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ORIGINAL ARTICLE

Reconsidering the Utility of Race-Specific Lung Function Prediction Equations

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Abstract

Rationale: African American individuals have worse outcomes in chronic obstructive pulmonary disease (COPD).

Objectives: To assess whether race-specific approaches for estimating lung function contribute to racial inequities by failing to recognize pathological decrements and considering them normal.

Methods: In a cohort with and at risk for COPD, we assessed whether lung function prediction equations applied in a race-specific versus universal manner better modeled the relationship between FEV_1, FVC, and other COPD outcomes, including the COPD Assessment Test, St. George's Respiratory Questionnaire, computed tomography percent emphysema, airway wall thickness, and 6-minute-walk test. We related these outcomes to differences in FEV_1 using multiple linear regression and compared predictive performance between fitted models using root mean squared error and Alpaydin's paired *F* test.

Measurements and Main Results: Using race-specific equations, African American individuals were calculated to have better lung function than non-Hispanic White individuals (FEV_1, 76.8% vs. 71.8% predicted; $P = 0.02$). Using universally applied equations, African American individuals were calculated to have worse lung function. Using Hankinson's Non-Hispanic White equation, FEV_1 was 64.7% versus 71.8% ($P < 0.001$). Using the Global Lung Initiative's Other race equation, FEV_1 was 70.0% versus 77.9% ($P < 0.001$). Prediction errors from linear regression were less for universally applied equations compared with race-specific equations when examining FEV_1% predicted with the COPD Assessment Test ($P < 0.01$), St. George's Respiratory Questionnaire ($P < 0.01$), and airway wall thickness ($P < 0.01$). Although African American participants had greater adversity ($P < 0.001$), less adversity was only associated with better FEV_1 in non-Hispanic White participants (*P* for interaction = 0.041).

Conclusions: Race-specific equations may underestimate COPD severity in African American individuals.

Clinical trial registered with www.clinicaltrials.gov (NCT01969344).

Keywords: respiratory function tests; racism; chronic obstructive pulmonary disease; health disparities

There is increasing concern that race is used unjustifiably in clinical medicine, widening rather than reducing disparities (1). This debate is much older in spirometry, in which the first American monographs highlighted the lower lung function of slaves relative to slaveholders in explicit defense of slavery (2). After the "correction factor" for African American individuals was found to vary widely and range between 3.5% and 23%, the current standard of normative derivations from race-specific populations was expected

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At a Glance Commentary

Scientific Knowledge on the Subject: Lung function is measured as a percent of predicted based on race-specific lung function equations. In this system, there are many large, unexplained racial disparities in chronic obstructive pulmonary disease severity and outcome.

What This Study Adds to the Field: This study suggests that race-specific lung function equations may inappropriately consider lung injury owing to discrimination against minorities as normal variation. This can be addressed through application of universally applied multiethnic lung function equations, which appear more accurate.

to increase accuracy and reduce bias (3). However, prevailing explanations of racial differences were informed by 1920s scholarship, which, relative to current understandings, emphasized biological differences between races and devalued differing social and environmental factors (4). Coupled with limitations in measuring long-term impacts of adverse exposures on lung health, pathological socioenvironmental contributors to racial differences in lung function were discounted. Although the current methodology of lung function prediction is derived from global data comparing an individual's performance with the distribution of others from the same self-identified racial and/or ethnic group, contributions from socioenvironmental exposures remain underappreciated.

Lung function testing in chronic obstructive pulmonary disease (COPD) follows the convention of reporting percent predicted values from race-specific prediction equations (5). However, race is a sociologic construct that attempts to categorize individuals with diverse ancestral, historical, cultural, geographical, and socioeconomic backgrounds. Marginalized races are disproportionately overrepresented in groups with low socioeconomic status (SES); they are disproportionately burdened by exposures that negatively impact lung function, in addition to other health conditions (6). In COPD, this dilemma is likely amplified (7). Importantly, scholars, such as Ida B. Wells, have hypothesized that historically, this overrepresentation was not coincidental but the result of organized multimodal suppression efforts against African American people (8). Reporting lung function with race-specific prediction equations may lead to greater inaccuracy in understanding disease by normalizing decrements in lung function suffered broadly by one racial group owing to long-standing inequities and discrimination. These inaccuracies may promote clinical misjudgments, thereby precipitating racial outcome disparities. Importantly, socioenvironmental contributions to disease morbidity represent potential targets for intervention, providing opportunities to improve health outcomes.

