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Regional Variations in Longitudinal Pulmonary Function: A Comparison of Hispanic and Non-Hispanic Subjects With Cystic Fibrosis in the United States

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Abstract

Background: Hispanic subjects with cystic fibrosis (CF) have increased morbidity and mortality than non-Hispanic white subjects. The ethnic disparity in mortality varies by region. Factors influencing pulmonary function vary by both ethnicity and region.

Objective: To determine if the ethnic difference in pulmonary function varies by region.

Methods: This retrospective cohort study compared differences in longitudinal pulmonary function (percent predicted FVC, FEV_1, $FEF_{25–75}$, FEV_1/FVC, FEV_1 decline) between Hispanic and non-Hispanic white subjects with CF by Census region of the U.S. (West, South, Midwest, Northeast). Subjects were ages 6–25 years and in the CF Foundation Patient Registry from 2008 to 2013. We used linear mixed effects models with subject-specific slopes and intercepts, adjusting for 14 demographic and clinical variables.

Results.—Of 14,932 subjects, 1,433 (9.6%) were Hispanic and 13,499 (90.4%) were non-Hispanic white. Hispanic subjects' FEV_1 was 9.0% (8.3–9.8%) lower than non-Hispanic white subjects in the West, while Hispanic subjects' FEV_1 was only 4.0% (3.0–5.0%) lower in the Midwest, 4.4% (3.1–5.7%) lower in the Northeast, and 4.4% (3.2–5.5%) lower in the South. Similarly, FVC and $FEF_{25–75}$ were lower among Hispanic subjects compared to non-Hispanic white subjects in all U.S. regions, with the biggest differences in the West. Only in the West was FEV_1/FVC significantly lower in Hispanic subjects (−0.019; −0.022 to −0.015). FEV_1 decline was not significantly different between ethnicities in any region.

Conclusions: In CF, Hispanic subjects have lower pulmonary function than non- Hispanic white subjects in all geographic regions with the largest difference in occurring in the West.

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Author contributions: MEM had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. MEM and JMN conducted the study analysis. MEM, JMN, DWN, and NPL contributed substantially to the study design, data interpretation, and the writing of the manuscript.

No conflicts of interest for MEM, JMN, DWN, and NPL.

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Introduction:

Despite great advancements in care and outcomes, Hispanic patients with cystic fibrosis (CF) have worse outcomes compared to non- Hispanic white patients. Hispanic patients have a higher rate of mortality than do non-Hispanic white patients[1,2] and Hispanic youth with CF have worse pulmonary function[3]. Our group has shown that Hispanic youth with CF have 5.8% lower percent predicted FEV_1 compared with non-Hispanic white youth[3]. The ethnic disparity in CF mortality varies significantly between United States Census regions[2]. It is not known whether the ethnic disparity in pulmonary function also varies across geographic regions in the United States.

It is not yet understood what factors contribute to Hispanic patients having more severe pulmonary disease; there are numerous factors that determine pulmonary function in CF. For example, pulmonary function is strongly influenced by CFTR mutation severity[4]; however, Hispanic subjects have worse pulmonary function than non-Hispanic white subjects in all CFTR mutation severity classes[3]. In our prior analysis of pulmonary function[3], Hispanic subjects still had worse pulmonary function[3], even when controlling for measures of respiratory infections, environmental exposures, and socioeconomic status known to affect pulmonary function[5–7]. Many of these factors may not uniformly affect Hispanic patients across the United States. Exposure to factors that influence pulmonary function vary across geographic regions of the United States for all patients[8–11]. Persons of Hispanic ethnicity, also referred to as Latino or the gender neutral LatinX, are disproportionately exposed to some of these factors, such as air pollution, however, this exposure is not uniform across the country[12]. Healthcare factors, such as newborn screening and Medicaid qualifications, vary state by state and may disproportionately affect Hispanic patients[13,14]. Biological factors affecting pulmonary function may also differ between Hispanic patients. Persons of Hispanic ethnicity are a heterogeneous group and vary genetically across the United States due to different immigration patterns and countries of origin[15,16]. Hispanic people originating from Mexico are more likely to have immigrated to the West, while those from the Caribbean are more likely to have immigrated to the Northeast[17]. These different immigration patterns result in diverse genetic ancestry admixture among the Hispanic population between regions.

Given that Hispanic patients have higher mortality rates than non-Hispanic white patients which varied by geographic region[2] and that factors influencing pulmonary function vary by both ethnicity and geographic region, we sought to examine if pulmonary function disparities between ethnicities also vary between U.S. geographic regions. We used the largest database of Hispanic and non-Hispanic white subjects with CF, the United States CF Foundation Patient Registry (CFFPR)[18], to compare whether pulmonary function between ethnicities varies by geographic region of the United States.

Methods:

This is a longitudinal study of Hispanic and non-Hispanic white subjects in the CFFPR, a retrospective observational study of patients from accredited CF centers which includes approximately 81–84% of patients with CF in the United States[18]. We included subjects

with CF, ages 6 to 25 years, enrolled between 2008 to 2013, with pulmonary function measured at least once. Each subject contributed between 1 and 19 years of pulmonary function measurements, with an average of 8.1 years. We analyzed all data from time of entry in CFFPR until December 31, 2013 or age ≥26 years. The study was approved by the University of California, San Francisco Institutional Review Board (15–17491) and the CF Foundation Registry/ Comparative Effectiveness Research Committee.

