New Mexican Hispanic Smokers Have Lower Odds of Chronic Obstructive Pulmonary Disease and Less Decline in Lung Function Than Non-Hispanic Whites

Shannon Bruse[1], Akshay Sood[2], Hans Petersen[1], Yushi Liu[1], Shuguang Leng[1], Juan C. Celedón[3], Frank Gilliland[4], Bartolomé Celli[5], Steven A. Belinsky[1], and Yohannes Tesfaigzi[1]

[1]Lovelace Respiratory Research Institute, Albuquerque, New Mexico; [2]University of New Mexico School of Medicine, Albuquerque, New Mexico; [3]Division of Pulmonary Medicine, Allergy, and Immunology, Children's Hospital of Pittsburgh of the University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; [4]Department of Preventive Medicine, University of Southern California, Los Angeles, California; and [5]Department of Medicine, Harvard Medical School, Boston, Massachusetts

Rationale: **The epidemiology of cigarette smoking–related chronic obstructive pulmonary disease (COPD) is not well characterized in Hispanics in the United States. Understanding how ethnicity influences COPD is important for a number of reasons, from informing public health policies to dissecting the genetic and environmental effects that contribute to disease.**

Objectives: **The present study assessed differences in risk between Hispanics and non-Hispanic whites for longitudinal and cross-sectional COPD phenotypes. Genetic ancestry was used to verify findings based on self-reported ethnicity. Hispanics in New Mexico are primarily differentiated from non-Hispanic whites by their proportion of Native American ancestry.**

Methods: **The study was performed in a New Mexican cohort of current and former smokers. Self-reported Hispanic and non-Hispanic white ethnicity was validated by defining genetic ancestry proportions at the individual level using 48 single-nucleotide polymorphism markers. Self-reported ethnicity and genetic ancestry were independently used to assess associations with cross-sectional and longitudinal measures of lung function. Multivariable models were adjusted for indicators of smoking behavior.**

Measurements and Main Results: **Self-reported Hispanic ethnicity was significantly associated with lower odds of COPD (odds ratio, 0.49; 95% confidence interval, 0.35–0.71; $P = 0.007$), and this protection was validated by the observation that Hispanic smokers have reduced risk of rapid decline in lung function (odds ratio, 0.48; 95% confidence interval, 0.30–0.78; $P = 0.003$). Similar findings were noted when Native American genetic ancestry proportions were used as predictors instead of self-report of Hispanic ethnicity.**

Conclusions: **Hispanic ethnicity is inversely associated with cross-sectional and longitudinal spirometric COPD phenotypes even after adjustment for smoking. Native American genetic ancestry may account for this "Hispanic protection."**

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

It is generally accepted that ethnicity affects susceptibility to chronic obstructive pulmonary disease (COPD). Although previous studies have suggested that Hispanics have reduced risk for COPD compared with non-Hispanic whites, the decline in lung function over time has not been compared among these ethnic groups. In addition, in previous studies Hispanic ethnicity was not defined using genetic ancestry markers.

What This Study Adds to the Field

The present study demonstrates that Hispanic smokers have a significantly reduced rate of decline in lung function compared with non-Hispanic white smokers. This finding was confirmed when comparing the risk for COPD at baseline. Genetic analyses showed that New Mexican Hispanics have approximately one third Native American and two thirds European ancestry. The Native American proportion appeared to protect against lung function decline and COPD risk. These findings highlight the need for comprehensive studies in Hispanics to identify genetic factors that may be responsible for protection against COPD.

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death in the United States (1). Understanding how ethnicity influences COPD is important for several reasons, from informing public health policies to dissecting the genetic and environmental effects that contribute to disease. Although Hispanics comprise the largest minority population in the United States, they typically have been excluded from most genetic and clinical research, which may be partly due to the difficulty in recruiting subjects from minority populations (2). Hispanics are an ethnic population characterized by significant heterogeneity in terms of culture, location, and genetic ancestry. Hispanic genetic ancestry is generally comprised of European, Native American, and African proportions, and these proportions vary widely among different Hispanic subgroups (3). For example, Hispanics in Puerto Rico and the Southeastern United States display relatively higher African ancestry, whereas Hispanics in the Southwestern United States display relatively higher Native American and lower African ancestry (4). The ancestry of Hispanics in New Mexico can be traced to the original Spanish conquistadores, Native American tribes of the region, and Mexican immigrants. In the United States, New Mexico has the highest percentage

(*Received in original form March 29, 2011; accepted in final form August 25, 2011*)

Supported by the State of New Mexico (appropriation from the Tobacco Settlement Fund) and National Institutes of Health grants RO1 ES015482 (Y.T.) and U01 CA 097,356 (S.B.).

Author Contributions: Y.T., S.B., A.S., B.C., F.G., and S.A.B. made substantial contributions to conception and design; H.P., Y.L., and S.L. made substantial contributions to acquisition of data or analysis and interpretation of data. All authors made substantial contributions to drafting the article or revising it critically for important intellectual content and final approval of the version to be published.