To this end, we endeavored to quantify the effect of socioenvironmental exposures, especially those that may have been influenced by systemic racism. Because this can deeply influence health outcomes (9), we reason that racism not only imposed lowered life chances on African American individuals but increased their exposures deleterious to lung function. This is true whether racism was given the power of law, as during the childhood of many of our study's participants, or operates more subtly, as contemporarily through the assumptions that underlie policy-making. This highlights the utility of studying the non-Hispanic White experience as a comparator to understand the impact of racism (10). Following this logic, we calculated percent predicted FEV_1 ($ppFEV_1$) and FVC (ppFVC) using both the current, race-specific standard for lung function prediction equations and the universally applied Hankinson's non-Hispanic White equation (NHW-H) as an alternative. Although this was clearly inappropriate as a general standard, and does not acknowledge differences like body proportion, we believed that it would allow an estimate of the maximal impact of racism, because non-Hispanic White individuals, as a group, were the beneficiaries of the historically unfair social system (11–13). Third, we selected the Global Lung Initiative's Other race equation (GLI-O) as a practical alternative standard because it averages estimates from multiple racial and/or ethnic groups (14). Using the $ppFEV_1$ and ppFVC for each of the three lung function prediction equations, we assessed which best correlated to symptom burden, exercise capacity, and radiographic disease. In addition, we considered whether race remains an independent predictor of airflow obstruction in persons with or at risk for COPD after considering socioenvironmental factors using a composite measure for adversity. Some of the results of this study have been previously reported in the form of an abstract (15).

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This article has a related editorial.

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

Methods

Procedures

SPIROMICS (the Sub-Populations and InteRmediate Outcome Measures In COPD Study) is a previously described multicenter cohort of ever-smokers with or at risk for COPD (16). We included all ever-smokers (≥20 pack-years), as any can have significant symptoms (17). We defined race by self-report, considering only participants identifying solely as African American or non-Hispanic White. Data were assessed cross-sectionally from each participant's baseline visit 1 at their enrollment.

Spirometry

Our analyses center on $ppFEV_1$ and ppFVC. We compared three methods to derive predicted values. First, we applied the race-specific equations recommended by Hankinson and colleagues (18). Second, we used the NHW-H (18) across the entire study population, regardless of race. Finally, we used the GLI-O (13). Both the Hankinson study from which we use the race-specific and NWH-H equations and Quanjer's study from which we use the GLI-O excluded people of African descent other than those living in the United States and reported African American populations derived primarily from the National Health and Nutrition Examination Surveys conducted between 1988 and 2010 (14, 18).

Response Variables

The COPD Assessment Test (CAT) is a self-reported symptom survey with a minimum clinically important difference of 2 units (19). The St. George's Respiratory Questionnaire (SGRQ) is a widely used self-report of health status with a minimum clinically importance difference of 4 (19, 20). The 6-minute-walk test (6MWT) is a commonly used measure of functional exercise capacity with known correlation to mortality (20). Quantitative percent emphysema and quantitative wall thickness for a standard airway (Pi10) are computed tomography–based measurements of lung disease (16).

Adversity–Opportunity Index

Previous reports suggest composite indices better capture the impact of latent variables such as discrimination (21). In contrast to indices such as the Area Deprivation Index (ADI), which summarizes contemporary neighborhood exposures, our Adversity–Opportunity Index (AOI) incorporates the measurement of historic, cumulative experiences, focused at the individual level. Paralleling prior work (21), we equally weighted and summed household income (22), education (23), *in utero* tobacco smoke exposures (24), occupational respiratory exposures (25), and access to fresh and healthy food (26, 27) as five representative indicators of social and structural determinants of health to create the AOI. Lower scores represent more adverse conditions.

Covariates

We selected additional covariates from literature demonstrating their negative impact on long-term lung function. These included body mass index (BMI) (28), childhood pneumonia (29), pack-years first-hand tobacco smoke exposure (20), asthma diagnosis, and ADI (30). More adverse conditions are represented as higher scores on the ADI (30).

