

Lower Bronchodilator Responsiveness in Puerto Rican than in Mexican Subjects with Asthma

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In the United States, Puerto Ricans and Mexicans have the highest and lowest asthma prevalence, morbidity, and mortality, respectively. To determine whether ethnicity-specific differences in therapeutic response, clinical response, and/or genetic factors contribute to differences in asthma outcomes, we compared asthma-related clinical characteristics among 684 Mexican and Puerto Rican individuals with asthma recruited from San Francisco, New York City, Puerto Rico, and Mexico City. Puerto Ricans with asthma had reduced lung function, greater morbidity, and longer asthma duration than did Mexicans with asthma. Bronchodilator responsiveness, measured as percentage change from baseline FEV₁, was significantly lower among Puerto Ricans with asthma than among Mexicans with asthma. Puerto Ricans with asthma had on average 7.3% (95% confidence interval [CI], 4.6 to 9.9; $p < 0.001$) lower bronchodilator reversibility in FEV₁, higher risk of an emergency department visit in the previous year (odds ratio, 2.63; 95% CI, 1.6 to 4.3; $p < 0.001$), and of previous hospitalization for asthma (odds ratio, 1.94; 95% CI, 1.2 to 3.2; $p = 0.009$) than Mexicans. Subgroup analysis corroborated that Puerto Ricans with asthma had more severe disease than did Mexicans on the basis of lung function measurements, responsiveness to β_2 -adrenergic agonists, and health care use. We conclude that Puerto Ricans with asthma respond less to albuterol than do Mexicans with asthma. These findings underscore the need for additional research on racial/ethnic differences in asthma morbidity and response to therapy.

Keywords: asthma; bronchodilator; clinical characteristics; Mexicans and Puerto Ricans

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Studies of racial/ethnic health disparities often define populations based on U.S. census definitions, which categorize Latinos as a single ethnic group. Latinos are the largest minority population in the United States, and Latino children represent the largest demographic group of all U.S. children (1). Although the terms “Hispanic” and “Latino” American describe a common language and cultural heritage, these terms do not refer to race, uniform ethnicity, or a common genetic background. The two largest Latino ethnic groups in the United States, Mexicans (63%) and Puerto Ricans (11%) (1), are genetically complex and composed of various proportions of Native American, African, and European genetic origins (2). The relative ancestral contributions to the contemporary Latino gene pool make each Latino ethnic group genetically unique (2).

U.S. vital statistics of asthma suggest that asthma prevalence, morbidity, and mortality are higher among Puerto Ricans and lower among Mexicans, for a total fourfold difference in asthma burden between these two ethnic groups (3, 4). This discrepancy in asthma burden, as well as the paucity of studies of asthma in Latinos and especially among different Latino ethnic groups, has led the American Academy of Pediatrics to identify asthma among Latinos as an urgent priority for further research (5). There are many potential explanations for the observed differences in asthma burden between Mexicans and Puerto Ricans in the United States, including environmental (6) and socioeconomic factors (7, 8). However, some of these differences in asthma burden may also result from genetic differences among Latino ethnic groups. The Genetics of Asthma in Latino Americans (GALA) Study is an ongoing multicenter international collaborative effort designed to identify and directly compare clinical and genetic risk factors associated with asthma and asthma severity among Puerto Ricans and Mexicans.

In this report, we compare the clinical and spirometric characteristics among Mexican and Puerto Rican subjects with asthma to determine whether any differences in known risk factors for asthma account for the differences in disease burden in these two ethnic groups. Specifically, we compared the clinical characteristics, baseline spirometry, bronchodilator responsiveness, and health care utilization between Puerto Rican and Mexican subjects with asthma recruited from the continental United States, Puerto Rico, and Mexico.

METHODS

Study Participants

Subjects with asthma and their biological parents were enrolled over a 4-year period in the San Francisco Bay Area, California (SF); New York City, New York (NY); Puerto Rico (PR); and Mexico City, Mexico (MX). Investigators recruited subjects from community schools, clinics,

and hospitals that cared for Latino populations. In all health care centers, medical records were reviewed to identify patients with physician-diagnosed asthma, who then were contacted to participate in the study. Subjects with asthma between the ages of 8 and 40 years, with physician-diagnosed asthma and two or more asthma symptoms (among wheezing, coughing, and shortness of breath) in the last 2 years, were eligible to participate. Our goal was to recruit equal proportions of subjects with mild and moderate–severe asthma as defined by the study protocol (*see below*). Only subjects with asthma classified as mild or moderate–severe according to the study protocol were included in this analysis comparing subjects of Puerto Rican ethnicity with subjects of Mexican ethnicity. Local institutional review boards, school boards, and clinics approved the study. Recruitment was standardized across all clinical centers. Bilingual and bicultural physicians specialized in asthma were present at all interviews. All forms and questionnaires for subjects were available in English and Spanish. Although questionnaires at each recruitment site were identical, culturally and linguistically competent recruiters interviewed all subjects to account for differences in local Spanish dialects.

