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Pulmonary Function Disparities Exist and Persist in Hispanic Patients With Cystic Fibrosis: A Longitudinal Analysis

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Abstract

Background—Hispanic patients with cystic fibrosis (CF) have decreased life expectancy compared to non-Hispanic white patients. Pulmonary function is a main predictor of life expectancy in CF. Ethnic differences in pulmonary function in CF have been understudied. The objective was to compare longitudinal pulmonary function between Hispanic and non-Hispanic white patients with CF.

Methods—This cohort study of 15,018 6–25 years old patients in the CF Foundation Patient Registry from 2008 to 2013 compared FEV_1 percent predicted and longitudinal change in FEV_1 percent predicted in Hispanic to non-Hispanic white patients. We used linear mixed effects models with patient-specific slopes and intercepts, adjusting for 14 demographic and clinical variables. We did sub-analyses by CFTR class, F508del copies, and PERT use.

Results—Hispanic patients had lower FEV_1 percent predicted (79.9%) compared with non-Hispanic white patients (85.6%); (−5.8%, 95% CI −6.7% to −4.8%, $p<0.001$), however, there was no difference in FEV_1 decline over time. Patients on PERT had a larger difference between Hispanic and non-Hispanic white patients in FEV_1 percent predicted than patients not on PERT (−6.0% vs. −4.1%, $p=0.02$). The ethnic difference in FEV_1 percent predicted was not statistically significant between CFTR classes (Class I–III: −6.1%, Class IV–V: −5.9%, Unclassified: −5.7%, $p>0.05$) or between F508del copies (None: −7.6%, Heterozygotes: −5.6%, Homozygotes: −5.3%, $p>0.05$).

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Conclusions—Disparities in pulmonary function exist in Hispanic patients with CF early in life and then persist without improving or worsening over time. It is valuable to investigate the factors contributing to pulmonary function in Hispanic patients with CF.

Keywords

Cystic Fibrosis (CF); Epidemiology; Pulmonary Function Testing (PFT); Social Dimensions of Pulmonary Medicine; Healthcare Disparities; Hispanic Latino

Introduction

Cystic Fibrosis (CF) is the second most common life-shortening childhood disease. CF causes chronic lung damage from infections leading to respiratory failure. While CF predominately affects non-Hispanic white patients (94%), the percentage of Hispanic patients with CF has doubled in the past 20 years in the CF Foundation Patient Registry (CCFPR)[1]. As birthrates in Hispanic Americans increase in the US compared with non-Hispanic white Americans[2], the proportion of patients with CF who are Hispanic will likely increase commensurately. Despite great advances in CF treatment and survival, Hispanic patients have an 85% increased risk of death annually due to CF[3] compared with non-Hispanic white patients. It is not known why Hispanic patients with CF have shorter life expectancy.

Pulmonary function is the strongest predictor of life expectancy in CF[4]. Pulmonary function is determined by environmental, healthcare-related, and biological factors, some of which are known to be different in Hispanic patients. CF transmembrane receptor (*CFTR*) gene mutation severity affects pulmonary function[5]. Hispanic and non-Hispanic white patients have different distributions of *CFTR* mutations[6–8], including Hispanic patients are more likely to have rare or *de novo* mutations[7]. Pancreatic insufficiency is associated with more severe pulmonary function and Hispanic patients are less likely to have pancreatic insufficiency[9]. Hispanic patients acquire Pseudomonas at an earlier age, which negatively affects pulmonary function[8]. The effect of many of these factors on pulmonary function in Hispanic patients is unknown.

While ethnic disparities in pulmonary function in CF have been described previously, the analyses were unadjusted for confounders known to affect pulmonary function[8; 10]. We used a large database of Hispanic patients with CF, the CFFPR[1], to investigate longitudinal change in pulmonary function between Hispanic and non-Hispanic white patients with CF.