The primary outcome was longitudinal forced expiratory volume in one second (FEV_1) percent predicted. We also analyzed longitudinal forced vital capacity (FVC) percent predicted, forced expiratory flow at 25%−75% of FVC ($FEF_{25–75\%}$) percent predicted, FEV_1/FVC, and FEV_1 decline as secondary outcomes. Annual pulmonary function was the average of the 4 highest quarterly values during a calendar year based on Global Lung Initiative (GLI) equations[19]. We did not include data obtained after lung transplantation. FEV_1 decline was not analyzed in the 445 subjects with only 1 measurement of FEV_1 percent predicted.

The predictors were domicile location in the United States, defined as the West, Midwest, Northeast, or South according to the United States Census[20], and self-identified race and ethnicity, defined as Hispanic or non-Hispanic white.

All analyses were adjusted *a priori* based on previous medical literature for the following covariates: age, sex, pancreatic enzyme replacement therapy (PERT) use (yes/no), body mass index (BMI) (underweight = BMI <10th percentile if age <20 years or BMI <18.5 kg/m^2 if age ≥20 years[21]), sweat chloride concentration, methicillin-resistant *Staphylococcus aureus* (MRSA) (any positive cultures yearly*), Pseudomonas aeruginosa* (any positive cultures yearly*),* tobacco exposure (no tobacco, secondhand tobacco exposure, vs. active smoker), age at diagnosis, CF-related diabetes, CFTR mutation class (CFTR class I-III, CFTR class IV-V, or unclassified[4]), insurance status (Medicaid regardless of secondary insurance listed, no Medicaid, or no insurance), maternal education (high school or less compared with some college or more), rural urban commuting area codes (rural or urban). Rural Urban Commuting Area Codes (RUCA) are a Census tract-based classification scheme using subject's zip codes from the United States Department of Agriculture to categorize zip codes into rural or urban[22]. Covariates were recorded annually.

Statistical Analysis:

We fit linear mixed effects regression models to the longitudinal pulmonary function data with subject-specific random intercepts and random slopes to compare longitudinal pulmonary function between Hispanic and non-Hispanic white subjects for each United States geographic region. Models included ethnicity, geographic region, and their interaction as well potential confounding variables as predictors. The ethnicity by geographic region interaction terms measured the difference across geographic regions in the ethnic difference in pulmonary function. The following covariates were entered as time-dependent variables: age, PERT use, BMI, sweat chloride concentration, MRSA, *Pseudomonas aeruginosa*, tobacco exposure, CFRD, insurance status, maternal education, and RUCA. MRSA and *Pseudomonas aeruginosa* infections were recorded as any positive cultures yearly. Some

patients had multiple sweat chloride concentrations recorded over years so was entered as a time-dependent variable. If no sweat chloride concentration was done in a year, the last previously sweat chloride concentration value was used. Missing data in covariates was assessed as plausible to be missing at random since not all CF centers collect complete datasets, so we performed multiple imputations by chained equations (10 data sets were imputed and analyzed). Ethnic differences in clinical characteristics and demographics at time of study entry were compared between each geographic region using Chi square tests for categorical variables and Student *t* tests for continuous variables. A 2-sided P-value <0.05 was considered statistically significant. Statistical analysis was performed with Stata 14.1 (Stata Corporation, College Station, Texas).

Results:

Of the 14,932 subjects in our retrospective cohort study, 1,433 were Hispanic (9.6%) and 13,499 were non-Hispanic white (90.4%). Hispanic subjects were asymmetrically distributed across the United States with 36.1% in the West, 29.2% in the Midwest, 15.1% in the Northeast, and 19.5% in the South. Hispanic subjects made up varying proportions of the study cohort by region. In the West, 19.2% of the study cohort was Hispanic compared with 7.9% Hispanic in the Midwest, 6.6% Hispanic in the Northeast, and 7.7% Hispanic in the South.

The cohort's clinical characteristics and ethnic make-up showed great variation across geographic regions of the United States (Table 1). In the West, more Hispanic subjects had MRSA than non-Hispanic white subjects (+1.1%), while in other geographic regions fewer Hispanic subjects had MRSA than non- Hispanic white subjects (−0.9% to −5.9%). There were higher rates of *Pseudomonas aeruginosa* in Hispanic subjects in the West than in non-Hispanic white subjects (+11.1%) compared to other regions (1.1%−5.9%). The West had the largest difference in *Pseudomonas aeruginosa* between ethnicities due to the highest *Pseudomonas aeruginosa* rate (42.7%) of any group occurring in Hispanic subjects and the lowest rate (31.6%) occurring in non-Hispanic white subjects. More Hispanic subjects had government insurance than non-Hispanic white subjects in the West (+22.5%) compared to the other regions (15.2%−21.0%). In the West, fewer Hispanic mothers had completed education beyond high school than non-Hispanic white mothers (−18.7%) compared to other regions (−5.4% to −11.8%). More Hispanic subjects had Class IV-V (+2.5%) or unclassified (+22.0%) CFTR mutations than non-Hispanic white subjects in the West. There was no pattern in differences between ethnicities in CFTR classes in the other regions.