Analysis

We used separate univariable linear regression models to compare the performance of standard race-specific, NHW-H, and GLI-O $ppFEV_1$ and ppFVC in correlation with each selected outcome including CAT, SGRQ, percent emphysema, 6MWT, and Pi10. To maximize power, we allowed variable sample sizes between outcomes because of missingness in individual variables. We used Alpaydin's 5×2 cv paired F test to evaluate significant differences in prediction performance (31). This method is based on a fivefold cross-validation approach and has the advantage that it assesses "out of sample" performance in data not used to estimate the model. It is preferred to alternative tests because it addresses nonindependence of prediction measures arising from overlapping estimation and validation samples in the cross-validation procedure. The resulting approximate P values are derived from an F distribution. We repeated these analyses, adjusting for current smoking status as a sensitivity assessment. As a further sensitivity analysis, all analyses using variable sample sizes were repeated using a single sample of complete cases. To better distinguish clinical relevance from statistical significance, we performed paired t tests comparing the predicted symptom scores from race-specific, GLI-O, and universally applied NHW equations.

In our second analysis, we explored the degree to which socioenvironmental adversity explains the racial contribution to lung function prediction equations by developing a staged multivariable regression model with the absolute value of FEV_1 as our outcome and self-identified race as our primary predictor. We developed a directed acyclic graph to assess causality and used it to inform our approach. Directed acyclic graphs are an increasingly popular technique to systematize model-building while maximizing accessibility and minimizing the obligate assumptions about the nature of the data (32). Race was our exposure of interest. Lung function as measured by FEV_1 in milliliters was our outcome. Our goal was to identify the residual direct effect of race on lung function. Age, Age^2, $Height^2$, BMI, and childhood pneumonia were all considered competing exposures. Pack-years tobacco smoking and asthma diagnosis were confounders. The ADI and AOI were considered mediators. The AOI was also considered as an effect modifier. Model 1 accounted for anthropometrics, model 2 accounted for comorbidities, and model 3 included socioenvironmental exposures. The estimated mean difference in FEV_1 between race groups from each model was compared with the unadjusted estimate. Given the Wells hypothesis that structurally racist societies often specially target affluent minority individuals who have overcome structural barriers (8), we considered that the expected benefit of higher social position might be less impactful in African American as compared with non-Hispanic White individuals (8). In the most contemporary literature, these concepts are described as *Minorities Diminished Returns* Theory (33). To investigate this hypothesis, we tested for an interaction between race and AOI on FEV_1. As a sensitivity test, we repeated the above analyses incorporating clinical enrollment site.

All hypothesis tests were two-sided using a predetermined threshold for statistical significance of $\alpha < 0.05$. Analyses were performed in Stata v16 with additional graphical analysis in R v4.10 (34, 35).

Results

We included data from 2,652 current or former smokers in SPIROMICS who self-identified as non-Hispanic White or African American. To maximize power, we allowed variable sample sizes, including everyone who had complete information for the given analysis. We included between 88% and 99% of eligible participants across all analyses, and 92.4% in the multivariable analysis. The

variable with the single greatest missingness across all analyses was quantitative percent emphysema (12%). Included and excluded individuals in the multivariable analysis did not differ significantly by age, race, sex, smoking pack-years, or any subcomponent of the AOI save education. A higher proportion of the excluded than included individuals had the lowest category of educational attainment.

In comparison with non-Hispanic White participants, those who self-identified as African American were younger (58.1 vs. 65.0 yr; $P = <0.001$) and had higher lung function ($ppFEV_1$, 76.8% vs. 71.8%; ppFVC, 92.9% vs. 90.6%; $P = 0.001$) when estimated by Hankinson's race-specific lung function equations. However, when we applied lung function equations without incorporating race, as expected, this relationship was reversed; African American participants had lower lung function when estimated by either the NHW-H ($ppFEV_1$, 64.7% vs. 71.8%; FVC, 76.6% vs. 90.6%; Ps < 0.001) or GLI-O (FEV_1, 70.0% vs. 77.9%; ppFVC, 85.5% vs. 101.8%; Ps < 0.001) equations. African American participants also reported worse symptom burden as captured by CAT and SGRQ and had greater mean airway wall thickness, despite fewer reported tobacco pack-years (Table 1). The correlation between $ppFEV_1$ and respiratory symptoms is different in African American and non-Hispanic White participants when race-adjusted equations are used but almost identical when race adjustment is not applied (Figure 1). Asthma was more prevalent in our African American population (32.0% vs. 17.7%; $P = 0.001$). African American participants showed lower AOI scores than non-Hispanic White participants (4.8 vs. 5.5; $P < 0.001$) (Table 1).