Methods

Study Population

This is a cohort study of Hispanic and non-Hispanic white patients in the CFFPR, a retrospective observational study of individuals from accredited CF centers which includes approximately 81–84% of CF patients in the US[11]. We included 15,268 patients with CF, ages 6 to 25 years old, between January 1, 2008 to December 31, 2013, with pulmonary function measured at least once. Patients contributed between 1 and 19 measures of

pulmonary function, with an average of 8.1 measurements. We analyzed all data from time of entry to CFFPR until December 31, 2013 or age >25 years.

Outcome Variables

Percent predicted pulmonary function was calculated based on Global Lung Initiative (GLI) equations[12]. The primary outcomes were forced expiratory volume in one second (FEV_1) percent predicted and annual change in FEV_1 percent predicted. Forced vital capacity (FVC) percent predicted, forced expiratory flow at 25%–75% of FVC ($FEF_{25–75}$%) percent predicted, and FEV_1/FVC were secondary outcomes. Annual pulmonary function was the average of the 4 highest quarterly values during a calendar year. We did not include data obtained after lung transplantation. Change in FEV_1 percent predicted was not analyzed in the 445 patients with only 1 measurement of FEV_1 percent predicted.

Predictor Variable

The primary predictors were patient age and self-reported race and ethnicity, characterized as Hispanic or non-Hispanic white. Since age varies both within and between patients, we isolated the pure within-patient change by decomposing the age covariate into between- and within-patient components[13; 14]. Specifically, we calculated patient-specific mean age as the between-patient component, as well as the deviations of each patient's age from their patient-specific mean age as the within-patient component, and included both components in our models.

Covariates

The following variables were included *a priori* in all models: age, sex, pancreatic enzyme replacement therapy (PERT), body mass index (BMI), sweat chloride concentration, methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa*, tobacco exposure, age at diagnosis, CF-related diabetes, CFTR mutation class, and location. Insurance status, maternal education, and household income were considered as surrogates for socioeconomic status (SES)[15–17]. Insurance status and maternal education were statistically significant and included in all models.

Covariates were recorded annually. Patients were classified as underweight if their BMI was $<10^{th}$ percentile if age <20 years or BMI was <18.5 kg/m^2 if age ≥20 years[18]. Patients were considered MRSA or *Pseudomonas* positive if there was a positive respiratory culture. Maternal education was defined as high school or less compared with some college or more. Insurance type was defined as whether the patient had Medicaid regardless of secondary insurance listed, no Medicaid, or no insurance. Tobacco exposure was defined as no tobacco, secondhand tobacco exposure, and active smoker. Age at diagnosis was recorded in months. F508del copies were defined as homozygotes, heterozygotes, or no copies. CFTR mutation classes were defined as CFTR class I–III, CFTR class IV–V, or unclassified[5]. Location in the US was defined as West, Midwest, Northeast, or South by US census classification[19]. Missing data in covariates was assessed and assumed to be missing at random, as missingness is associated with CF center ID[20], perhaps due to some CF centers not collecting complete datasets.

Statistical Analysis

We fit linear mixed effects regression models to the longitudinal pulmonary function data with patient-specific random intercepts and random slopes to compare pulmonary function between Hispanic and non-Hispanic white patients. The models included the between- and within-patient components of age described above. The regression coefficient of the within-patient age component is the change in pulmonary function as a patient aged by one year. The regression coefficient of the between-patient age component is the difference in pulmonary function between two patients whose average age in the study differed by one year[13; 14]. To determine annual change in FEV_1 percent predicted, we assessed the interaction of ethnicity and within-patient age using a Wald test.

Since the missing at random assumption seemed reasonable, we performed multiple imputations by chained equations to address missing data (10 data sets were imputed and analyzed)[21]. For subgroup analyses, we included the interaction of ethnicity and the variable of interest into the model. We compared ethnic differences in FEV_1 percent predicted by PERT use, F508del copies, and CFTR mutation severity. To assure our findings were not an artifact of the GLI predictive equations[12], we compared the results to two other well-accepted predictive equations used for CF: Wang-Hankinson[22; 23] and CF-specific[24].