There were wide variations between ethnicities in percent predicted pulmonary function between geographic regions (Figure 1, Table 2). In the West, Hispanic subjects' percent predicted FEV_1 was 9.0 percentage points (8.3–9.8%) lower than non-Hispanic white subjects, while Hispanic subjects' percent predicted FEV_1 was only 4.0 percentage points (3.0–5.0%) lower in the Midwest, 4.4 percentage points (3.1–5.7%) lower in the Northeast, and 4.4 percentage points (3.2–5.5%) lower in the South. In the West, Hispanic subjects had the overall lowest percent predicted FEV_1 (78.1%) while non-Hispanic white subjects had close to the highest (87.1%) of any group. Hispanic subjects' percent predicted FVC was 7.7 percentage points (7.0–8.3%) lower than non-Hispanic white subjects in the West, while

Hispanic subjects' percent predicted FVC was only 4.4 percentage points (3.5–5.3%) lower in the Midwest, 4.1 percentage points (3.0–5.2%) lower in the Northeast, and 4.0 percentage points (2.9–5.0%) lower in the South. Only in the West did Hispanic subjects have lower FEV_1/FVC than non-Hispanic white subjects. In the West, Hispanic subjects' percent predicted $FEF_{25–75}$ was 6.5 percentage points (5.2–7.7%) lower than non-Hispanic white subjects, while Hispanic subjects' percent predicted $FEF_{25–75\%}$ was only 2.4 percentage points (2.0–4.1%) lower in the Midwest, 4.4 percentage points (2.0–6.7%) lower in the Northeast, and 2.7 percentage points (0.5–5.0%) lower in the South. There was no difference by ethnicity in the rate of percent predicted FEV_1 decline in any geographic region.

Discussion:

In the largest database of Hispanic patients with CF, we found that pulmonary function disparities between Hispanic and non-Hispanic white subjects vary between geographic regions, even with adjustment for factors known to influence pulmonary function. In all geographic regions, the difference in percent predicted FEV_1 between Hispanic and non-Hispanic white subjects varied from the overall ethnic disparity of 5.8% in percent predicted FEV_1 that we had found in our previous work[3]. The ethnic gap in pulmonary function was significantly wider in the West than in the other geographic regions for all measures (percent predicted FVC, FEV_1, FEV_1/FVC, $FEF_{25–75\%}$). The Midwest, Northeast, and South regions had similar ethnic gaps in pulmonary function. Non-Hispanic white subjects residing in the West had the highest pulmonary function values of any region, while Hispanic subjects residing in the West had the lowest pulmonary function values of any region. Despite Hispanic subjects having lower pulmonary function that non-Hispanic white subjects, there was no difference in the rate of decline in percent predicted FEV_1 by ethnicity in any geographic region. This is consistent with our prior findings on overall rate of percent predicted FEV_1 decline and pulmonary function differences by ethnicity[3].

Our study findings suggest there are geographical differences in disease severity among Hispanic patients with CF. Our findings are consistent with prior findings by J. Rho, who found there are significant geographical variations in CF mortality between ethnicities[2]. However, the difference in mortality between ethnicities was the widest in the Midwest, while our study found that the widest differences in pulmonary function occurred in the West. This incongruity in findings may be due to age differences between the two study populations; our study included subjects 25 years old and younger, while the mortality study included older subjects. This incongruity in findings may also be due to differences in the factors influencing mortality compared to those influencing pulmonary function in CF.

Our findings have the greatest implications for the CF population residing in the West, where the largest disparity in pulmonary function occurred. Not only does the West have the largest number of Hispanic CF subjects of all four regions, but also in the West, Hispanic patients make up the highest proportion of the regional CF population compared to the other regions.

There is a paucity of research examining factors that contribute to CF disease severity in Hispanic subjects. Focusing on factors that differentially impact Hispanic subjects residing

in the West, may provide insight into the observed ethnic disparities in pulmonary function between geographic regions. In this study, we have identified several factors known to be associated with reduced pulmonary function in CF that vary by ethnicity and geographic region.

Respiratory infections, which negatively affect pulmonary function, are known to vary by ethnicity[2,23] and by geographic region[8,24,25] outside of CF. We found that Hispanic subjects were more likely to have *Pseudomonas aeruginosa* than non-Hispanic white subjects in CF. Furthermore, we found significant geographic variations in the difference in the rate of *Pseudomonas aeruginosa* between ethnicities with the greatest difference occurring in the West. Consistent with our pulmonary function findings, we found that Hispanic subjects in the West had the highest rate of *Pseudomonas aeruginosa* of any group while non-Hispanic white subjects in the West had the lowest rate of any group. Interestingly, Hispanic subjects had a lower rate of MRSA than non-Hispanic white subjects except in the West where Hispanic subjects had a higher rate of MRSA. The significant geographic and ethnic differences in *Pseudomonas aeruginosa* and MRSA infections may contribute to the largest ethnic gap in pulmonary function occurring in the West. The ethnic gap in pulmonary function persisted despite adjustment for *Pseudomonas aeruginosa* and MRSA for a few possible reasons. Respiratory infections may differentially impact pulmonary function by ethnicity, such that *Pseudomonas aeruginosa* may cause a greater drop in pulmonary function in Hispanic subjects than in non-Hispanic white subjects. There may be differences between ethnicities in the treatment of respiratory infections. There may also be differences in timing of infection acquisition or conversion of non-mucoid to mucoid *Pseudomonas aeruginosa* between ethnicities. Further investigation into the pattern of respiratory infections in Hispanic subjects is needed.