Spirometry and COPD Outcomes

When applied to all participants regardless of race, NHW-H $ppFEV_1$ yielded regression equations with smaller errors than race-specific equations for the following outcomes: CAT score ($F = 12.8$; $P = 0.006$), SGRQ ($F = 11.1$; $P = 0.008$), and Pi10 ($F = 12.9$; $P = 0.006$). Compared with race-specific percent predicted values, universally applied GLI-O $ppFEV_1$ yielded smaller errors for Pi10 ($F = 16$; $P = 0.003$), CAT ($F = 13.4$; $P = 0.005$), SGRQ ($F = 41.8$; $P < 0.001$), and 6MWT ($F = 4.9$; $P = 0.037$) (Figure 2A). The magnitude of these changes exceeds the minimal clinically important difference for SGRQ but not CAT (Table 2). For percent emphysema, the race-specific equation had smaller errors than either the NHW-H ($F = 6.9$; $P = 0.02$) or GLI-O ($F = 19.7$; $P = 0.002$) (Figure 2A).

For ppFVC, universally applied NHW-H yielded smaller errors than race-specific equations when considering CAT ($F = 7.7$; $P = 0.02$) and SGRQ ($F = 6.2$; $P = 0.03$) scores (Figure 2B). Universally applied GLI-O ppFVC was also superior to the race-specific equations for CAT score ($F = 6$; $P = 0.03$), SGRQ ($F = 7.6$; $P = 0.02$), and Pi10 ($F = 12.6$; $P = 0.006$) (Figure 2B). These results did not differ meaningfully when using stable versus variable sample size across all tests (Tables E1 and E2 in the online supplement). After adjusting for current smoking status, the Hankinson race-specific equations performed equivalently against both universally applied alternatives for the relationship between percent emphysema and $ppFEV_1$, whereas they continued to perform worse on most other measured outcomes and better in none (Table E3). For ppFVC, CAT, Pi10, and percent emphysema, universally applied NHW-H equations yielded smaller error than the race-specific approach after adjustment for smoking status; the Hankinson race-specific equations persistently failed to demonstrate superiority in any outcome (Table E4). Equations comparing race-specific with universally applied approaches were equivalent with respect to 6MWT when using ppFVC, before and after adjustment for current smoking status (Table E4).

Contributors to Mean Racial Difference in FEV_1

In the model adjusted for anthropometrics, we observed that African American race was associated with lower FEV_1, relative to non-Hispanic White race (−293 ml; 95% confidence interval [CI], −374 to −213; $P < 0.001$). Controlling for pack-years, asthma, BMI, AOI, and neighborhood deprivation reduced the effect size of race (−222 ml; 95% CI, −303 to −141; $P < 0.001$) (Table 3).

We identified an interaction wherein African American participants had significantly lower FEV_1 (−41 ml; 95% CI, −81 to −2) than non-Hispanic White participants for each unit AOI increase (i.e., with increasing opportunity) (P-for-interaction = 0.041; Table 3). In participants scoring in the lowest AOI quartile, race was no longer associated with FEV_1 (mean FEV_1, 2,100 ml for non-Hispanic White vs. 2,010 ml for African American; $P = 0.09$). Notably, higher AOI was associated with better lung function in non-Hispanic White participants, but this positive association was not observed in African American participants (Figure 3 and Table E5). Similar patterns were observed when the analysis was repeated by FEV_1 using either the GLI-O or NHW-H equations (Tables E6 and E7). Additional adjustment for clinical enrollment site did not alter any of the above findings (results not shown).

Discussion

This analysis of a large cohort ($n = 2,652$) of ever-smokers with or at risk for COPD demonstrates that percent predicted values for FEV_1 and FVC derived from universally applied equations more accurately reflect clinically relevant outcomes than percent predicted values derived from race-specific equations. Compared with universally applied NHW-H or GLI-O equations for $ppFEV_1$, the race-specific approach was inferior in reflecting *1*) symptom burden as measured by the CAT or SGRQ, *2*) 6MWT test as a functional outcome, and *3*) radiographic airway disease as measured by Pi10. For ppFVC, the universally applied NHW-H was superior to the race-specific calculation for CAT and SGRQ. After adjustment for comorbid disease and measures of adversity, the association between race and FEV_1 was attenuated, suggesting that some component of observed lung function differences by race reflects differential exposures.