A P-value <0.05 was considered statistically significant. Statistical analysis was performed with Stata 14.1 (Stata Corporation, College Station, Texas). The study was approved by the University of California San Francisco IRB.

Results

Study Population Characteristics

The study sample consisted of 15,018 individuals with CF from the CFFPR who were Hispanic or non-Hispanic white, after excluding 523 patients due to no pulmonary function measurements and 210 patients due to missing race/ethnicity. Post-pulmonary transplant pulmonary function was not analyzed in 347 patients. Hispanic patients made up 9.9% of the study sample (Table 1). Compared to non-Hispanic white patients, Hispanic patients were diagnosed later (6.3 vs. 4.5 months), less likely to use PERT (88.5% vs. 92.5%), less likely to be F508del homozygotes (25.9% vs. 49.9%), and less likely to have CFTR Class I–III mutations (51.4% vs. 74.1%).

Pulmonary Function

Hispanic patients had lower FEV_1 percent predicted, FVC percent predicted, $FEF_{25–75}$ percent predicted, and FEV_1/FVC compared with non-Hispanic white patients (Figure 1, Table 2). There was no statistical difference in the between-patient change in FEV_1 percent predicted and in the within-patient change in FEV_1 percent predicted (Wald test p=0.1) (Table 2).

Sub-analyses

In patients on PERT, there was a larger different in FEV_1 percent predicted between Hispanic and non-Hispanic white patients compared to patients not on PERT (p=0.02, Table

3). The ethnic difference in FEV_1 percent predicted was not statistically different between F508del homozygotes, F508del heterozygotes, or those with no F508del copies (p>0.05, Table 3). Patients with Class I–III CFTR mutations had a slightly larger difference between Hispanic and non-Hispanic white patients than in patients with Class IV–V CFTR mutations or unclassified CFTR mutations, but it was not statistically significant (p>0.05, Table 3).

Sensitivity Analysis: Pulmonary Predictive Equations

Both Wang Hankinson[22; 23] pulmonary predictive equations(−6.3%, 95% CI −7.3% to −5.3%, p<0.001) and CF-specific pulmonary predictive equations[24] (−8.8; 95% CI −10.2 to −7.3%, p<0.001) had a larger difference in FEV_1 percent predicted by ethnicity than with the GLI pulmonary predictive equations.

Discussion

In a large cohort of patients with CF, we found that the gap in pulmonary function between Hispanic and non-Hispanic white patients begins early in life. The ethnic gap in pulmonary function exists when spirometry is first performed at 6 years old. This suggests that factors contributing to the ethnic difference in pulmonary function occur much earlier than the time of first performing spirometry, anywhere from prenatal to age 5 years. We observed that Hispanic patients had a 5.8% lower FEV_1 percent predicted than non-Hispanic white patients with CF. However, the degree of difference in FEV_1 percent predicted was independent of age, as there was no difference in the rate of decline in FEV_1 percent predicted by ethnicity from 6 to 25 years old. The ethnic gap in FEV_1 percent predicted neither worsens nor improves over time, as there is no difference in the rate of decline by ethnicity from 6 to 25 years old.

Previous studies of pulmonary function in Hispanic patients with CF also found that Hispanic patients had lower pulmonary function. In a smaller cohort, Buu et al. found that in California at age 6 years old, Hispanic patients with CF had 12% lower FEV_1 percent predicted than non-Hispanic patients, but was not adjusted for confounders[10]. Our results were similar to Watts et al. found that Hispanic patients had 5.5% lower FEV_1 percent predicted than non-Hispanic white patients, but was not adjusted for confounders[8]. Our study advances the understanding of pulmonary function in Hispanic patients with CF by finding that even after controlling for factors known to impact pulmonary function, there is still a gap in pulmonary function between Hispanic and non-Hispanics white patients. This indicates that there are factors that have yet to be identified that negatively impact pulmonary function in Hispanic patients early in life, but do not change the trajectory of pulmonary function decline.