Classification of Latino Ethnicity

Ethnicity was self-reported and ascertained by standardized questions. Both biological parents and all biological grandparents had to identify themselves as either of Puerto Rican ethnicity (for the NY and PR sites) or Mexican ethnicity (for the SF and MX sites) for the subject with asthma to be enrolled in the study. Families with mixed ethnic backgrounds were excluded.

Asthma and Medical Questionnaire

A trained interviewer administered a modified version of the 1978 American Thoracic Society–Division of Lung Diseases Epidemiology Questionnaire (9), which was modified to assess the frequency and duration of asthma and allergy symptoms. Questionnaires were available in Spanish and English.

Pulmonary Function Tests

Subjects with asthma were instructed to withhold their bronchodilator medications for at least 8 hours before spirometry. Spirometry was performed in the sitting position according to standards established by the American Thoracic Society (10) and the Asthma Clinical Research Network (11). Albuterol was administered through a spacer device from a standard metered dose inhaler: 180 μ g (two puffs) for subjects less than 16 years old, and 360 μ g (four puffs) for subjects 16 years old or older. Bronchodilator responsiveness to albuterol is reported as the percent change in FEV₁ after albuterol administration (post-FEV₁ in liters minus pre-FEV₁ in liters, times 100, divided by pre-FEV₁ in liters; *see* Table 2), and as absolute values (Table E1; *see* the online supplement). Pulmonary function tests are expressed as a percentage of the predicted normal value, using age-adjusted prediction equations from Hankinson and colleagues derived from healthy Mexican-American nonsmokers (12).

Asthma Severity

Classification of asthma severity is described in detail in the online supplement. Subjects were classified as having “mild” or “moderate–severe” asthma on the basis of four “yes/no” questions related to medication use, asthma symptoms, and FEV₁ (percentage of predicted value).

Total IgE Measurement

Total plasma IgE was measured in duplicate in all 659 subjects with asthma, using UniCAP technology (Pharmacia Diagnostics, Kalamazoo, MI).

Statistical Methods

Statistical methods are described in detail in the online supplement. Subjects were compared by Latino ethnicity (Mexican versus Puerto Rican) within asthma severity groups, using the nonparametric Mann–Whitney rank test for continuous variables and the χ^2 test for categorical variables. To determine whether the association between ethnicity and outcomes was due to confounders, we used multiple linear regression to analyze bronchodilator responsiveness, and logistic regression to

analyze health care utilization (hospitalizations or emergency department [ED] visits in the previous 12 months). Confounder variables are detailed in the online supplement and included age, sex, place of birth, body mass index, asthma duration, asthma medications, plasma IgE, personal and family history of atopy, tobacco exposure, and breast feeding.

RESULTS

A total of 684 Puerto Rican subjects (55.4%) and Mexican subjects (44.6%) with asthma and their parents were enrolled into the GALA Study. Among the subjects with asthma, 659 subjects were classified as having either mild or moderate–severe disease according to the study protocol and were included in this analysis comparing subjects of Puerto Rican ethnicity with subjects of Mexican ethnicity.

Subject Characteristics

Puerto Ricans with asthma had earlier onset of asthma, longer duration of asthma, and were breast-fed less frequently than Mexicans with asthma regardless of asthma severity as defined by protocol (Table 1). Most subjects recruited from Mexico City had moderate–severe asthma and were older than those from all other sites because of recruitment source, which explains the observed difference in age between the two ethnic groups. Mexican subjects, particularly those with moderate–severe asthma, had significantly higher body mass index than Puerto Rican subjects with asthma ($p < 0.0001$) even after adjusting for age, sex, and asthma severity ($p < 0.001$). Because asthma develops at an earlier age in Puerto Ricans compared with Mexicans ($p < 0.0001$), the duration of asthma was significantly longer in Puerto Ricans than in Mexicans ($p < 0.0001$), even after adjusting for age, sex, and asthma severity ($p < 0.001$). There were no significant differences in total plasma IgE levels between the two ethnic groups, between the two severity groups (Table 1), or among centers (data not shown).