Through the present study, we interrogated the central hypothesis that the current use of race in lung function prediction equations is significantly influenced by the lurking variable of negative structural forces experienced widely among African American individuals. As expected, we found that symptom burden, one functional outcome, and radiographic airway disease correlate more poorly to $ppFEV_1$ by race-specific than by universally applied prediction equations. Secondarily, it was our expectation that explicit inclusion of adverse exposures and social conditions would reduce the effect size of the race term in a multivariable model of lung function. Our data supported this hypothesis. Finally, as we hypothesized about the downstream impact of the Wells hypothesis (8), we observed that improvement in AOI was associated with

Table 1. Baseline Characteristics of Non-Hispanic White and African American Smokers in SPIROMICS

	Non-Hispanic White	African American
n (%)	2,122 (80)	530 (20)
Age, yr	**65.0 ± 0.8.4**	**58.1 ± 8.9**
Sex, M	**1,169 (55.1)**	**263 (49.6)**
BMI	27.8 ± 5.1	28.1 ± 6
Current smoker	**704 (33.7)**	**335 (63.9)**
Smoking pack-years	**51.6 ± 28.7**	**41 ± 17.4**
Childhood pneumonia	**302 (15.4)**	**52 (10.8)**
Asthma		
Diagnosed	**368 (17.7)**	**166 (32.0)**
Unknown	**78 (3.7)**	**18 (3.5)**
In utero smoke exposure		
Yes	**408 (19.7)**	**40 (7.8)**
Unsure/refused	**568 (27.4)**	**195 (37.9)**
Income*		
Low	**918 (46.7)**	**331 (68.5)**
High	**728 (37)**	**50 (10.3)**
Unreported	**320 (16.3)**	**102 (21.1)**
Maximal educational attainment		
Less than HS	**204 (10.4)**	**91 (18.8)**
HS diploma	**472 (24)**	**178 (36.9)**
Any post-HS	**690 (35.1)**	**165 (34.2)**
4-yr college or beyond	**600 (30.5)**	**49 (10.1)**
Occupational respiratory exposure		
Ever	**796 (40.5)**	**222 (46.1)**
2	**197 (10)**	**51 (10.6)**
N	**14 (0.7)**	**7(1.4)**
Low food access census tract	**708 (34.1)**	**97 (18.8)**
Area Deprivation Index	**38 ± 27**	**59 ± 33**
Adversity–Opportunity Index	**5.5 ± 2**	**4.8 ± 1.8**
COPD Assessment Test	**13.7 ± 8.1**	**16 ± 8.9**
St. George's Respiratory Questionnaire	**33 ± 23**	**39 ± 24**
Mean airway wall thickness, Pi10	**3.72 ± 0.1**	**3.74 ± 0.1**
% Emphysema	6.6 ± 10.4	6.2 ± 11.1
6-minute-walk test % predicted	**82.2 ± 27**	**79.3 ± 28**
Measured FEV_1, ml	**2,105 ± 899**	**2,015 ± 890**
GLI-O % predicted FEV_1	**77.9 ± 28.3**	**70.0 ± 24.9**
NHW-H % predicted FEV_1	**71.8 ± 26.1**	**64.7 ± 23.1**
Hankinson's race-specific % predicted FEV_1	**71.8 ± 26.1**	**76.8 ± 27.5**
Measured FVC, ml	**3,514 ± 1,016**	**3,093 ± 955**
GLI-O % predicted FVC	**101.8 ± 20.1**	**85.5 ± 18.3**
NHW-H % predicted FVC	**90.6 ± 17.9**	**76.6 ± 16.4**
Hankinson % predicted FVC	**90.6 ± 17.9**	**92.9 ± 20.1**
FEV_1/FVC	**77.8 ± 21.2**	**80.3 ± 20.9**

Definition of abbreviations: 2 = never; BMI = body mass index; COPD = chronic obstructive pulmonary disease; GLI-O = Global Lung Initiative's Other race equation; HS = high school; N = unsure/declines to respond; NHW-H = Hankinson's non-Hispanic White equation; Pi10 = quantitative wall thickness for a standard airway; SPIROMICS = Sub-Populations and InteRmediate Outcome Measures In COPD Study.
Data are shown as *n* (%) or mean ± SD.
Bolded values are statistically significant.
*Income is defined as "low" if <$50,000/yr and "high" if greater.

improved lung function in non-Hispanic White participants but not in African American participants. These results are consistent with our concern that race-specific prediction equations may present pathological reductions in lung function as normal, racially specific variation.