To combat health disparities in Hispanic patients with CF, it is essential to first understand the complex factors contributing to pulmonary function. There are several factors that influence the severity of pulmonary disease in CF and can be grouped into 3 classes: environmental (socioeconomic, air pollution, tobacco exposure); healthcare-related (medication compliance, medical literacy, medications prescribed); and biological (infections, genetics)[16]. Hispanic patients may have increased exposure to these factors or a

differential response. To elucidate and address the stark disparities in pulmonary function require examination of all potential factors.

Environmental Contributing Factors

Approximately 50% of variation in pulmonary function in CF is due to environmental factors or exposures[25–27]. Overall, 20% of children with CF report tobacco exposure, while some CF centers report 90% of patients exposed[1]. Hispanic children are more likely to be exposed to both tobacco[28] and air pollution[29]. Tobacco and air pollution negatively impact pulmonary function in children both with and without CF[26; 27; 30–32], which may contribute to the observed ethnic disparity in CF. Hispanic patients may be differentially exposed of effected by environmental exposures early in life. This exposure may lower pulmonary function in Hispanic patients, but not steepen decline. Investigations are needed in the ethnic differences in both the differential exposure and effects of environmental factors, such as air pollution and secondhand tobacco.

There are socioeconomic factors unmeasured by the CFFPR that may influence Hispanic patients' pulmonary function. Poor Hispanic individuals are more likely to live in higher poverty neighborhoods than poor non-Hispanic white individuals[17]. Wealth (e.g. savings, home ownership) can help buffer times of illness[17], however, wealth varies by ethnicity in similar income brackets[17]. Future studies of disparities in CF should strive to collect as many measures of SES as possible.

Hispanic Specific Contributing Factors

Separate from SES, there are factors that affect pulmonary function in Hispanic patients in particular. Language spoken, fluency, and interpreter use affect understanding of CF, treatments, and medications[33]. Language barriers result in worse health outcomes in Hispanic patients[34; 35] but have not been studied in CF. Language barriers may play a more significant role early in life when parents are learning about the diagnosis and treatments; this may lead to lower pulmonary function early in life, but not a steeper decline later in life. However, language is not the only barrier for Hispanic patients with CF. We found that Hispanic patients with CF are more likely to have Medicaid or no insurance. In CF, children with Medicaid have lower pulmonary function than those with non-Medicaid insurance[15]. Hispanic patients who have undocumented immigration status are at higher risk for not having insurance, even when the child is a US citizen[36]. Level of acculturation and immigration status negatively affect asthma severity in Hispanic patients[37], but have not been studied in CF. Hispanic patients with CF are a diverse group culturally and have diverse barriers to adequate healthcare. There should be future studies of the effects of language, acculturation, and insurance status on pulmonary function in Hispanic patients with CF.

Healthcare-Related Contributing Factors

There is a high rate of medication non-adherence in CF, which reduces effectiveness. The treatment regimen is complex and time-consuming. Adherence is related to disease knowledge and understanding the medication[38]. Hispanic families potentially have greater barriers to adherence due to level of acculturation and language spoken. A pilot study found that parents of Hispanic patients with CF were more likely to have inadequate or marginal

health literacy[39]. Parents with lower health literacy may take longer to learn about CF, medications, and treatments, which could differentially affect pulmonary function early in life while the parents are learning. In asthma, medication adherence is lowest in Hispanic patients[40]; ethnic differences in medication adherence may contribute to disparities in CF and should be studied further.

Improvements in pulmonary function in CF are attributable, at least in part, to new medications. However, these medications have not been sufficiently studied in Hispanic patients, as Hispanic patients were proportionally underrepresented, taking part in only 7.5% of studies[41]. When included, Hispanic patients comprised only 2% of patients, which is insufficient to investigate ethnic differences in drug response. There are risks to extrapolating trial results to Hispanic patients; as certain drugs are metabolized differently in non-Hispanic white patients compared to Hispanic patients[42]. The effect or use of CF drugs may be different in Hispanic patients, which could lead to lower pulmonary function early in life. Future CF drug studies should be designed and conducted in a manner to enroll enough Hispanic patients to not just represent the baseline CF population but to detect differences in drug response.