Lung Function Measurements and Bronchodilator Responsiveness

Lung function tests (FEV₁, FVC, FEV₁/FVC, mean forced expiratory flow during the middle half of the FVC, and peak expiratory flow) were measured before and after albuterol administration. Results from 633 subjects (Puerto Ricans, $n = 343$; Mexicans, $n = 290$) who performed lung function tests according to American Thoracic Society standards (13) are shown in Table 2.

Two notable differences in lung function measurements were found between ethnic groups. First, most measurements of pulmonary function (pre- and postbronchodilator) were significantly lower for Puerto Ricans than for Mexicans. The second notable difference between Puerto Rican and Mexican subjects was in bronchodilator responsiveness. Bronchodilator responsiveness for all spirometric measurements except FEV₁/FVC and peak expiratory flow was significantly lower for Puerto Rican subjects with asthma than for Mexican subjects with asthma (Table 2). Among those with prebronchodilator FEV₁ values at 80% or less of the predicted value, fewer Puerto Ricans than Mexicans demonstrated the ability to reverse their FEV₁ value by 12% or more from baseline (34.6 versus 57.3%; $p = 0.001$). This ethnicity-specific difference was more marked in subjects younger than 16 years of age (34.3 versus 61.0%, $n = 140$; $p = 0.004$) than in those older than 16 years (35.1 versus 54.2%, $n = 85$; $p = 0.08$).

Multiple linear regression analysis of bronchodilator responsiveness was performed to adjust for potential confounders, as described in METHODS. In this model, Puerto Rican ethnicity was associated with an average 7.3% (95% confidence interval

TABLE 1. CHARACTERISTICS OF STUDY SUBJECTS ACCORDING TO ETHNICITY AND ASTHMA SEVERITY

Characteristic	Comparison by Ethnicity			Comparison by Asthma Severity					
				Mild Asthma			Moderate–Severe Asthma		
	Puerto Ricans (n = 365)	Mexicans (n = 294)	p Value	Puerto Ricans (n = 119)	Mexicans (n = 97)	p Value	Puerto Ricans (n = 246)	Mexicans (n = 197)	p Value
Age, yr	11.9 (10:15)	13.2 (11:20)	< 0.0001	12.1 (9:15)	11.9 (10:15)	0.45	11.8 (10:15)	14.5 (11:24)	< 0.0001
Sex, % male	55.6	53.8	0.64	59.1	62.9	0.58	53.9	49.2	0.33
Body mass index, kg/m ²	21.2 (17:26)	23.7 (20:28)	< 0.0001	21.8 (18:27)	22.8 (19:27)	0.20	20.8 (17:26)	24.0 (20:29)	< 0.0001
Mainland-U.S.-born, %	15.1	43.2	< 0.001	11.8	55.7	< 0.0001	16.7	37.1	< 0.0001
Asthma onset, yr	1 (1:4)	6 (3:11)	< 0.0001	2 (1:4)	6 (3:9)	< 0.0001	1 (1:4)	6 (3:14)	< 0.0001
Asthma duration, yr	9.6 (8:13)	7.4 (4:11)	< 0.0001	9.4 (7:12)	6.7 (4:10)	< 0.0001	10.0 (8:13)	7.5 (4:11)	< 0.0001
Breast-fed, %	43.0	81.6	< 0.001	38.6	84.5	< 0.001	45.0	79.5	< 0.001
Parental smoking, %	28.5	21.3	0.13	30.0	19.0	0.15	27.8	22.9	0.41
Serum IgE, IU/ml	259 (92:624)	249 (93:601)	0.73	225 (82:693)	254 (84:567)	0.81	265 (100:594)	246 (94:619)	0.79

Values are expressed as medians (25th:75th percentile). Parental smoking and breast-feeding data were asked only for subjects with asthma who were younger than 13 years of age (n = 362). Analysis by Mann–Whitney rank test for continuous variables, and by χ^2 test for categorical variables.

[CI], 4.6 to 9.9%; $p < 0.001$) lower degree of bronchodilator responsiveness than Mexican ethnicity. In addition, as expected, prebronchodilator FEV₁ (percent predicted) was inversely related to the degree of reversibility in FEV₁ (regression coefficient, -0.34 [95% CI, -0.39 to -0.28]; $p < 0.001$). When the same analysis was performed for centers instead of ethnicity, a lower degree of FEV₁ reversibility was associated with centers that recruited Puerto Rican subjects compared with those centers that recruited Mexican subjects. Subjects from New York had on average 9.6% (95% CI, 5.5 to 13.6%; $p < 0.001$) lower FEV₁ reversibility, and subjects from San Juan had 6.1% (95% CI, 2.8 to 9.4; $p = 0.001$) lower FEV₁ reversibility, than those from San Francisco (used as the reference group). Adjusted FEV₁ reversibility was not significantly different between subjects from Mexico City and San Francisco ($p = 0.75$), or between subjects from New York City and San Juan ($p = 0.14$). Subgroup analyses depicted in Figure 1 show that FEV₁ reversibility was lower in Puerto Ricans than in Mexicans regardless of either dose of albuterol given at the visit, which varied by age (Figure 1A) or asthma severity (Figure 1B).