Correspondence and requests for reprints should be addressed to Yohannes Tesfaigzi, Ph.D., Lovelace Respiratory Research Institute, 2425 Ridgecrest Dr. S.E., Albuquerque, NM 87108. E-mail: YTesfaig@lrri.org

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 184. pp 1254–1260, 2011

Originally Published in Press as DOI: 10.1164/rccm.201103-0568OC on September 7, 2011
Internet address: www.atsjournals.org

(45%) of Hispanics, and New Mexican Hispanics are mostly native born (84%) (5).

The epidemiology of COPD has previously been investigated in New Mexican Hispanics using self-report and public records to define ethnicity. Early studies using prevalence surveys found that chronic bronchitis, emphysema, airway obstruction, and mortality from COPD were lower in New Mexican Hispanics than in their non-Hispanic white (NHW) counterparts (6, 7), although these studies did not account for the heterogeneous nature of Hispanic ethnicity (8). Because cigarette smoking is the leading risk factor for the development of COPD, we previously compared cross-sectional COPD outcomes between Hispanics and NHW individuals in a New Mexican cohort of heavy smokers (9). That study used self-reported ethnicity to compare 248 Hispanic and 1,185 NHW women in the Lovelace Smokers Cohort (LSC) and determined that Hispanic female smokers have less airway obstruction than their NHW counterparts and that this difference could not be fully explained by differences in cigarette smoking (9).

On the basis of our prior findings in New Mexico, we hypothesized that Hispanic ethnicity is associated not only with a reduced risk of airflow obstruction at baseline but also with reduced decline in lung function during follow up. Because prior studies comparing COPD and COPD-related phenotypes in Hispanic and NHW populations in the United States have not used genetic estimates of ancestry, we used ancestry informative markers (AIMs) to more objectively define Hispanic ethnicity. In addition, we extended prior studies through evaluating a larger number of LSC participants that included both sexes.

Some of the results of this study have been previously reported in the form of an abstract (International ATS Society Meeting, 2011).

METHODS

Study Population

Study participants were drawn from the Lovelace Smokers' Cohort from the Albuquerque, New Mexico metropolitan area. Inclusion criteria for entry into the current study were age 40 to 75 years, current or former cigarette smoking (with a minimum of 10 pack-years), and the ability to understand English. Information related to demographics and smoking history was obtained by self-report.

Lung Function Measurements

All tests were conducted at Lovelace Scientific Resources as previously described (9). Briefly, pre- and postbronchodilator spirometry measures were obtained by certified and registered respiratory therapists strictly adhering to the 1994 American Thoracic Society guidelines (10). Only postbronchodilator measures were used in the current study, and subjects with reversible airflow limitation were excluded from all analyses.

Outcomes

COPD. COPD was defined according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria ($FEV_1/FVC < 0.70$) and an FEV_1/FVC ratio below the 5th percentile of the predicted value, also referred to as the lower limit of normal (LLN) (11). Ethnicity specific reference equations from NHANES III were used (12).

Lung Function Decline. Rapid decliners were defined as individuals with greater than 3% decline, and nondecliners were defined as individuals with static or increasing absolute FEV_1 per year. This divided the cohort approximately into tertiles so that case-control comparisons could be made between those in the lowest and highest tertile. The rate of decline was calculated as ml/yr decline of absolute FEV_1.

Chronic bronchitis. Participants with self-reported cough productive of phlegm for at least 3 months per year for at least 2 consecutive years were considered to have chronic bronchitis (13).

Ancestry Informative Markers and Estimation of Genetic Ancestry

Forty-eight AIMs were chosen from a set of 233 AIMs used previously to assess ancestry and control for confounding by population stratification (14). Estimates of population substructure based on the 48 AIMs are similar to those based on analyses using the 233 AIMs. The 48 AIM single-nucleotide polymorphisms used in the STRUCTURE analyses, their allele frequencies in relevant populations (when available), and their delta values are contained in Tables E1 and E2 in the online supplement.

TABLE 1. DISTRIBUTION OF RISK FACTORS AND OUTCOMES IN SELF-REPORTED NON-HISPANIC WHITES AND HISPANIC INDIVIDUALS

	Hispanic ($n = 369$)		NHW ($n = 1,580$)		
Characteristic	n (%)	Mean (SD)	n or Mean	(%) or (SD)	*P* Value
Female	273 (74.0)		1,223 (77.4)		0.16
Age, yrs		53.9 (8.8)		57.0 (9.5)	<0.001
At least HS education	166 (45.0)		1,189 (75.3)		<0.001
Obese (BMI ⩾ 30 kg/m^2)		125 (33.9)		462 (29.2)	0.08
BMI, kg/m^2		28.7 (6.0)		28.0 (6.2)	0.02
Height, in		63.9 (3.24)		65.6 (3.38)	<0.001
Cumulative pack-years		33.7 (15.5)		41.3 (21.5)	<0.001
Packs smoked per day		1.01 (0.40)		1.24 (0.50)	<0.001
Current smoker	284 (77.0)		851 (53.9)		<0.001
Age of onset smoking, yr		16.7 (3.8)		16.9 (3.8)	0.45
Smoking duration, yr		33.4 (8.6)		33.4 (9.7)	0.98
COPD (GOLD)	55 (14.9)		466 (29.5)		<0.001
COPD (NHANES III LLN)	54 (14.6)		398 (25.2)		<0.001
FEV_1/FVC		77.1 (9.9)		72.8 (11.0)	<0.001
$FEV_{1\%}$ predicted		95.9 (18.4)		90.7 (19.5)	<0.001
Chronic bronchitis	129 (35.0)		496 (31.4)		0.19
Rate of decline, ml/yr		13.8 (99.3)		37.1 (106.6)	0.006
Rapid decliners	37 (21.6)*		283 (31.6)*		0.009
Available AIM data	307 (83.2)		1,404 (88.9)		