Biological Contributing Factors

Despite having a lower detection rate on newborn screen, Hispanic patients are diagnosed with CF at the same age or earlier as non-Hispanic white patients[8; 10]. Hispanic patients are diagnosed primarily from respiratory symptoms, which could possibly be from early respiratory infections. Non-Hispanic white infants with early respiratory symptoms have lower pulmonary function in childhood[43]. Early infections, such as *Pseudomonas*, negatively affect pulmonary function later in life[44]. Hispanic patients acquire *Pseudomonas* four years earlier than non-Hispanic white patients[8; 10]. Earlier acquisition of *Pseudomonas* may explain why Hispanic patients have lower pulmonary function by 6 years old. We found that Hispanic patients are more likely to have *Pseudomonas* overall, but less likely to have MRSA than non-Hispanic white patients, which may explain why we did not observe a different in FEV_1 decline. Studies are needed to investigate the effect of other respiratory infections, such as atypical mycobacteria, viruses, and bacteria, on pulmonary function in Hispanic patients.

Hispanic patients are less likely to be treated with PERT, a marker of pancreatic insufficiency, which is associated with lower pulmonary function[9]. We found that there was a smaller gap in FEV_1 percent predicted in patients not on PERT than those on PERT. We adjusted for being underweight, but there may be other nutritional differences in pancreatic insufficient Hispanic patients contributing to pulmonary function. Nutritional status is protective to pulmonary function in non-Hispanic white patients[45]; the effect of nutrition in Hispanic patients is not known. Early life nutrition may lead lower pulmonary function early in life but not change decline and needs to be investigated.

Even though CFTR mutation severity is a leading predictor of pulmonary function[5] and Hispanic patients have a different distribution of CFTR mutations[7; 8], we found that CFTR mutation severity did not explain the ethnic disparity in pulmonary function. Even when comparing patients who are F508del homozygous, Hispanic patients had lower pulmonary

function indicating the disparity is driven by something other than CFTR mutations, such as modifier genes. CFTR and modifier genes are estimated to account for 50% of pulmonary function variability[25]. Modifier genes have not been studied specifically in Hispanic patients and may explain why Hispanics have lower pulmonary function early in life. A third of Hispanic patients have CFTR mutations with unclassified function, most rare or *de novo*[7]. Since pulmonary function decline is similar between ethnicities despite Hispanic patients being less likely to have severe mutations or F508del homozygote, many of these unclassified CFTR mutations likely lead to a non-functional CFTR channel and severe effects on pulmonary function. Further exploration of the function and effect of these unclassified mutations is needed, with particular focus on mutations in Hispanic patients.

Limitations

We recognize several limitations of our study. First, patients could have been misclassified as Hispanic or non-Hispanic white, which would underestimate the association of ethnicity with pulmonary function. This is unlikely to be a significant factor given that in the CFFPR, less than 2% of race and ethnicity was inaccurate[11]. Second, only the GLI and the CF-specific predictive equations were created using Hispanic individuals. The GLI has a predictive equation created from individuals in Europe, North America, and South American, including Latin American and Mexican American datasets[12]. None of the 3 sets of predictive equations have an equation specifically for Hispanic individuals only. The observed ethnic differences in pulmonary function may be an artifact of the predictive equations themselves; however, we found that Hispanic patients had lower pulmonary function in all 3 sets of equations. Third, only 81–84% of patients with CF in the U.S. are included in the CFPR[11]. CF continues to be under-recognized in Hispanic Americans and Hispanic patients are less likely to be diagnosed via newborn screen[7]. Hispanic patients with mild CF are more likely than non-Hispanic white patients to be misdiagnosed and thus may not be included in the CFFPR. Thus, our findings may be due to the CFPR not including Hispanic patients with mild disease. However, since the ethnic disparity exists in patients with CFTR Class I–III mutations, underrepresentation is less likely to explain the pulmonary function disparity.