Personal and Family History of Atopy

Overall, there were no significant differences in the frequencies of reported personal history of allergic rhinitis or of atopic ec-

zema between Mexican and Puerto Rican subjects with asthma (Table 3). Parental history of atopy differed significantly only for the higher frequency of atopic eczema in both mothers and fathers of Puerto Rican subjects with asthma than in parents of Mexican subjects with asthma (Table 3).

Asthma Morbidity

We measured asthma morbidity by the number of asthma-related visits to a physician or ED in the previous 12 months and by lifetime asthma-related ED visits, hospitalizations, or intensive care unit admissions (Table 4). All measures of asthma morbidity except for admission to an intensive care unit were significantly higher among Puerto Rican subjects with asthma than among Mexican subjects with asthma, regardless of asthma severity. Even among subjects with mild asthma, Puerto Ricans were twice more likely to have visited the ED in the previous year than Mexicans. In addition, a large proportion of subjects with mild asthma in both ethnic groups reported at least one ED visit or hospitalization for asthma care in the past.

Using logistic regression to adjust for confounders (see METHODS in the online supplement), Puerto Rican ethnicity was associated with an odds ratio (OR) of 2.63 (95% CI, 1.6 to 4.3; $p < 0.001$) for having at least one ED visit in the previous 12 months,

TABLE 2. PULMONARY FUNCTION TEST RESULTS

	Comparison by Ethnicity			Comparison by Asthma Severity					
				Mild Asthma			Moderate–Severe Asthma		
	Puerto Ricans (n = 343)	Mexicans (n = 290)	p Value	Puerto Ricans (n = 110)	Mexicans (n = 97)	p Value	Puerto Ricans (n = 233)	Mexicans (n = 193)	p Value
Baseline spirometry									
FEV ₁ , % predicted	83 (74:93)	90 (77:100)	0.0001	91 (84:99)	96 (88:104)	0.007	80 (71:91)	84 (73:98)	0.004
FVC, % predicted	94 (83:105)	97 (86:109)	0.03	95 (88:106)	103 (95:113)	0.001	93 (81:104)	93 (80:108)	0.77
FEV ₁ /FVC, % predicted	90 (82:97)	92 (87:99)	0.006	96 (88:101)	93 (88:99)	0.16	88 (79:94)	92 (85:98)	0.0001
FEF _{25–75%} , % predicted	64 (48:81)	71 (56:88)	0.0004	79 (63:94)	79 (66:100)	0.36	57 (41:73)	66 (49:83)	0.0002
PEF, % predicted	80 (67:94)	95 (81:107)	< 0.0001	87 (75:100)	100 (89:113)	< 0.0001	78 (63:90)	92 (76:103)	< 0.0001
Bronchodilator responsiveness									
FEV ₁ reversibility, %	4.8 (0.5:10)	7.4 (4:12)	< 0.0001	2.1 (–1.5:7)	5.6 (2.6:8)	< 0.0001	6.7 (1.6:12)	8.4 (4.9:17)	0.0001
FVC reversibility, %	0.8 (–3.4:5)	2.5 (0.5:7)	< 0.0001	0.0 (–4.3:3)	1.8 (–0.1:4)	0.003	1.7 (–2.8:6)	3.8 (0.7:9)	< 0.0001
FEV ₁ /FVC reversibility, %	4.3 (0.1:9)	4.3 (1.3:8)	0.92	2.3 (–0.8:6)	3.2 (1.1:7)	0.12	5.3 (0.8:10)	4.7 (1.7:9)	0.41
FEF _{25–75%} reversibility, %	15.9 (2:37)	20.9 (9:36)	0.01	7.5 (–2:24)	16 (7:29)	0.004	21 (4:41)	24 (11:38)	0.23
PEF reversibility, %	4.4 (–4.9:15)	5.5 (0.6:13)	0.07	2.0 (–7.2:12)	4.7 (–0.9:9)	0.16	5.9 (–2.9:17)	6.6 (1.3:15)	0.16

Definition of abbreviations: FEF_{25–75%} = forced expiratory flow between 25 and 75% of FVC.

