study benefits from having a large and diverse sample of subjects from throughout the United States and Puerto Rico, including multiple racial and ethnic subgroups. However, the results may not apply to other racial/ethnic populations. Moreover, these findings have potential clinical implications for black and Latino children, particularly because these groups have more severe asthma morbidity and mortality than do white children, but are understudied.[30-34] Variations in asthma prevalence and morbidity among different racial/ethnic populations suggest that asthma is a heterogeneous disease with varied risk profiles; this emphasizes the importance of studying diverse populations.

Obese children and adolescents who are bronchodilator unresponsive represent a unique pediatric asthma population. This group does not respond to albuterol, the most commonly used asthma medication. Obese bronchodilator-unresponsive patients have increased morbidity from their asthma symptoms, which results in missed days from school and decreased quality of life.[35] This group requires increased levels of asthma controller medications, which carry a substantial financial burden.[36] This bronchodilator-unresponsive obese phenotype is likely to become more common given the rising rates of obesity and the high prevalence of asthma during childhood,[1-3] which is important from a public health perspective. Longitudinal studies are needed to determine whether weight reduction could alter bronchodilator response and reduce morbidity. The mechanisms of how obesity affects bronchodilator response will give us further insight into the complex mechanisms of asthma development and may result in novel therapies.

Conclusions

Obesity is associated with bronchodilator unresponsiveness among black and Latino children and adolescents with asthma. Children and adolescents who are obese and bronchodilator unresponsive have increased asthma morbidity caused by symptoms despite increased controller medication prescriptions. This group represents a unique opportunity to study the characteristics associated with uncontrolled asthma in a minority pediatric population who exhibit a high burden of obesity and asthma.

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