Our findings further previous observations questioning race-based spirometric predictions. The seeming paradox of our percent emphysema results are likely from the finding, in both our study and previously, that percent emphysema was significantly influenced by current smoking and paradoxically associated with higher FEV_1 (36, 37). In the general population, mortality correlates better with spirometric measures when they are expressed through universally applied approaches in which race is not considered rather than as a percent of predicted function from a race-specific formula (38–40). Unlike Burney and Hooper's contributions (38), which were critiqued as a "classical epidemiological error" lacking plausible mechanism (41), we demonstrate specific metrics of disease control that rationalize a connection between lung function and the previously reported poor outcomes. In Figure 1 we show that the correlation between FEV_1 and respiratory symptoms is different in African American and non-Hispanic White individuals when race-adjusted equations are used but almost identical when no racial adjustment is applied. This argues that race adjustment is not needed in the first place. In fact, it suggests that race adjustment may distort the true relationship between impairment in lung function and resultant symptoms, to the detriment of one racial group. The Genetic Epidemiology of COPD Study investigators reported that absolute value and race-specific percent predicted FEV_1 were comparable in their predictive value for SGRQ score, modified Medical Research Council dyspnea score, and 6MWT, calling into question the need for race-specific equations (42). Outside the particularities of statistical analysis, this study's finding, coupled with our own, may be viewed, at a minimum, as challenging the assumption that race-specific equations offer greater clinically relevant data than alternatives. In fact, our results extend findings by demonstrating that excluding race from prediction equations may yield results that are not merely comparable but superior for several important clinical outcomes in COPD. Therefore, significant evidence highlights the limitations of using race-specific prediction equations as guides for clinical practice.

The finding that improvements in adversity were not associated with better lung function in African American individuals parallel results in other domains of health care and warrant further investigation (43, 44). With decreasing adversity, one might expect improving lung function across all races. This expectation was realized in the University of Southern California Children's health study, in which improving air quality was associated with increased FEV_1, regardless of race (45). Instead, our results illustrate the *Minorities' Diminished Returns* theory, which suggests that the observed protective health effects of higher SES for non-Hispanic White