Definition of abbreviations: AIM = Ancestry information marker; BMI = body mass index; COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; HS = high school; LLN = lower limit of normal.

*Percentage based on number of individuals with two or more visits.

TABLE 2. ODDS RATIOS FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE (GLOBAL INITIATIVE FOR CHRONIC OBSTRUCTIVE LUNG DISEASE) USING SELF-REPORTED ETHNICITY IN ANALYSIS OF HISPANIC (N = 369) AND NON-HISPANIC WHITE (N = 1,580) INDIVIDUALS*

	Univariate				Multivariable			
Categorical	OR	Lower 95%	Upper 95%	*P* Value	OR	Lower 95%	Upper 95%	*P* Value
Hispanic ethnicity	0.42	0.31	0.57	<0.001	0.49	0.35	0.71	0.007
Male sex	1.96	1.57	2.45	<0.001	1.97	1.38	2.80	<0.001
Not currently smoking	1.11	0.9	1.36	0.33	0.71	0.55	0.90	0.006
Education < HS	0.98	0.79	1.22	0.84	1.09	0.85	1.41	0.49
Continuous								
Height, in	1.06	1.03	1.09	<0.001	1.00	0.96	1.05	0.88
Pack-years (10 yr)	1.32	1.25	1.39	<0.001	1.18	1.12	1.24	<0.001
BMI, kg/m^2	0.95	0.93	0.97	<0.001	0.95	0.93	0.97	<0.001
Age (10 yr)	2.10	1.87	2.35	<0.001	2.00	1.74	2.30	<0.001

Definition of abbreviations: BMI = body mass index; HS = high school; OR = odds ratio.
*Total n = 1,949. Analysis includes all Hispanic and non-Hispanic white individuals with available baseline data.

Population structure was analyzed using the Bayesian Markov Chain Monte Carlo algorithm implemented in STRUCTURE 2.3.3 (15) under the admixture model and using the locprior function (16). STRUCTURE runs were performed using k = 3, with 10,000 burn-ins and 10,000 Markov Chain Monte Carlo repetitions.

Statistical Analysis

Chi-square and Fisher's exact tests were used for the univariate analyses of categorical variables. Two-sample *t* tests and Kruskal-Wallis tests were used for continuous variables (Table 1).

For multivariable analysis of quantitative and categorical outcomes, linear and logistic regression was performed using STRUCTURE proportions or self-reported ethnicity as a predictor. Additional covariates included age, height, body mass index (BMI), sex, pack-years smoking, education, and current smoking status. Analyses involving longitudinal decline were adjusted for absolute FEV_1 at baseline. In supplementary analysis, lung function decline was assessed using mixed models, treating absolute FEV_1 as a repeated measure with time as a random effect.

All statistical analyses were performed in R version 2.12.0 (17) or SAS version 9.2.

RESULTS

Of the 1,949 eligible participants in the Lovelace Smokers' Cohort, 369 (18.9%) were Hispanic and 1,580 (81.1%) were NHW; 1,135 (58.2%) were current smokers; 1,506 were women (77.3%); and 521 (26.7%) had COPD, as defined by the GOLD criteria (Table 1). Compared with NHW individuals, Hispanics were more likely to be younger, to be current smokers, to have higher BMI, to be shorter; and to have lower pack-years of smoking, fewer packs smoked per day while smoking, and an education not exceeding high school ($P \leq 0.02$ for all comparisons). Duration and age of onset of smoking were similar between Hispanic and NHW participants.

Cross-Sectional Analysis Showed that Self-Identified Hispanics Are Less Likely Than NHW to Have COPD

Hispanics were significantly less likely to have COPD than NHW individuals using GOLD or LLN definitions ($P < 0.001$ in both analyses) (Table 1). Compared with NHW individuals, Hispanics were also more likely to have higher FEV_1 percent predicted and higher absolute FEV_1/FVC values ($P < 0.001$, both analyses) (Table 1). There was no difference in chronic bronchitis status between the two groups. In adjusted analysis, Hispanic ethnicity was associated with a lower odds of COPD (GOLD) (odds ratio [OR], 0.49; $P = 0.007$) (Table 2). Effect sizes for the association of ethnicity with COPD remained similar in univariate and multivariable modeling (Table 2). Other significant predictors of COPD were pack-years of smoking, current smoking status, BMI, sex, and age ($P \leq 0.006$ for all analyses).