CFTR mutations and genes other than CFTR have been shown to influence pulmonary function severity in CF[4,26]. Hispanic subjects in all geographic regions were more likely to have unclassified CFTR mutations and less likely to have CFTR class I-III. We have previously shown that there were no significant differences in the ethnic gap in pulmonary function between CFTR mutation severity classes[3]. The Hispanic ethnicity is heterogeneous with genetically diverse heritages that vary across the United States regions due to distinct migration patterns. Hispanic people residing in the West are more likely to originate from Mexico or Central America, while those in the Northeast are more likely to originate from the Caribbean[17]. Gene modifiers that influence pulmonary function may vary between Hispanic populations by region. It would be important to identify gene modifiers in future studies to guide care and reduce the ethnic gaps between geographic regions.

Markers of lower socioeconomic status, including government insurance and maternal education, are associated with poor outcomes in CF, including lower pulmonary function[7,27]. Consistent with our findings of differences in pulmonary function between Hispanic and non-Hispanic subjects, Hispanic subjects were more likely to have government insurance in every region compared to non-Hispanic white subjects with the largest difference occurring in the West. In all regions, Hispanic subjects had the lowest rate of maternal education beyond high school again with the largest difference between ethnicities occurring in the West. Socioeconomic factors, such as poor health literacy, discrimination, acculturation

level, English proficiency, and language spoke at home[28–30] are more likely to affect Hispanic than non-Hispanic white subjects and may contribute to our findings of ethnic and geographic variations in pulmonary function. Unfortunately, these socioeconomic markers are not collected by the CFFPR and could not be examined in this study. Further studies are needed to examine the influence of these other socioeconomic factors on our findings, including the socioeconomic factors that specifically affect Hispanic subjects.

We found that there was no significant difference in age of diagnosis between Hispanic and non-Hispanic white subjects except for in the West where Hispanic subjects were diagnosed at an older age. Newborn screening leads to earlier diagnosis and initiation of treatment which is associated with higher pulmonary function in CF[31]. Hispanic infants are less likely to be diagnosed via newborn screening than non-Hispanic white infants, however, this varies state by state[32] due to differences in newborn screening protocols. For example, in the California newborn screening, Hispanic babies were more likely than non-Hispanic white babies to be diagnosed with CFTR-related metabolic syndrome (CRMS)[33]. CRMS is a positive newborn screening for CF but does not meet diagnostic criteria for CF with either an indeterminate sweat chloride concentration or less than 2 disease-causing CFTR genes. Many babies with CRMS go on to have a delayed diagnosis of CF[34]. Delay in diagnosis in Hispanic subjects in the West may explain the larger ethnic disparity in pulmonary function occurring in the West.

We could not account for environmental exposures in this study as they are not collected by the CFFPR, but air pollution and pesticide exposure may be contributing to the observed geographic differences in pulmonary function between ethnicities. Early life exposure to air pollution and pesticides negatively impact pulmonary function[35–37]. Hispanic children are more likely than non-Hispanic white children to be exposed to air pollution[12] and to pesticides[38]. Furthermore, air pollution and pesticide exposure are not uniform across all areas of the United States[39].

We recognize several limitations of our study. First, subjects could have been misclassified as Hispanic or non-Hispanic white, which would underestimate the association of ethnicity with pulmonary function. This is unlikely to have been a significant factor given that in the CFFPR, less than 2% of race and ethnicity have been found to be inaccurate[40]. Second, dividing the U.S. into Census regions is a crude measure that doesn't fully account for differences in Hispanic patients with CF by genetic background or environmental exposures. It is interesting that despite using a crude measure, significant differences between geographic regions were found. Although we were not able to demonstrate causality, factors known to be associated with more severe pulmonary function, such as *Pseudomonas aeruginosa* and government insurance, were also higher in Hispanic subjects, especially in the West.

In conclusion, we found that Hispanic subjects have lower pulmonary function than non-Hispanic white subjects in all geographic regions. However, the most striking difference in pulmonary function between ethnicities occurred in the West. Factors influencing pulmonary function vary by both ethnicity and geographic region with the greatest differences occurring in the West, similar to the differences in pulmonary function. There is an urgent need to

identify modifiable factors contributing to severe disease in Hispanic subjects with CF to guide CF treatment and reduce ethnicity gaps in CF mortality.

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MEM takes responsibility for the content of the manuscript, including the data and analysis.