Values are expressed as medians (25th:75th percentile), and were missing for some subjects. Reversibility refers to the percentage change after albuterol administration, based on absolute values. Analysis by Mann–Whitney rank test.

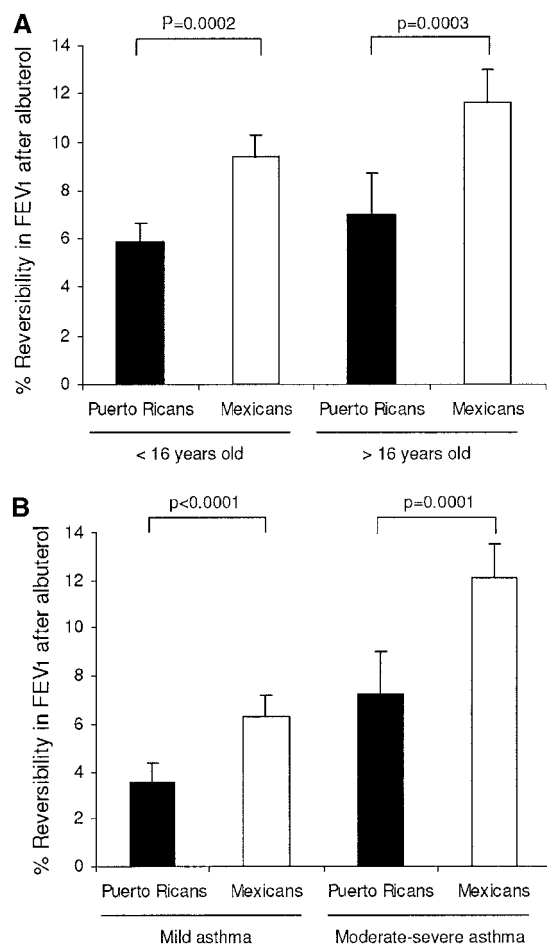


Figure 1. FEV₁ reversibility in Puerto Ricans and Mexicans with asthma according to age (A) and asthma severity (B). Reversibility is expressed as percent change in baseline FEV₁ values (liters) after albuterol administration. Subjects younger than 16 years of age received two puffs (180 μ g) of albuterol, whereas those aged 16 years and older received four puffs of albuterol (360 μ g). Columns and bars represent means and standard error of the mean, respectively. Analysis by Mann-Whitney rank test.

and with an OR of 1.94 (95% CI, 1.2 to 3.2; $p = 0.009$) for ever having been hospitalized for asthma care. When analyses were stratified by severity group, Puerto Rican ethnicity was associated with a higher risk of at least one ED visit in the previous year among subjects with mild asthma (OR, 2.40; 95% CI, 0.99 to 5.9; $p = 0.053$), and more significantly so among subjects with moderate-severe asthma (OR, 2.82; 95% CI, 1.5 to 5.4; $p = 0.002$). Puerto Rican ethnicity was also associated with a higher risk of any past hospitalization for asthma care among subjects with moderate-severe asthma (OR, 2.33; 95% CI, 1.2 to 4.4; $p = 0.009$), but not among those with mild disease (OR, 1.59; 95% CI, 0.62 to 4.1; $p = 0.33$).

Medication Use

There were significant differences in the use of medications for the moderate-severe groups among centers, which may reflect not only disease severity, but also regional differences in practice standards for asthma management, access to medical care, and access to medications. Similar proportions of Puerto Rican subjects with asthma and of Mexican subjects with asthma were using rescue short-acting bronchodilators as the only treatment for their asthma, because of the recruitment strategy of enrolling equal proportions of subjects with mild asthma of either ethnicity. Among subjects with moderate-severe asthma, significant differences were found in the use of chronic medications to control asthma (Table E2; *see the online supplement*).

Puerto Rican subjects with moderate-severe asthma were using short-acting bronchodilators regularly, oral corticosteroids regularly, and leukotriene antagonists more often than Mexican subjects. In addition, Puerto Rican subjects were using inhaled corticosteroids less frequently than Mexicans. When centers were compared, the New York City center was notable for the lowest frequency in use of inhaled corticosteroids and the highest use of cromolyn. Subjects with moderate-severe asthma recruited from the subspecialty center in Mexico City had the highest frequency of oral corticosteroid use among all centers, and those from the San Francisco center had the highest frequency of use of inhaled corticosteroids.