Alternative analytical strategies. The above results evaluating COPD (GOLD) were similar for COPD (LLN) (Table E3). Prevalence ratios were also calculated to assess the potential for bias in estimates of the ORs (18). Prevalence ratios and ORs were similar for all analyses, as demonstrated when comparing Tables 2 and E4. An analysis was performed in which only individuals with GOLD stage 2 through 4 were defined as having COPD, and Hispanic ethnicity remained significantly associated with lower odds of COPD ($P < 0.001$) (Table E5). Although men were more likely to have COPD than women in the LSC, sex-

TABLE 3. ODDS RATIOS FOR RAPID DECLINE IN ABSOLUTE FEV_1 USING SELF-REPORTED ETHNICITY IN ANALYSIS OF HISPANIC (N = 171) AND NON-HISPANIC WHITE (N = 895) INDIVIDUALS*

	Univariate				Multivariable			
Categorical	OR	Lower 95%	Upper 95%	*P* Value	OR	Lower 95%	Upper 95%	*P* Value
Hispanic ethnicity	0.53	0.34	0.82	0.004	0.48	0.30	0.78	0.003
Male sex	0.82	0.54	1.24	0.34	0.63	0.35	1.14	0.13
Not currently smoking	1.12	0.82	1.52	0.47	0.89	0.62	1.26	0.50
Education < HS	1.36	0.97	1.91	0.07	1.53	1.06	2.19	0.02
Continuous								
Height, in	0.98	0.94	1.03	0.49	0.95	0.88	1.02	0.12
Pack-years (10 yr)	1.09	1.02	1.17	0.02	1.08	1.00	1.17	0.06
BMI, kg/m^2	0.99	0.96	1.01	0.25	0.99	0.97	1.02	0.51
Age (10 yr)	1.22	1.04	1.44	0.02	1.41	1.12	1.77	0.004
Baseline FEV_1,100 ml	1.00	0.98	1.02	0.87	1.06	1.02	1.09	0.001

Definition of abbreviations: BMI = body mass index; HS = high school; OR = odds ratio.
*Total n = 1,066. Analysis includes all Hispanic and non-Hispanic white individuals with available longitudinal data.

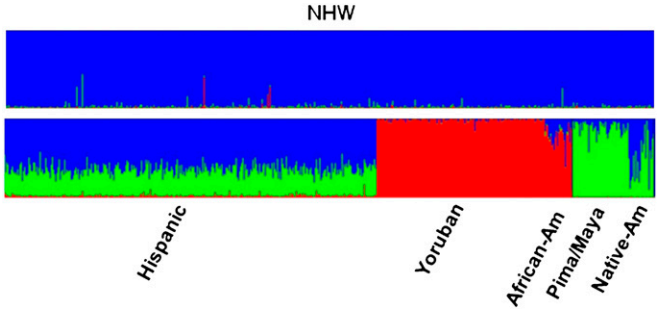

Figure 1. Analysis of population genetic STRUCTURE using 48 ancestry informative marker single-nucleotide polymorphisms. Each *vertical line* represents an individual subject. Self-reported ethnic groups are indicated above (in the case of non-Hispanic white [NHW] individuals) and below the *bar plots*. Analysis was performed using STRUCTURE (*see* METHODS). Colors in the bar graph correspond to assumed ancestral populations represented by the k = 3 clusters: *blue* = European; *red* = African-American, *green* = Native American. A representative subset of the NHW sample is shown.

stratified analysis revealed that Hispanic ethnicity was associated with reduced odds of COPD in men and in women (Table E6). Statistical significance was not reached in men possibly due to their smaller number.

Ethnicity effect is not confounded by smoking intensity. Additional analyses were performed to assess potential confounding of ethnicity by smoking behaviors. Hispanics appear to smoke less intensely than NHW individuals, given their lower packs per day while smoking (Table 1). Therefore, NHW and Hispanic participants were matched on smoking intensity (packs per day while smoking or cumulative pack-years, in separate analyses) using a random sampling approach (*see* MATERIALS AND METHODS in the online supplement) to determine if Hispanic ethnicity was still independently associated with lower odds of COPD. The median P value obtained in analyses matched for packs per day while smoking was $P = 0.001$, with 97.5% of all P values falling below the 0.05 threshold over 1,000 random samplings (data not shown). The median P value obtained in analyses matched for cumulative pack years was 0.002, with 96.8% of all P values falling below the 0.05 threshold over 1,000 random samplings (data not shown). These analyses suggest that smoking intensity alone is unlikely to explain the Hispanic protection against COPD.