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References:

1. Buu MC, Sanders LM, Mayo JA, Milla CE, Wise PH. Assessing differences in mortality rates and risk factors between Hispanic and non-Hispanic patients with cystic fibrosis in California. CHEST Journal 2016;149(2):380–389.
2. Rho J, Ahn C, Gao A, Sawicki GS, Keller A, Jain R. Disparities in Mortality of Hispanic Cystic Fibrosis Patients in the United States: A National and Regional Cohort Study. American journal of respiratory and critical care medicine 2018(ja).
3. McGarry ME, Neuhaus J, Nielson DW, Burchard EG, Ly NP. Pulmonary function disparities exist and persist in Hispanic patients with cystic fibrosis: A longitudinal analysis. Pediatric pulmonology 2017;52(12):1550–1557. [PubMed: 29082671]
4. De Gracia J, Mata F, Alvarez A, Casals T, Gatner S, Vendrell M, de la Rosa D, Guarner L, Hermosilla E. Genotype-phenotype correlation for pulmonary function in cystic fibrosis. Thorax 2005;60(7):558–563. [PubMed: 15994263]
5. Oates GR, Schechter MS. Socioeconomic status and health outcomes: cystic fibrosis as a model. Expert review of respiratory medicine 2016;10(9):967–977. [PubMed: 27268142]
6. Schechter MS. Nongenetic influences on cystic fibrosis outcomes. Current opinion in pulmonary medicine 2011;17(6):448–454. [PubMed: 21897254]
7. Schechter MS, Shelton BJ, Margolis PA, FitzSimmons SC. The association of socioeconomic status with outcomes in cystic fibrosis patients in the United States. American journal of respiratory and critical care medicine 2001;163(6):1331–1337. [PubMed: 11371397]
8. Collaco JM, McGready J, Green DM, Naughton KM, Watson CP, Shields T, Bell SC, Wainwright CE, ACFBAL Study Group, Cutting GR. Effect of temperature on cystic fibrosis lung disease and infections: a replicated cohort study. PloS one 2011;6(11):e27784. [PubMed: 22125624]
9. Adjemian J, Olivier KN, Prevots DR. Nontuberculous mycobacteria among patients with cystic fibrosis in the United States. Screening practices and environmental risk. American journal of respiratory and critical care medicine 2014;190(5):581–586. [PubMed: 25068291]
10. Adjemian J, Olivier KN, Seitz AE, Falkinham JO III, Holland SM, Prevots DR. Spatial clusters of nontuberculous mycobacterial lung disease in the United States. American journal of respiratory and critical care medicine 2012;186(6):553–558. [PubMed: 22773732]
11. Geller DE, Kaplowitz H, Light MJ, Colin AA. Allergic bronchopulmonary aspergillosis in cystic fibrosis: reported prevalence, regional distribution, and patient characteristics. CHEST Journal 1999;116(3):639–646.
12. Clark LP, Millet DB, Marshall JD. National patterns in environmental injustice and inequality: outdoor NO2 air pollution in the United States. PloS one 2014;9(4):e94431. [PubMed: 24736569]
13. Rosenfeld M, Sontag MK, Ren CL. Cystic fibrosis diagnosis and newborn screening. Pediatric Clinics 2016;63(4):599–615. [PubMed: 27469178]