Although all subjects who were classified as moderate-severe by the study protocol met criteria for use of inhaled corticosteroids according to National Asthma Education and Prevention Program Guidelines, 65.0% of Puerto Ricans and 80.2% of Mexicans ($p < 0.001$) in the moderate-severe group were using any chronic daily medication for asthma. Similar differences in use

TABLE 3. HISTORY OF ATOPY FOR SUBJECTS AND FAMILIES

Characteristic	Comparison by Ethnicity			Comparison by Asthma Severity					
			p Value	Mild Asthma			Moderate-Severe Asthma		
	Puerto Ricans (n = 364)	Mexicans (n = 294)		Puerto Ricans (n = 118)	Mexicans (n = 97)	p Value	Puerto Ricans (n = 246)	Mexicans (n = 197)	p Value
Subject history of:									
Allergic rhinitis, %	83.8	80.5	0.28	77.4	83.5	0.27	86.8	79.0	0.03
Atopic eczema, %	32.5	30.5	0.58	23.5	29.9	0.29	36.8	30.8	0.19
Maternal history of:									
Asthma, %	35.7	31.6	0.27	35.6	24.7	0.09	35.8	35.0	0.87
Allergic rhinitis, %	28.2	30.4	0.54	30.8	32.0	0.85	26.9	29.6	0.54
Atopic eczema, %	10.8	5.5	0.015	11.1	1.0	0.003	10.6	7.7	0.29
Paternal history of:									
Asthma, %	24.2	24.7	0.90	26.5	13.5	0.02	23.2	30.1	0.10
Allergic rhinitis, %	24.1	24.1	0.99	20.5	25.0	0.43	25.8	23.7	0.61
Atopic eczema, %	12.2	5.2	0.002	11.1	1.0	0.003	12.7	7.2	0.06

Analysis by χ^2 test.

TABLE 4. HEALTH CARE UTILIZATION FOR ASTHMA

Variable	Comparison by Ethnicity			Comparison by Asthma Severity					
				Mild Asthma			Moderate-Severe Asthma		
	Puerto Ricans (n = 365)	Mexicans (n = 294)	p Value	Puerto Ricans (n = 119)	Mexicans (n = 97)	p Value	Puerto Ricans (n = 246)	Mexicans (n = 197)	p Value
Number of doctor visits in the previous 12 mo	3 (1:6)	2 (1:3)	0.0002	2 (1:4)	1 (1:2)	0.05	3 (2:6)	2 (1:4)	0.0007
Have ever had ED visit, %	88.0	74.3	< 0.001	83.5	57.7	< 0.001	90.1	82.6	0.02
Had any ED visits in the previous 12 mo, %	67.1	45.2	< 0.001	52.9	26.8	< 0.001	74.0	54.3	< 0.001
Number of lifetime ED visits	10 (2:26)	3 (0:10)	< 0.0001	5 (1:18)	1 (0:5)	0.0001	12 (4:30)	3 (1:14)	< 0.0001
Have ever hospitalized, %	64.4	41.8	< 0.001	53.0	24.7	< 0.001	69.8	50.3	< 0.001
Have ever been in ICU, %	9.9	10.5	0.77	10.1	6.2	0.30	9.8	12.7	0.33

Definition of abbreviations: ED = emergency department; ICU = intensive care unit.

Values are expressed as medians (25th:75th percentile). Analysis by Mann-Whitney rank test for continuous variables, and by χ^2 test for proportions.

of chronic asthma medications among the subjects with moderate-severe asthma were observed when we analyzed subjects with prebronchodilator FEV₁ (percent predicted) values of 80% or less. Among those subjects with moderate-severe airway obstruction, 58.1% of Puerto Ricans versus 67.4% of Mexicans ($p = 0.16$) were taking any chronic asthma medication, 41.2 versus 60.7% ($p = 0.004$) were taking inhaled corticosteroids, and 25.0 versus 5.6% ($p < 0.001$) were taking leukotriene antagonists. We considered chronic asthma medications as those taken daily for asthma control, including regular oral or inhaled corticosteroid, leukotriene antagonist, inhaled cromolyn, or theophylline. Finally, the proportion of patients using none, one, two, or three or more chronic medications for asthma differed significantly between Puerto Ricans and Mexicans with moderate-severe asthma ($p < 0.001$, by χ^2): none (35.0 versus 19.8%), one (34.6 versus 56.4%), two (19.5 versus 19.3%), and three or more medications (11.0 versus 4.6%). Thus, among subjects with moderate-severe asthma, Puerto Ricans were using fewer controller medications, fewer inhaled corticosteroids, and more leukotriene antagonists than Mexicans. Inhaled cromolyn was most commonly used among subjects with asthma recruited from New York City. These differences in medication use reflect severity of disease and regional differences in practice standards for asthma management, access to medical care, and access to medications.