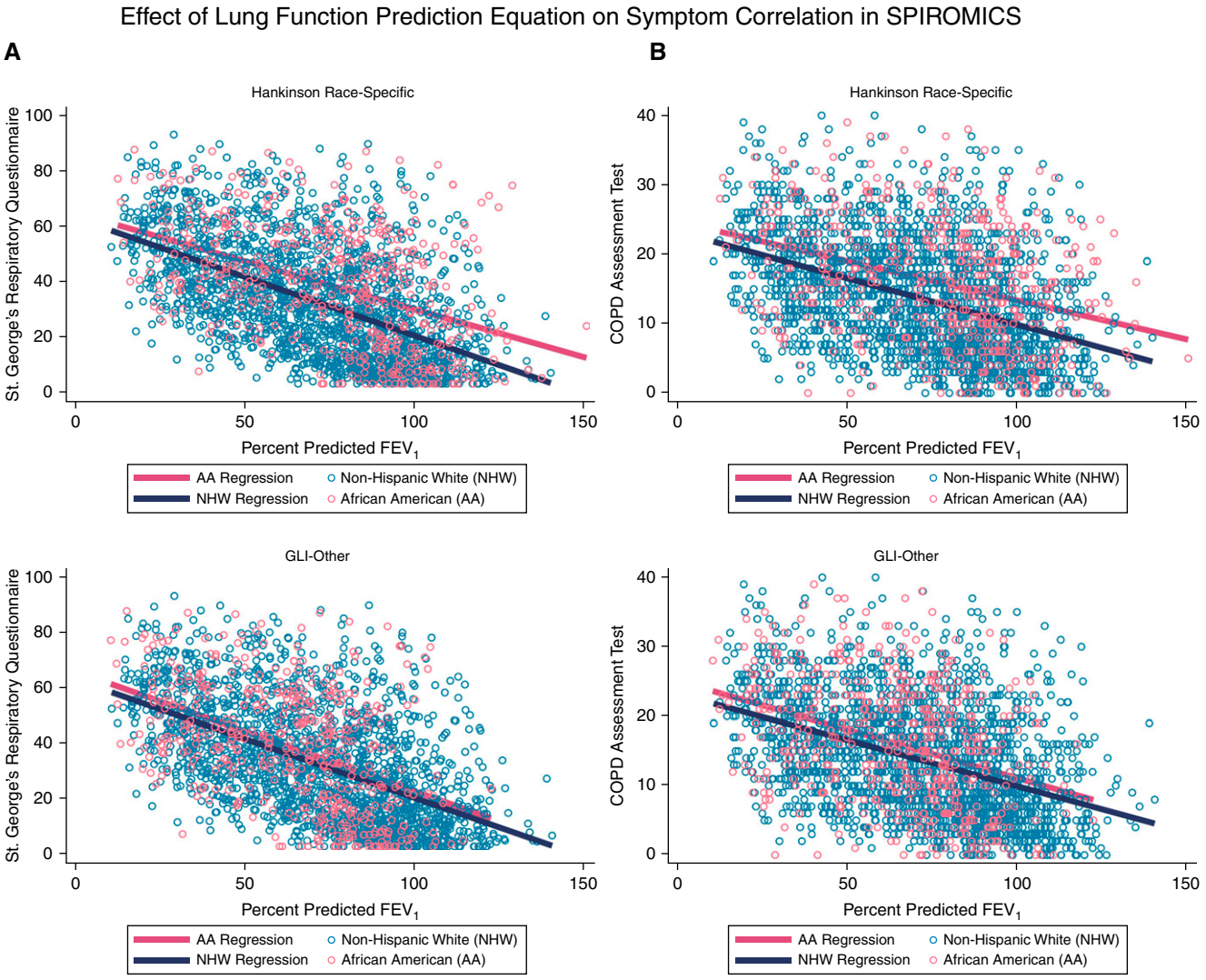

Figure 1. For each patient-reported outcome (St. George's Respiratory Questionnaire and COPD Assessment Test), participants' scores are plotted against percent predicted FEV_1. Separate univariable linear regressions for each self-identified racial group are superimposed. The relationships between symptoms and lung function are more consistent with a universally applied lung function prediction equation (GLI-Other). AA = African American; COPD = chronic obstructive pulmonary disease; GLI = Global Lung Initiative; NHW = non-Hispanic White; SPIROMICS = Sub-Populations and InteRmediate Outcome Measures In COPD Study.

populations may be weaker or completely absent for marginalized social groups (33). Although exact mechanisms may differ, all are believed to evidence racism as a latent variable (46). Racism represents a plausible mechanism for widespread harm to our African American participants that is unmeasured in our data set. Structurally, residential segregation is associated with increased exposure to air pollution and worse respiratory outcomes (47, 48). Anti-Black discrimination is experienced across all socioeconomic strata (49) and associated with higher incident asthma (49). Such findings concur with our hypothesis about the American racial system and demonstrate the complexity of its consequent social ills, which are believed to extend beyond the effects of SES alone (49–52). Ida B. Wells' hypothesis (8) highlights why a social order predicated on the inferiority of one group might have found it desirable to create circumstances wherein that group has poorer outcomes independent of other factors. South Africa, where racist policy-making was also central (53) but more infamous, similarly provides incisive commentary on these dynamics. Researchers from this milieu noted that because of discrimination, "the general living environment of middle-class Blacks is rather similar to that of working-class Blacks. One might therefore still expect residual differences" (54).

Our data suggest future research priorities should focus on elaborating the clinical utility of multiethnic over race-specific lung function prediction equations and on drivers of racial disparities in lung function. The mechanisms we theorize to underlie the associations described here are not unique to COPD but are common to the human condition. Similar analyses of the value of racial adjustment are needed to understand relevance in other pulmonary disease states and in the general population.