14. Brooks T, Wagnerman K, Artiga S, Cornachione E, Ubri P. Medicaid and chip eligibility, enrollment, renewal, and cost sharing policies as of january 2017: Findings from a 50-state survey Washington: Kaiser Family Foundation 2017.
15. López G, Patten E. The Impact of Slowing Immigration: Foreign-Born Share Falls Among 14 Largest U.S. Hispanic Groups Washington D.C: Pew Reseach Center; 9 2015.
16. Price AL, Patterson N, Yu F, Cox DR, Waliszewska A, McDonald GJ, Tandon A, Schimer C, Neubauer J, Bedoya G, et al. A genomewide admixture map for Latino populations. The American Journal of Human Genetics 2007;80(6):1024–1036. [PubMed: 17503322]
17. Brown A, Patten E. Hispanics of Puerto Rican Origin in the United States, 2011 Washington, DC, Pew Research Center 2013.
18. Cystic Fibrosis Foundation Patient Registry, 2016 Annual Data Report Bethesda, Maryland.
19. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, Enright PL, Hankinson JL, Ip MS, Zheng J, Stocks J, ERS Global Lung Function Initiative. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. European Respiratory Journal 2012;40(6):1324–1343. [PubMed: 22743675]
20. U.S. Census Bureau. Language Apoken At Home, 2016 American Community Survey 1-Year Estimate 2016.
21. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, Flegal KM, Guo SS, Wei R, Mei Z, Curtin LR, Roche AF, Johnson CL. CDC growth charts: United States. Advance data 2000(314):1–27.
22. Morrill R, Cromartie J, Hart G. Metropolitan, urban, and rural commuting areas: toward a better depiction of the United States settlement system. Urban Geography 1999;20(8):727–748.
23. Watts KD, Seshadri R, Sullivan C, McColley SA. Increased prevalence of risk factors for morbidity and mortality in the US Hispanic CF population. Pediatric pulmonology 2009;44(6):594–601. [PubMed: 19437506]
24. Adjemian J, Olivier KN, Prevots DR. Epidemiology of Pulmonary Nontuberculous Mycobacterial Sputum Positivity in Patients with Cystic Fibrosis in the United States, 2010–2014. Annals of the American Thoracic Society 2018(ja).
25. Ranganathan SC, Skoric B, Ramsay KA, Carzino R, Gibson AM, Hart E, Harrison J, Bell SC, Kidd TJ, Australian Respiratory Early Surveillance Team for Cystic Fibrosis (AREST-CF). Geographical differences in first acquisition of Pseudomonas aeruginosa in cystic fibrosis. Annals of the American Thoracic Society 2013;10(2):108–114. [PubMed: 23607838]
26. Collaco JM, Cutting GR. Update on gene modifiers in cystic fibrosis. Current opinion in pulmonary medicine 2008;14(6):559. [PubMed: 18812833]
27. Quon BS, Psoter K, Mayer-Hamblett N, Aitken ML, Li CI, Goss CH. Disparities in access to lung transplantation for patients with cystic fibrosis by socioeconomic status. American journal of respiratory and critical care medicine 2012;186(10):1008–1013. [PubMed: 22983958]
28. Flores G, Tomany-Korman SC. The language spoken at home and disparities in medical and dental health, access to care, and use of services in US children. Pediatrics 2008;121(6):e1703–e1714. [PubMed: 18519474]
29. O'Connor GT, Quinton HB, Kneeland T, Kahn R, Lever T, Maddock J, Robichaud P, Detzer M, Swartz DR. Median household income and mortality rate in cystic fibrosis. Pediatrics 2003;111(4):e333–e339. [PubMed: 12671148]
30. Kern AS, Watts KD, Rychlik K, McColley SA. Disparities in parental health literacy at a pediatric cystic fibrosis center. Pediatric Allergy, Immunology, and Pulmonology 2015;28(1):55–59.
31. Padman R, McColley SA, Miller DP, Konstan MW, Morgan WJ, Schechter MS, Ren CL, Wagener JS, Investigators and Coordinators of the Epidemiologic Study of Cystic Fibrosis. Infant care patterns at epidemiologic study of cystic fibrosis sites that achieve superior childhood lung function. Pediatrics 2007;119(3):e531–e537. [PubMed: 17332172]
32. Pique L, Graham S, Pearl M, Kharrazi M, Schrijver I. Cystic fibrosis newborn screening programs: implications of the CFTR variant spectrum in nonwhite patients. Genetics in Medicine 2017;19(1): 36. [PubMed: 27148940]
33. Salinas DB, Sosnay PR, Azen C, Young S, Raraigh KS, Keens TG, Kharrazi M. Benign outcome among positive cystic fibrosis newborn screen children with non-CF-causing variants. Journal of Cystic Fibrosis 2015;14(6):714–719. [PubMed: 25824995]

34. Groves T, Robinson P, Wiley V, Fitzgerald DA. Long-term outcomes of children with intermediate sweat chloride values in infancy. The Journal of pediatrics 2015;166(6):1469–1474. e1463. [PubMed: 25812778]

35. Goss CH, Newsom SA, Schildcrout JS, Sheppard L, Kaufman JD. Effect of ambient air pollution on pulmonary exacerbations and lung function in cystic fibrosis. American journal of respiratory and critical care medicine 2004;169(7):816–821. [PubMed: 14718248]

36. Salam MT, Li Y-F, Langholz B, Gilliland FD. Early-life environmental risk factors for asthma: findings from the Children's Health Study. Environmental health perspectives 2004;112(6):760. [PubMed: 15121522]

37. Raanan R, Balmes JR, Harley KG, Gunier RB, Magzamen S, Bradman A, Eskenazi B. Decreased lung function in 7-year-old children with early-life organophosphate exposure. Thorax 2015:thoraxjnl-2014–206622.

38. Schwartz NA, von Glascoe CA, Torres V, Ramos L, Soria-Delgado C. "Where they (live, work and) spray": Pesticide exposure, childhood asthma and environmental justice among Mexican-American farmworkers. Health & place 2015;32:83–92. [PubMed: 25659530]

39. NASS U. 2012 Census of Agriculture, Ag Census Web Maps

40. Knapp EA, Fink AK, Goss CH, Sewall A, Ostrenga J, Dowd C, Elbert A, Petren KM, Marshall BC. The Cystic Fibrosis Foundation Patient Registry: Design and Methods of a National Observational Disease Registry. Annals of the American Thoracic Society 2016;13(7):1173–1179. [PubMed: 27078236]