DISCUSSION

Our data show that even when similar recruitment and characterization criteria were employed, Puerto Rican subjects with asthma were significantly less responsive to short-acting bronchodilators than were Mexican subjects with asthma. This difference remained significant and clinically meaningful even after adjustment for multiple potential confounders. Because short-acting inhaled β_2 -adrenergic agonists are the most commonly prescribed medications for the treatment of asthma, the finding of a differential response among ethnic subgroups is unique and important (14). In addition, we found that Puerto Ricans have an earlier age of onset of asthma and more severe airway obstruction than do Mexicans with asthma. Last, our findings of greater health care utilization among Puerto Ricans than Mexicans are concordant with prior studies of national vital statistics (3, 4).

There are several potential explanations for the reduced responsiveness to bronchodilator medication in Puerto Ricans. For example, asthma in Puerto Ricans could be associated with more airway remodeling, with less bronchospasm, with greater impairment of smooth muscle relaxation, with greater β_2 -adrenergic

receptor downregulation, or with different frequencies in genetic polymorphisms for proteins involved in the β_2 -adrenergic receptor pathway. By design, neither environmental nor cultural differences were a primary focus of the GALA Study and, therefore, could be confounders. However, because the differences in disease severity and responsiveness to bronchodilator medication were observed between Puerto Ricans and Mexicans regardless of recruitment criteria and geographic location, we hypothesize that such differences may be determined at least in part by genetic differences between these two groups.

In addition to reduced pulmonary function and lower bronchodilator responsiveness, Puerto Ricans also had greater asthma-related health care utilization than Mexicans even after adjustment for numerous potential confounders. Factors that could explain the increased asthma morbidity in Puerto Ricans compared with Mexicans are socioeconomic factors (e.g., acculturation, lifestyle behaviors, access to care and medications), differences in environmental factors, and/or genetic predisposition to greater asthma severity. Puerto Ricans are U.S. citizens by birth and thus have access to the privileges afforded to all U.S. citizens. In contrast, many Mexicans are recent or undocumented immigrants (1). Despite higher poverty rates, less education, and reduced access to health care among Mexicans compared with other Latino groups, health outcomes of many Mexicans living in the United States today are equal to, or better than, those of other minority groups living within the United States (15). This epidemiologic paradox has often been referred to as the "Hispanic paradox" (16) and has been hypothesized to be related to the "healthy migrant" effect, that is, better dietary and lifestyle habits as well as family structure of newly arrived immigrants compared with later generations of U.S.-born immigrants. The etiology of observed differences in health outcomes, such as asthma morbidity, between Mexicans and Puerto Ricans is poorly understood and merits further investigation. Our study had limited data to analyze the Hispanic paradox, that is, to compare U.S.-born (later generation) subjects with subjects born abroad (first generation) but living in the United States. Only the San Francisco center had a sizable number of subjects in both categories ($n = 127$ and 68 , respectively) and they did not differ in their FEV₁ percent predicted, FEV₁ reversibility, or ED visits in the previous 12 months (data not shown).

Recruitment for this family-based study was difficult and took longer than expected because of the high single parent household rate, which disproportionately affects minority communities (17). Other recruitment difficulties that we encountered included the following: high rate of mobility leading to outdated contact information in medical records, lack of trust in medical research,

and fear that personal information would be disclosed to third parties. Other investigators have encountered similar difficulty in recruiting racial and ethnic minorities for biomedical research (18). To overcome difficulties of recruitment, we organized a team of bilingual and bicultural Latino field workers specialized in asthma.

This study has three potential sources of bias: absence of spirometry reference values for Puerto Ricans, recruitment strategy, and recall bias for questions related to past medical history. Concerning spirometry reference values, we used Hankinson reference equations derived from Mexican-Americans (12) for all of our subjects because there are no such reference equations published for the Puerto Rican population. Thus, it is possible that Puerto Ricans could have smaller lungs than Mexicans, as black subjects have smaller lungs compared with white subjects (19–22). If this were true, our findings of lower spirometric values in Puerto Rican subjects with asthma would be due to their ethnic background and not to more severe asthma. However, the FEV₁/FVC ratio, an index of airway obstruction adjusted for individual vital capacity, was significantly lower in Puerto Ricans than in Mexicans, indicating more severe airway obstruction in Puerto Ricans. In addition, Puerto Ricans not only have lower spirometric values, but they also have more severe asthma based on health care utilization.