Conclusion

Disparities in pulmonary function exist in Hispanic patients with CF early in life and then persist without improvement or worsening over time. It is valuable to investigate the factors contributing to pulmonary function in Hispanic patients with CF.

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Abbreviation List

BMI	Body Mass Index
CF	Cystic Fibrosis
CFFPR	Cystic Fibrosis Foundation Patient Registry
CFRD	Cystic Fibrosis Related Diabetes
CFTR	Cystic Fibrosis Transmembrane Receptor
$FEF_{25–75}$	Forced Expiratory Flow At 25%–75% Of FVC
FEV_1	Forced Expiratory Volume in One Second
FVC	Forced Vital Capacity
GLI	Global Lung Initiative
MRSA	Methicillin-Resistant Staphylococcus aureus
PERT	Pancreatic Enzyme Replacement Therapy
SES	Socioeconomic Status

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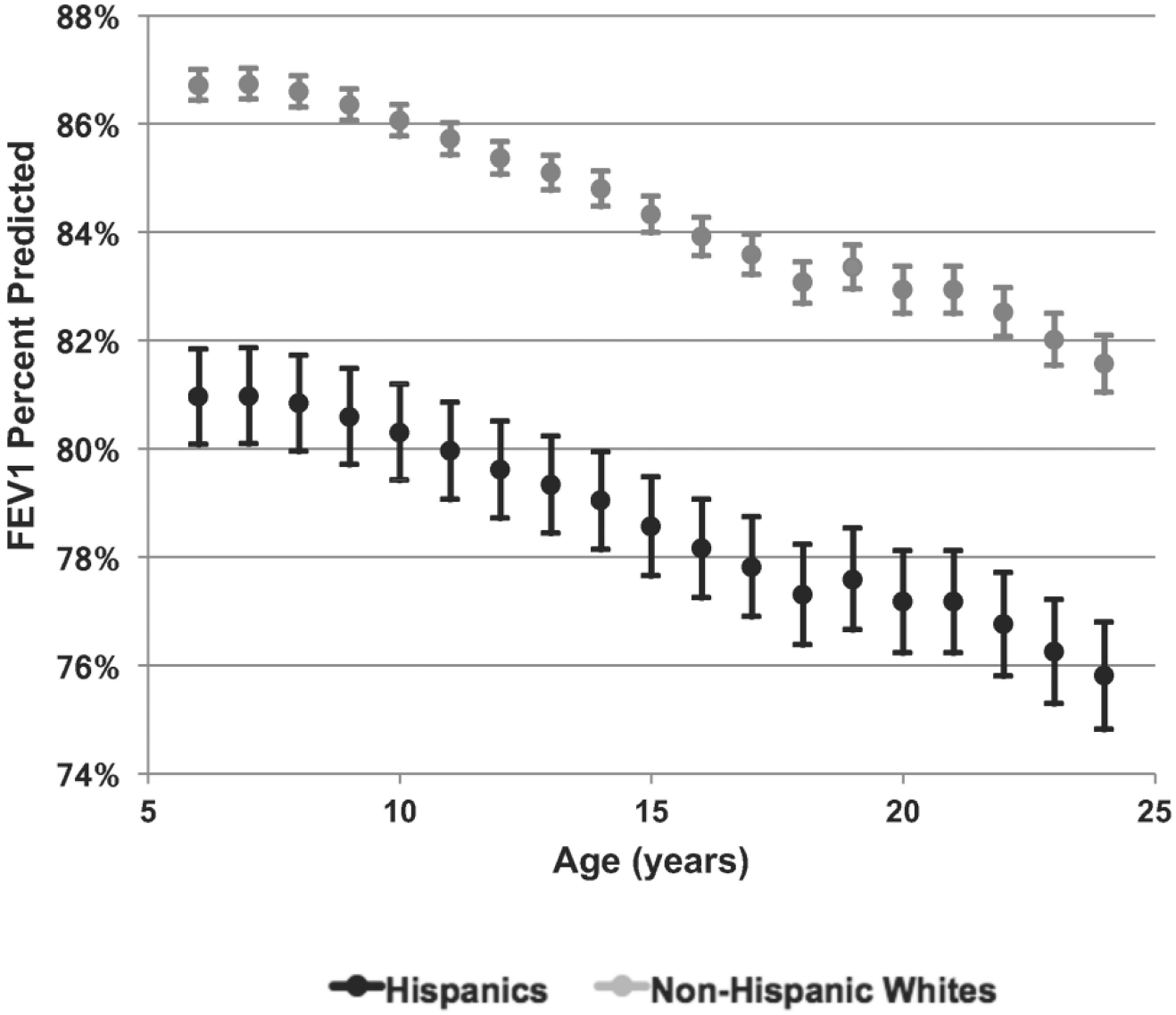