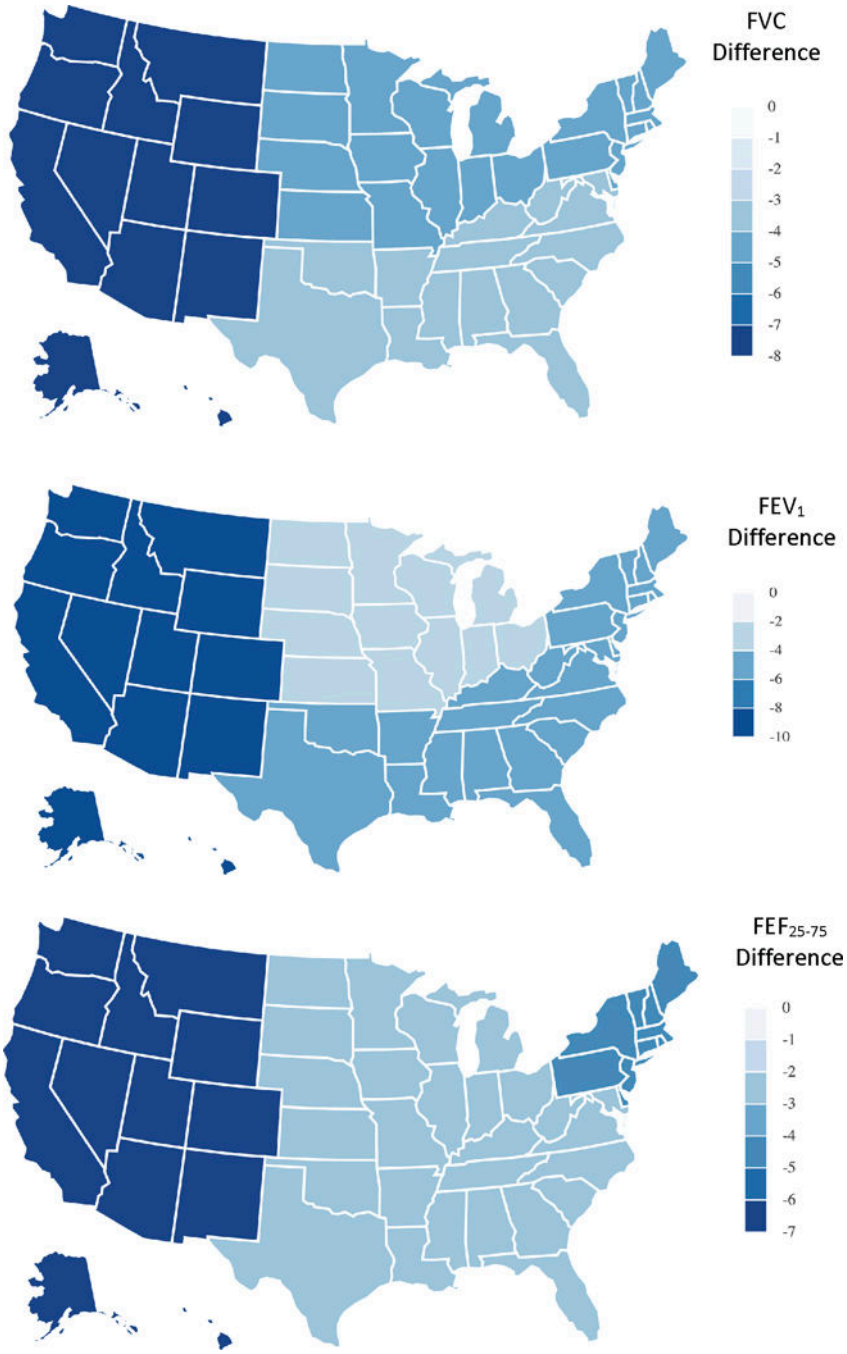

Figure 1.
Difference In Pulmonary Function Between Hispanic and Non-Hispanic Subjects

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Table 1:

Study Population Characteristics at Cohort Entry

	United States		West		Midwest		Northeast		South	
	Hispanic	**Non-Hispanic White**	**Hispanic**	**Non-Hispanic White**	**Hispanic**	**Non-Hispanic White**	**Hispanic**	**Non-Hispanic White**	**Hispanic**	**Non-Hispanic White**
Number (%)	1,433 (9.6%)	13,499 (90.4%)	518 (19.2%)	2,183 (80.8%)	419 (7.9%)	4,878 (92.1%)	217 (6.6%)	3,071 (93.4%)	279 (7.7%)	3,367 (92.4%)
Age*	10.3 (7.8–13.9)	10.6 (8.0–14.4)	10.4 7.8–14.1	10.6 8.0–14.1	9.6 7.6–13.2	10.5 7.9–14.3	10.7 8.2–14.7	10.8 8.1–14.8	10.4 7.9–13.8	10.7 7.9–14.3
Sex, male	52.6%	50.9% +1.7%	52.9%	49.0% +3.9%	55.4%	50.9% +4.5%	48.2%	52.0% −3.8%	50.9%	51.2% −0.3%
Age at Diagnosis, mths*	6.2	4.4 +1.8 (+0.7 to +12.4)	6.0	4.9 +1.1 (+0.5 to +11.5)	5.8	4.5 +1.3 (−0.4 to +10.9)	7.1	3.0 +4.1 (+0.8 to +15.5)	7.0	5.1 +1.9 (+0.8 to +10.1)
PERT use	87.3%	90.7% -3.4%	91.9%	91.8% +0.1%	88.3%	91.5% −3.2%	81.6%	87.7% −6.1%	85.0%	91.8% −6.8%
Sweat Chloride Concentration	95.5	97.6 −2.0 (−0.89 to −3.2)	96.1	97.7 −1.6 (−3.7 to +0.5)	97.4	98.2 −0.8 (−2.9 to +1.3)	91.5	96.5 −5.0 (−8.1 to −1.9)	95.0	97.5 −2.5 (−5.0 to −0.7)
CFTR Class I-III	53.2%	75.5% −22.3%	53.5%	78.0% −24.5%	52.5%	75.1% −22.6%	47.9%	71.1% −23.2%	57.7%	78.3% −20.6%
CFTR Class IV-V	8.9%	7.1% +1.8%	8.3%	5.8% +2.5%	8.8%	7.3% +1.5%	9.2%	9.8% −0.6%	9.7%	5.3% +4.4%
CFTR Unclassified	37.9%	17.4% +20.5%	38.2%	16.2% +22.0%	38.7%	17.6% +21.1%	42.9%	19.1% +23.8%	32.6%	16.4% +16.2%
BMI, percentile	53.8	50.4 +3.4 (1.7 to 4.9)	51.5	48.7 +2.8 (1.3 to 4.2)	55.6	50.4 +5.2 (3.1 to 7.3)	56.3	52.7 +3.4 (0.7 to 6.7)	53.1	49.5 +3.6 (1.0 to 6.2)
CF-Related Diabetes	4.8%	4.8% +0%	4.8%	4.2% +0.6%	5.7%	5.2% +0.5%	1.8%	4.1% −2.3%	5.4%	5.4% +0%