Longitudinal Analysis Showed That Self-Identified Hispanics Have Less Rapid Decline in Lung Function Than NHW Individuals

The association between self-reported ethnicity and decline in lung function was investigated in 895 NHW and 171 Hispanic participants for whom longitudinal spirometric data were available. Individuals included in the longitudinal analysis did not differ from those included in the cross-sectional analysis in terms of ethnicity, smoking behavior, and baseline lung function (data not shown). Univariate analysis revealed that Hispanics were less likely to be categorized as rapid decliners than were NHW individuals ($P = 0.009$) (Table 1) and that average yearly decline in absolute FEV_1 was lower among Hispanics (13.8 ml/year) compared with NHW individuals (37.1 ml/yr) ($P = 0.006$) (Table 1). After adjustment for smoking and other covariates, Hispanic ethnicity remained associated with lower odds of rapid decline (OR, 0.48; $P = 0.003$) (Table 3) and lower rate of yearly decline in FEV_1 (PE = 26.13 ml/yr; $P = 0.005$) (Table E7). Hispanic ethnicity was similarly associated with reduced decline in a confirmatory analysis using mixed modeling and treating absolute FEV_1 as a repeated measure ($P = 0.002$).

High Native American Genetic Ancestry Proportion Is Associated with Lower Cross-Sectional Likelihood of COPD and Less Longitudinal Decline in Lung Function

There was a general agreement between self-reported ethnicity and STRUCTURE-defined clustering using a set of 48 ancestry informative markers to estimate individual ancestry proportions (Figure 1). Self-declared ethnicity is highly correlated with Native American genetic ancestry. We regressed NA genetic ancestry against self-declared ethnicity, and it was highly predictive ($P < 2 \times 10^{-16}$). Additionally, we calculated the pseudo R^2 (19) and observed that more than 80% of the variation in self-declared ethnicity can be explained by Native American genetic ancestry. STRUCTURE clusters were likely defining European (blue), African (red), and Native American (green) ancestral populations (*see* MATERIALS AND METHODS for analyses and Figure E1). The means and ranges of ancestry proportions for self-reported Hispanics, NHW individuals, Native Americans, and African-Americans in the LSC (as well as for Pima/Mayan and Yoruban reference populations) are summarized in Table 4 and depicted in Figure 1. New Mexican Hispanics showed a mean Native American ancestry proportion of 0.33 (range, 0.18–0.54), whereas NHW individuals showed a mean proportion of 0.01. There was evidence of significant admixture within the self-reported African-American and Native American groups and for moderate European admixture within the Pima/Maya group, consistent with previous studies of these Pima and Maya samples (3, 20). Due to the small sample sizes of self-reported Native Americans and African Americans within the LSC, all analyses of COPD phenotypes were restricted to Hispanics and NHW individuals.

Native American genetic ancestry proportions were used to investigate associations with COPD-related phenotypes. Higher Native American ancestry was associated with lower odds for COPD, higher FEV_1 percent predicted, and higher absolute

TABLE 4. MEAN GENETIC ANCESTRY PROPORTION (AND RANGE) FOR EACH SELF-REPORTED RACIAL OR ETHNIC GROUP

	n	Cluster 1 (European)	Cluster 2 (Native American)	Cluster 3 (African)
LSC sample				
NHW	1,404	0.98 (0.56–1.00)	0.01 (0.00–0.44)	0.00 (0.00–0.40)
Hispanic	307	0.65 (0.44–0.81)	0.33 (0.18–0.54)	0.02 (0.00–0.17)
African-American	25	0.24 (0.05–0.91)	0.02 (0.00–0.10)	0.74 (0.09–0.95)
Native-American	23	0.50 (0.03–0.91)	0.50 (0.09–0.97)	0.00 (0.00–0.00)
Public samples				
Yoruban	153	0.01 (0.00–0.16)	0.00 (0.00–0.02)	0.99 (0.83–1.00)
Pima/Mayan	50	0.12 (0.03–0.43)	0.88 (0.57–0.97)	0.00 (0.00–0.01)

Definition of abbreviations: LSC = Lovelace Smokers Cohort; NHW = non-Hispanic white.

TABLE 5. ODDS RATIOS FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE (GLOBAL INITIATIVE FOR CHRONIC OBSTRUCTIVE LUNG DISEASE) USING NATIVE AMERICAN GENETIC ANCESTRY AS A PREDICTOR IN ANALYSIS OF HISPANIC (N = 305) AND NIN-HISPANIC WHITE (N = 1,404) INDIVIDUALS*

	Multivariable			
Categorical	OR	Lower 95%	Upper 95%	*P* Value
Native American genetic ancestry	0.47†	0.33	0.69	<0.001
Male sex	2.49	1.77	3.51	<0.001
Not currently smoking	0.78	0.60	1.01	0.06
Education < HS	1.00	0.79	1.35	0.82
Continuous				
Height, in	0.97	0.94	1.01	0.15
Pack-years (10 yr)	1.21	1.14	1.28	<0.001
BMI, kg/m^2	0.94	0.92	0.97	<0.001
Age (10 yr)	1.91	1.64	2.20	<0.001

Definition of abbreviations: BMI = body mass index; HS = high school; OR = odds ratio.

*Total n = 1,709. Analysis includes all Hispanic and non-Hispanic white individuals with available baseline and ancestry informative marker data.