Our recruitment strategy may have resulted in an ascertainment bias. The requirement for participation of both parents made recruitment difficult, especially in New York City, where a large proportion of potential Puerto Rican subjects with asthma were from single parent households. Although this requirement could have biased our study populations, affecting its representation of the general population, such bias occurred in both ethnic groups and likely results in the recruitment of comparable populations of Puerto Ricans and Mexicans. We are not aware of any sociodemographic, economic, or cultural reasons that could have caused recruitment of patients with different disease severity between the two ethnic groups, or among all four centers. Last, recall bias may affect accuracy of answers to questions inquiring about events in the distant past. However, this bias likely occurred to the same extent in both ethnic groups. Despite these potential biases in interpretation of spirometry results, in recruitment, and in subject recall, none of them can explain our main finding, which is the lower bronchodilator responsiveness in Puerto Ricans with asthma than in Mexicans with asthma. In addition, our results corroborate those of other studies, which show that asthma is more severe in Puerto Ricans than in Mexicans in the United States (3, 4, 23–29). However, this investigation differs from earlier studies of asthma among Latinos in that we compared not only questionnaire responses, but also spirometry and bronchodilator responsiveness among Puerto Ricans with asthma and Mexicans in the continental United States, in Mexico, and in Puerto Rico.

To our knowledge, the GALA Study is the first investigation specifically aimed at identifying factors related to asthma severity in Latino ethnic groups. Our findings may point to new factors that can explain why Puerto Ricans have more severe asthma than Mexicans including earlier age of asthma onset, worse airway obstruction, greater health care utilization, and decreased response to albuterol. The fact that clinical trials of asthma therapy have been performed in predominantly white populations has limited the ability of the medical community to assess the efficacy of current therapies in racially admixed populations such as Latino ethnic groups. Thus, studies of asthma in racially diverse populations appear to be warranted. In particular, our study demonstrates that the two largest Latino ethnic groups in the United States have different levels of asthma severity and

different responses to medications, and therefore should be considered as separate groups in asthma trials.

Conflict of Interest Statement: E.G.B. has no declared conflict of interest; P.C.A. has no declared conflict of interest; S.N. has no declared conflict of interest; J.C. has no declared conflict of interest; A.T. has no declared conflict of interest; J.R.R.-S. has no declared conflict of interest; M.T. has no declared conflict of interest; J.S.S. has no declared conflict of interest; M.A. has no declared conflict of interest; M.S. has no declared conflict of interest; I.G. has no declared conflict of interest; J.K.F. received \$1,000 in 2000 for speaking at a conference sponsored by Novartis; J.S. has no declared conflict of interest; C.L. has no declared conflict of interest; H.M. has no declared conflict of interest; E.Z. has no declared conflict of interest; R.C. has no declared conflict of interest; M.S. has no declared conflict of interest; R.C. has no declared conflict of interest; D.S. has no declared conflict of interest; S.T.W. received a grant for \$900,065, Asthma Policy Modeling Study, from AstraZeneca from 1997–2003, was Co-Investigator on a grant from Millennium Pharmaceuticals to pursue asthma genetics in China from 1996–2001, received a grant from Pfizer to examine diabetes mellitus and its relationship to lung function between 2000–2003, was a consultant for Schering-Plough and received \$5,000 from 1999–2000, has been a Co-Investigator on a grant from Boehringer Ingelheim to investigate a COPD natural history model which began in 2003 (has received no funds for his involvement in this project), has been a consultant for Variagenics on human subjects issues and received \$5,000 in 2003, has been a consultant to Genome Therapeutics in 2003 and received \$1,500, was a consultant for Merck Frost on asthma genetics in 2002 and received \$2,000, has been an advisor to the TENOR Study for Genentech and has received \$5,000 for 2002–2003, received a grant from Glaxo-Wellcome for \$500,000 for genomic equipment from 2000–2003, was a consultant for Roche Pharmaceuticals in 2000 and received no financial remuneration for this consultancy; J.C.F. has no declared conflict of interest; H.A.B. has received \$200,000 from GlaxoSmithKline in 2001 for a research project conducted at UCSF and has served as an uncompensated member of an advisory committee and of a research study's scientific Advisory Board for the company and holds a share of a patent for a genetic test to identify patients at risk for adverse reactions to B-agonist therapy (<\$250 per year); W.R.-C. has no declared conflict of interest; J.M.D. has no declared conflict of interest; E.K.S. received a research grant from GlaxoSmithKline to study COPD genetics of approximately \$250,000 per year from 2000–2003.

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