Figure 1. FEV_1 Percent Predicted In Hispanic And Non-Hispanic White Patients With Cystic Fibrosis

Longitudinal FEV1 Percent Predicted adjusted for the following confounders: age, sex, BMI, sweat chloride concentration, PERT use, MRSA, pseudomonas aeruginosa, maternal education level, insurance type, tobacco exposure, age at diagnosis, CF-related diabetes, CFTR mutation severity, and location in the U.S.

Table 1

Study Population Characteristics At Cohort Entry

	Hispanic Patients	Non-Hispanic White Patients	Difference (95% CI)	p-Value
Number (%)	1,493 (9.9)	13,525 (90.1)		
Age, year[a]	6.9 (6.5–7.4)	6.8 (6.5–7.1)	0.1 (0 to 0.3)	<0.001
Sex, male	826 (53.1)	7,233 (51.1)	2.0 (−1.7 to 5.6)	0.1
PERT	1,343 (88.5)	12,755 (92.3)	3.8 (2.1 to 5.7)	<0.001
Sweat Chloride Concentration[a]	94.7 (93.5–95.9)	97.1 (96.7–97.5)	−2.4 (−3.5 to −1.2)	<0.001
Age At Diagnosis, mths[a]	6.3 (1.6–38.4)	4.5 (0.7–25.7)	1.8 (0.9 to 12.7)	<0.001
Body Mass Index[a]				
Percentile (if <20yo)	54.1 (53.6–55.6)	50.6 (50.1–51.0)	3.6 (2.0 to 5.1)	<0.001
BMI kg/m^2 (if ≥20yo)	24.0 (21.0–27.0)	23.3 (22.1–24.5)	0.7 (−2.6 to 3.9)	0.7
Pseudomonas aeruginosa	597 (38.3%)	4,766 (33.6%)	4.7 (0.6 to 9.0)	<0.001
MRSA	195 (12.5%)	2,272 (16.0%)	−3.5 (−4.5 to −2.3)	0.001
CF Related Diabetes	63 (4.1%)	688 (4.9%)	−0.8 (−7.6 to 4.7)	<0.001
Tobacco Exposure				<0.001
None	776 (49.8%)	6,476 (45.7%)	4.1 (0.3 to 7.9)	
Secondhand	100 (6.4%)	1,288 (9.1%)	−2.7 (−7.0 to 4.2)	
Active Smoker	8 (0.5%)	84 (0.6%)	−0.1 (−5.0 to 37.1)	
Maternal Education				<0.001
College & Higher	231 (15.5%)	3,625 (26.8%)	−11.3 (−12.3 to −10.0)	
No College	316 (20.3%)	2,051 (14.5%)	5.8 (1.2 to 10.9)	
Insurance				<0.001
No Medicaid	539 (34.6%)	7.718 (54.5%)	−19.9 (−24.1 to −15.6)	
Medicaid	901 (57.9%)	5,878 (41.5%)	16.4 (12.9 to 19.9)	
No Insurance	31 (2.0%)	88 (0.6%)	1.4 (−3.7 to 14.2)	
F508del				<0.001
Two copies	403 (25.9%)	7,070 (49.9%)	−24.0 (−28.4 to −19.3)	
One copy	583 (37.4%)	5,100 (36.0%)	1.4 (−2.8 to 5.7)	
No copies	469 (30.1%)	1,472 (10.4%)	19.7 (15.3 to 24.3)	
CFTR Mutation Class				<0.001
Class I–III	800 (51.4%)	10,503 (74.1%)	−22.7 (−26.3 to −19.1)	
Class IV–V	133 (8.5%)	1,033 (7.3%)	1.2 (−3.3 to 7.5)	
Not Classified	522 (33.5%)	2,106 (14.9%)	18.6 (14.3 to 23.1)	
Location In U.S.				<0.001
West	545 (35.0%)	2,266 (16.0%)	19 (14.7 to 23.4)	
Midwest	451 (29.0%)	5,070 (35.8%)	−6.8 (−11.2 to −2.2)	
Northeast	236 (15.2%)	3,181 (22.5%)	−7.3 (−11.9 to −1.9)	
South	282 (18.1%)	3,511 (24.8%)	−6.3 (−11.2 to −1.5)	