† This odds ratio for chronic obstructive pulmonary disease represents the reduction in odds when Native American genetic ancestry proportion is increased by 0.32; this is the mean difference in Native American genetic ancestry between Hispanics and non-Hispanic whites.

TABLE 6. ODDS RATIOS FOR RAPID DECLINE IN ABSOLUTE FEV_1 USING SELF-REPORTED ETHNICITY IN ANALYSIS OF HISPANIC (N = 169) AND NON-HISPANIC WHITE (N = 891) INDIVIDUALS

	Multivariable			
Categorical	OR*	Lower 95%	Upper 95%	*P* Value
Native American genetic ancestry	0.51†	0.32	0.83	0.006
Male sex	0.62	0.34	1.13	0.12
Not currently smoking	0.89	0.63	1.26	0.50
Education < HS	1.57	1.09	2.26	0.02
Continuous				
Height, in	0.95	0.89	1.02	0.15
Pack-years (10 yr)	1.08	1.00	1.17	0.06
BMI, kg/m^2	0.99	0.97	1.02	0.53
Age (10 yr)	1.40	1.10	1.76	0.005
Baseline FEV_1, 100 ml	1.06	1.02	1.09	0.001

Definition of abbreviations: BMI = body mass index; HS = high school; OR = odds ratio.

* This odds ratio for decline in FEV_1 represents the reduction in odds when Native American genetic ancestry proportion is increased by 0.32; this is the mean difference in Native American genetic ancestry between Hispanic and non-Hispanic white individuals.

† Total n = 1,060. Analysis includes all Hispanic and non-Hispanic white individuals with available longitudinal and AIM data.

FEV_1/FVC (Table E8). Native American genetic ancestry was not significantly associated with chronic bronchitis. The ORs when evaluating COPD (GOLD) were similar whether using self-reported ethnicity (Table 2) or Native American genetic ancestry (Table 5) as predictors. A unit, which was equivalent to the mean difference in Native American proportion between Hispanics and NHW individuals in the LSC, was used to convert the ORs and confidence intervals in Table 5 so that they are comparable to those based on self-reported ethnicity in Table 2. This OR for COPD represents the reduction in odds when NA genetic ancestry proportion is increased by 0.32; this is the mean difference in NA genetic ancestry between Hispanics and NHW individuals (Table 4).

Higher Native American genetic ancestry was also associated with reduced odds of rapid decline of absolute FEV_1 (OR, 0.51; $P = 0.006$) (Table 6). Again, a unit equivalent to the mean difference in Native American genetic ancestry between Hispanics and NHW individuals was used to make the results of Table 6 comparable to those of Table 3. When evaluating, the adjusted point estimate based on ethnicity defined by genetic ancestry was much larger (78.32 ml/yr) than that obtained using self-reported ethnicity (26.13 ml/yr) (Tables E7 and E9). Native American genetic ancestry was similarly associated with reduced decline in a confirmatory analysis using mixed modeling and treating absolute FEV_1 as a repeated measure ($P < 0.002$).

Further cross-sectional analysis examining Native American genetic ancestry within the self-identified "Hispanics only" subset showed that Hispanics with high Native American genetic ancestry were less likely to have COPD than Hispanics with low Native American genetic ancestry (Table E10). For this analysis, Hispanics were dichotomized into high and low Native American genetic ancestry using the mean Native American proportion as the cut point. Although these differences did not reach statistical significance, the OR in this subset (0.55) (Table E10) was similar to that seen for the entire group (OR, 0.47) (Table 5). Linear modeling also revealed similar trends for higher Native American genetic ancestry and higher FEV_1 and FEV_1/FVC, although these results did not reach statistical significance (data not shown).

DISCUSSION

Ethnicity is a cultural construct with environmental, social, and genetic components, which influences the prevalence and morbidity of complex diseases. This longitudinal study of current and former smokers of Hispanic and NHW ethnicity in New Mexico demonstrates two important findings: (*1*) Self-reported Hispanic ethnicity is significantly associated with lower odds of COPD in cross-sectional analysis as well as less decline in absolute FEV_1 in longitudinal analysis, and (*2*) similar associations are noted when Native American genetic ancestry proportions are used as a predictor. We further demonstrate that the "protective effect" of self-reported Hispanic ethnicity in New Mexican smokers toward lung disease is more likely explained by their Native American ancestry rather than by their lower pack-years of smoking. The present study validates our previous findings (9) using a larger sample of smokers that now includes men and extends those findings by evaluating longitudinal decline in lung function and using genetic ancestry in addition to self-reported ethnicity.

Previous reports have shown that among smokers in New Mexico, Hispanics consume fewer cigarettes per day than NHW individuals (21). Consistent with this, Hispanics in the LSC had fewer pack years but similar duration of smoking as NHW individuals. However, they also were significantly more likely to be currently smoking. Examination of these smoking variables and appropriate adjustment in the regression models indicated that Hispanic protection against poor lung function outcomes is not explained by differences in smoking behaviors between Hispanics and NHW individuals. This was further confirmed by analyses that matched Hispanics and NHW individuals on cumulative pack years of smoking or packs per day while smoking.