	United States		West		Midwest		Northeast		South	
	Hispanic	Non-Hispanic White	Hispanic	Non-Hispanic White	Hispanic	Non-Hispanic White	Hispanic	Non-Hispanic White	Hispanic	Non-Hispanic White
MRSA	13.5%	16.3%	11.0%	9.9%	15.8%	16.7%	12.0%	14.2%	15.8%	21.7%
		−2.8%		+1.1%		−0.9%		−2.2%		−5.9%
Pseudomonas	39.9%	33.8%	42.7%	31.6%	38.7%	32.8%	34.1%	33.0%	40.9%	37.6%
		+6.1%		+11.1%		+5.9%		+1.1%		+3.3%
NTM	2.4%	1.2%	1.7%	1.7%	1.9%	1.0%	2.8%	0.8%	3.9%	1.7%
		+1.2%		+0%		+0.9%		+2.0%		+2.2%
Tobacco Exposure	6.1%	9.7%	3.5%	5.5%	8.6%	10.7%	8.3%	9.6%	5.4%	11.0%
		−3.6%		−2.0%		−2.1%		−1.3%		−5.6%
Government Insurance	58.8%	41.5%	53.7%	31.2%	62.8%	44.3%	59.9%	38.9%	61.7%	46.5%
		+17.3%		+22.5%		+18.5%		+21.0%		+15.2%
Mat. Ed, College	15.4%	27.4%	8.3%	27.0%	21.5%	26.1%	17.5%	29.3%	17.9%	27.7%
		−12.0%		−18.7%		−5.4%		−11.8%		−9.8%
RUCA, rural	7.4%	13.9%	6.0%	11.9%	9.8%	17.5%	4.2%	10.3%	9.0%	13.0%
		−6.5%		−5.9%		−7.7%		−6.1%		−4.0%

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Table 2:

Ethnic Differences In Pulmonary Function Vary By Geographic Region

	Hispanic FVC	Non-Hispanic Whites FVC	Difference in FVC %	95% CI	p-value
West	86.7%	94.4%	−7.7%	−8.3% to −7.0%	Ref.
Midwest	88.5%	92.9%	−4.4%	−5.3% to −3.5%	<0.001
Northeast	89.8%	93.9%	−4.1%	−5.2% to −3.0%	<0.001
South	87.8%	91.8%	−4.0%	−5.0% to −2.9%	<0.001
	Hispanic FEV_1	**Non-Hispanic Whites FEV_1**	**Difference in FEV_1%**	**95% CI**	**p-value**
West	78.1%	87.1%	−9.0%	−9.8% to −8.3%	Ref.
Midwest	81.4%	85.4%	−4.0%	−5.0% to −3.0%	<0.001
Northeast	82.9%	87.3%	−4.4%	−5.7% to −3.1%	<0.001
South	79.6%	84.0%	−4.4%	−5.5% to −3.2%	<0.001
	Hispanic FEV_1/FVC	**Non-Hispanic Whites FEV_1/FVC**	**Difference in FEV_1/FVC**	**95% CI**	**p-value**
West	0.793	0.812	−0.019	−0.022 to −0.015	Ref.
Midwest	0.814	0.811	0.003	−0.001 to 0.008	<0.001
Northeast	0.816	0.820	−0.004	−0.009 to 0.002	0.005
South	0.803	0.806	−0.003	−0.008 to 0.003	0.002
	Hispanic $FEF_{25–75}$	**Non-Hispanic Whites $FEF_{25–75}$**	**Difference in $FEF_{25–75}$**	**95% CI**	**p-value**
West	65.1%	71.6%	−6.5%	−7.7% to −5.2%	Ref.
Midwest	68.5%	70.9%	−2.4%	−4.1% to −2.0%	0.015
Northeast	67.7%	72.1%	−4.4%	−6.7% to −2.0%	0.3
South	66.8%	69.5%	−2.7%	−5.0% to −0.5%	0.055

-West region is the reference group

-Model adjusted for age, sex, pancreatic enzyme replacement use, body mass index, sweat chloride concentration, methicillin-resistant *Staphylococcus aureus, Pseudomonas aeruginosa,* maternal education level, insurance type, tobacco exposure, age at diagnosis, CF-related diabetes, Rural Urban Commuting Area Codes (RUCA), CFTR mutation class.