[a] Median (Interquartile range)

-All other values are reported as percentages

Table 2

Pulmonary Function In Hispanic and Non-Hispanic White Patients With CF

	Hispanic Patients	Non-Hispanic White Patients	Difference	95% CI	p-value
FVC	87.6%	93.0%	−5.3%	−6.2% to −4.5%	<0.001
FEV_1	79.9%	85.6%	−5.8%	−6.7% to −4.8%	<0.001
FEV_1 Between Patient Change	−1.02%	−1.25%	0.23%	−0.00% to 0.46%	0.05
FEV_1 Within Patient Change	−0.03%	−0.02%	−0.01%	−0.06% to 0.04%	0.6
$FEF_{25–75}$	67.3%	71.0%	−3.8%	−5.4% to −2.2%	<0.001
FEV_1/FVC	0.806	0.812	−0.006	−0.01 to −0.002	0.004

a) 1,375 patients did not have $FEF_{25–75}$% data. 445 patients did not have FEV_1 decline data.

b) Models adjusted for age, sex, PERT, BMI, sweat chloride concentration, MRSA, Pseudomonas aeruginosa, maternal education level, insurance type, tobacco exposure, age at diagnosis, CF-related diabetes, CFTR mutation class, and location.

c) All values shown are percent predicted except FEV_1/FVC

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Table 3

Ethnic Differences In FEV_1 Percent Predicted By PERT Use, F508del copies, and CFTR Mutation Class

	FEV_1 In Hispanic Patients	FEV_1 In Non-Hispanic White Patients	Difference In FEV_1 Percent Predicted	95% CI	p-value
Pancreatic Enzyme Replacement					
Yes	79.3%	85.3%	−6.0%	−6.6% to −5.3%	<0.001
No	87.7%	91.8%	−4.1%	−5.0% to −3.2%	<0.001
F508del Copies					
Homozygote	79.8%	85.1%	−5.3%	−7.0% to −5.6%	<0.001
Heterozygote	80.8%	86.3%	−5.7%	−6.5% to −4.6%	<0.001
No Copies	81.1%	88.7%	−7.6%	−8.3% to −7.0%	<0.001
CFTR Mutation Class					
Class I–III	79.0%	85.1%	−6.1%	−7.0% to −5.3%	<0.001
Class IV–V	87.8%	93.7%	−5.9%	−7.7% to −4.0%	<0.001
Unclassified	81.8%	87.5%	−5.7%	−6.5% to −5.0%	<0.001

a) F508del copies were defined as homozygotes, heterozygotes, or no copies. CFTR mutation class was defined as CFTR class I–III, CFTR class IV–V, and unclassified.

b) Models included the variable of interest (PERT use, F508del copies, or CFTR mutation class) with ethnicity interaction, adjusted for age, sex, PERT, BMI, sweat chloride concentration, MRSA, Pseudomonas aeruginosa, maternal education level, insurance type, tobacco exposure, age at diagnosis, CF-related diabetes, CFTR mutation class, and location in U.S.