Self-reported Hispanic and NHW ethnicity was reasonably well correlated with estimates of genetic ancestry in the current study. Significant associations between ethnicity and COPD outcomes are observed whether using the estimated Native American proportion as a continuous predictor or using self-reported ethnicity as a categorical predictor. These findings suggest that the difference in susceptibility to COPD between NHW individuals and Hispanics may be explained by disease protective or risk alleles being present at higher frequencies in the Native American or European genetic backgrounds, respectively. Given the differences in risk for COPD between Hispanics and NHW individuals,

admixture mapping in Hispanics is an attractive approach for identifying genetic risk factors (8, 22). A number of reports have identified reduced panels of markers appropriate for admixture mapping in Hispanics (20, 23, 24). The current study provides evidence that the phenotypes of COPD and longitudinal decline in FEV_1 are excellent candidate phenotypes for admixture mapping in New Mexican Hispanics.

In "Hispanics only" analyses, higher Native American genetic ancestry was associated with less COPD, although this finding did not reach statistical significance. The current study has limited power for "Hispanics only" analysis, given the relatively small number of Hispanics in the LSC. Nonetheless, the overall findings of the current study may help explain observations reported in the PLATINO study in five Latin American cities (25). In that study, the prevalence of COPD was significantly lower (7.8%) in Mexico City, where the population has a larger proportion of Native American ancestry, than in Montevideo (20%), where the population has a much larger proportion of European ancestry. We hypothesize that detailed studies of the Native American genetic proportion of the Hispanic populations in those cities would help clarify these findings.

The "Hispanic Paradox" refers to the fact that, despite worse socioeconomic indicators and higher prevalence of comorbidities, Hispanics have a lower all-cause mortality rate than NHW individuals. Hispanics in the LSC had significantly lower educational level and income than NWH individuals (data not shown). Lower education level and lower income has previously been shown to be independently associated with a wide array of poor COPD-related health outcomes (26). However, Hispanics show protection against FEV_1 decline and COPD in spite of these lower socioeconomic indicators, suggesting a large influence by unknown protective factor(s) against COPD. Although we did not assess correlations between ethnicity and mortality, it is likely that the apparent protective effect of Hispanic ethnicity against COPD and lung function decline translates into reduced mortality and thus may partly explain the Hispanic paradox. Indeed, previous data by Samet and colleagues showed that mortality from COPD in New Mexican Hispanics is lower than that for NHW individuals (7).

A limitation of our study is that AIMs are highly correlated with self-reported ethnicity; hus, the observed associations could primarily be due to unstudied environmental covariates, such as diet, exposure to outdoor and work place air pollution, or psychosocial stress factors. In addition, smoking behavior is a complex variable that may not be completely captured by measures such as pack years and current smoking status. It is difficult to account for factors such as type of cigarettes, depth of inhalation, or number of puffs per cigarette, which may differ between NHW individuals and Hispanics. However, previous reports provide evidence that Hispanics may underreport amount of cigarette smoking (27), which, if underestimated in our study, would only strengthen the observed protective nature of Hispanic ethnicity. Finally, because the participants to the LSC were recruited from the community using newspaper and radio advertisement, our study cohort may not be representative of all smokers in New Mexico and in other parts of the United States.

The current study, using well defined estimates of genetic ancestry to investigate risk for COPD, provides a foundation for understanding differences in COPD risk in other Hispanic subgroups in future studies. Future directions in the LSC include recruitment of a larger number of Hispanic participants to identify specific genetic loci that may confer resistance to COPD.

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript. The State of New Mexico and the National Institutes of Health had no influence in each of the following: design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

References

1. Minino A, Xu J, Kochanek K. Deaths: preliminary data for 2008: National vital statistics reports [internet]. December 2010. Available from: http://www.cdc.gov/nchs/data/nvsr/nvsr59/nvsr59_02.pdf [accessed December 16, 2010].
2. Gifford AL, Cunningham WE, Heslin KC, Andersen RM, Nakazono T, Lieu DK, Shapiro MF, Bozzette SA. Participation in research and access to experimental treatments by HIV-infected patients. *N Engl J Med* 2002;346:1373–1382.
3. Bryc K, Velez C, Karafet T, Moreno-Estrada A, Reynolds A, Auton A, Hammer M, Bustamante CD, Ostrer H. Colloquium paper: Genome-wide patterns of population structure and admixture among hispanic/latino populations. *Proc Natl Acad Sci USA* 2010;107:8954–8961.
4. Bertoni B, Budowle B, Sans M, Barton SA, Chakraborty R. Admixture in Hispanics: Distribution of ancestral population contributions in the continental united states. *Hum Biol* 2003;75:1–11.
5. Pew Hispanic Center. Demographic profile of Hispanics in New Mexico, 2009. Available from: http://pewhispanic.org [accessed December 16, 2010].
6. Samet JM, Schrag SD, Howard CA, Key CR, Pathak DR. Respiratory disease in a New Mexico population sample of hispanic and non-hispanic whites. *Am Rev Respir Dis* 1982;125:152–157.
7. Samet JM, Wiggins CL, Key CR, Becker TM. Mortality from lung cancer and chronic obstructive pulmonary disease in new mexico, 1958–82. *Am J Public Health* 1988;78:1182–1186.
8. Brehm JM, Celedon JC. Chronic obstructive pulmonary disease in Hispanics. *Am J Respir Crit Care Med* 2008;177:473–478.
9. Sood A, Stidley CA, Picchi MA, Celedon JC, Gilliland F, Crowell RE, Belinsky SA, Tesfaigzi Y. Difference in airflow obstruction between Hispanic and non-Hispanic white female smokers. *COPD* 2008;5:274–281.
10. American Thoracic Society. Standaridization of spirometry: 1994 update. *Am J Respir Crit Care Med* 1995;152:1107–1136.
11. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, Coates A, van der Grinten CP, Gustafsson P, Hankinson J, *et al.* Interpretative strategies for lung function tests. *Eur Respir J* 2005;26:948–968.
12. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999;159:179–187.
13. American Thoracic Society. Chronic bronchitis, asthma, and pulmonary emphysema: a statement by the Committee on Diagnostic Standards for Nontuberculous Respiratory Diseases. *Am Rev Respir Dis* 1962; 85:762.
14. Conti DV, Lee W, Li D, Liu J, Van Den Berg D, Thomas PD, Bergen AW, Swan GE, Tyndale RF, Benowitz NL, *et al.* Nicotinic acetylcholine receptor beta2 subunit gene implicated in a systems-based candidate gene study of smoking cessation. *Hum Mol Genet* 2008;17:2834–2848.
15. Pritchard JK, Stephens M, Donnelly P. Inference of population structure using multilocus genotype data. *Genetics* 2000;155:945–959.
16. Hubisz MJ, Falush D, Stephens M, Pritchard JK. Inferring weak population structure with the assistance of sample group information. *Mol Ecol Resour* 2009;9:1322–1332.
17. The R project for statistical computing [internet]. Available from: http://wwwr-projectorg/ [accessed November 11, 2010].
18. Thompson ML, Myers JE, Kriebel D. Prevalence odds ratio or prevalence ratio in the analysis of cross sectional data: What is to be done? *Occup Environ Med* 1998;55:272–277.
19. Shtatland ES, Kleinman K, Cain EM. One more time about r2 measures of fit in logistic regression [internet]. Statistics, data analysis & econometrics. Available from: http://www.lrz.de/∼wlm/ST004.pdf [accessed December 16, 2010].
20. Tian C, Hinds DA, Shigeta R, Adler SG, Lee A, Pahl MV, Silva G, Belmont JW, Hanson RL, Knowler WC, *et al.* A genomewide single-nucleotide-polymorphism panel for Mexican American admixture mapping. *Am J Hum Genet* 2007;80:1014–1023.
21. Humble CG, Samet JM, Pathak DR, Skipper BJ. Cigarette smoking and lung cancer in 'Hispanic' whites and other whites in New Mexico. *Am J Public Health* 1985;75:145–148.

22. Gonzalez Burchard E, Borrell LN, Choudhry S, Naqvi M, Tsai HJ, Rodriguez-Santana JR, Chapela R, Rogers SD, Mei R, Rodriguez-Cintron W, *et al*. Latino populations: a unique opportunity for the study of race, genetics, and social environment in epidemiological research. *Am J Public Health* 2005;95:2161–2168.
23. Mao X, Bigham AW, Mei R, Gutierrez G, Weiss KM, Brutsaert TD, Leon-Velarde F, Moore LG, Vargas E, McKeigue PM, *et al*. A genomewide admixture mapping panel for Hispanic/Latino populations. *Am J Hum Genet* 2007;80:1171–1178.
24. Price AL, Patterson N, Yu F, Cox DR, Waliszewska A, McDonald GJ, Tandon A, Schirmer C, Neubauer J, Bedoya G, *et al*. A genomewide admixture map for Latino populations. *Am J Hum Genet* 2007;80:1024–1036.
25. Menezes AM, Lopez MV, Hallal PC, Muino A, Perez-Padilla R, Jardim JR, Valdivia G, Pertuze J, de Oca MM, Talamo C, *et al*. Prevalence of smoking and incidence of initiation in the latin american adult population: The platino study. *BMC Public Health* 2009;9:151.
26. Eisner MD, Blanc PD, Omachi TA, Yelin EH, Sidney S, Katz PP, Ackerson LM, Sanchez G, Tolstykh I, Iribarren C. Socioeconomic status, race and copd health outcomes. *J Epidemiol Community Health* 2011;65:26–34.
27. Perez-Stable EJ, Marin BV, Marin G, Brody DJ, Benowitz NL. Apparent underreporting of cigarette consumption among Mexican American smokers. *Am J Public Health* 1990;80:1057–1061.