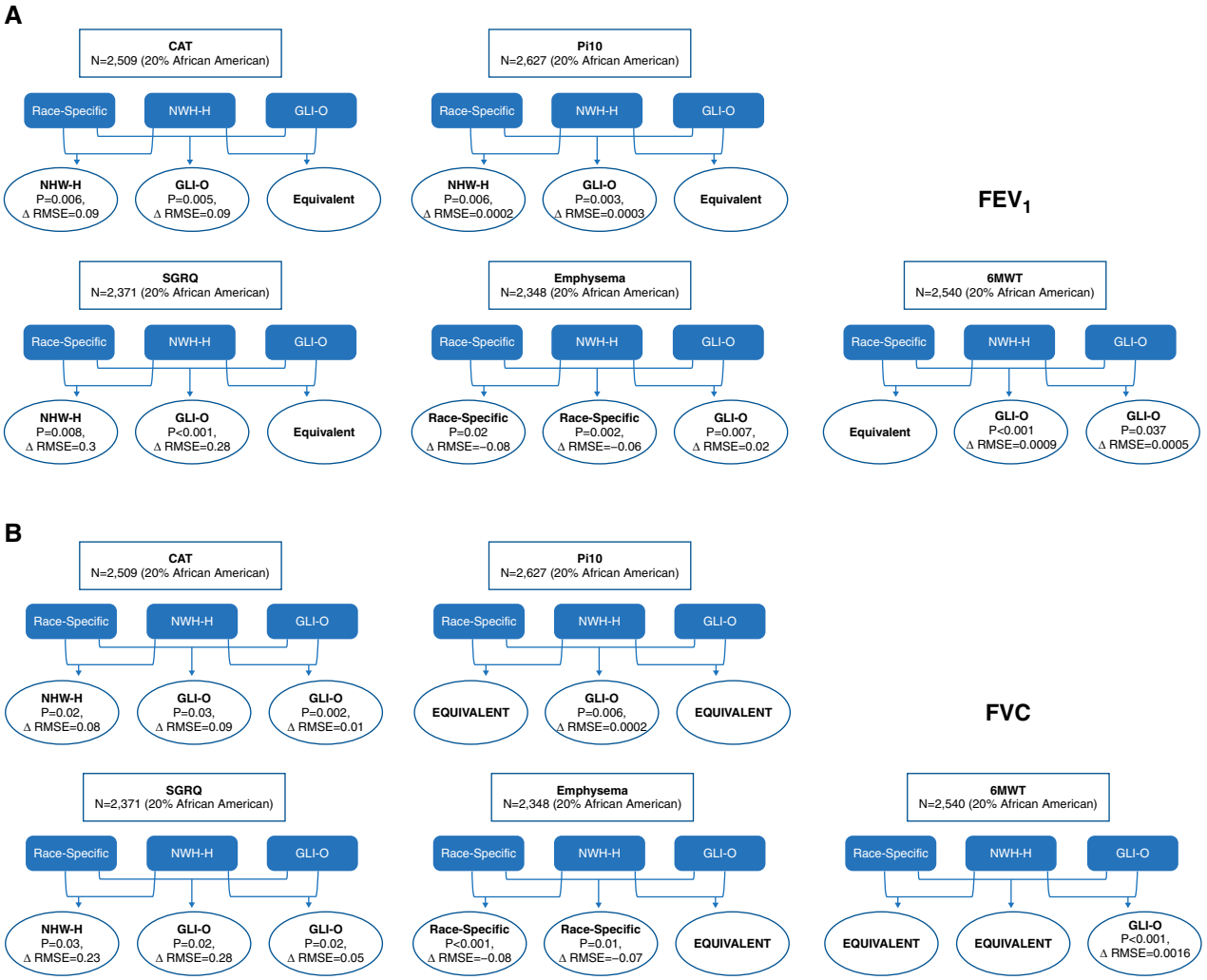

Figure 2. Each COPD-relevant outcome is organized in a separate descending bracket. Arrows indicate each head-to-head comparison, with the best-performing equation (the lowest RMSE) bolded in the circle beneath. ΔRMSE indicates the difference in RMSE between the two equations being compared, and its values are reflective of the magnitude of the scale of responses in each particular outcome.
6MWT = 6-minute-walk test; CAT = COPD Assessment Test; COPD = chronic obstructive pulmonary disease; GLI-O = Global Lung Initiative's Other race equation; NHW-H = Hankinson's Non-Hispanic White equation; Pi10 = quantitative wall thickness for a standard airway; RMSE = root mean square error; SGRQ = St. George's Respiratory Questionnaire.

Table 2. Mean Difference in Estimated Symptom Burden by Pulmonary Reference Equation in African American SPIROMICS Participants

	MCID	NHW-H Mean*	Proportion Exceeding MCID NHW-H (%)	GLI-O*	Proportion Exceeding MCID GLI-O (%)
CAT (FEV_1)	2	1.3 (1.3–1.2)	4.0	1.3 (1.3–1.2)	3.6
SGRQ (FEV_1)	4	**4.1 (4.2–4)**	**55.6**	**4.1 (4.2–4)**	**53.5**
CAT (FVC)	2	1.9 (1.9–1.8)	26.3	1.9 (2–1.9)	36.6
SGRQ (FVC)	4	**6.0 (6.1–5.8)**	**87.7**	**6.2 (6.3–6.0)**	**88.8**

Definition of abbreviations: CAT = COPD Assessment Test; COPD = chronic obstructive pulmonary disease; GLI-O = Global Lung Initiative's Other race equation; MCID = minimally clinically importance difference; NHW-H = Hankinson's Non-Hispanic White equation; SGRQ = St. George's Respiratory Questionnaire; SPIROMICS = Sub-Populations and InteRmediate Outcome Measures In COPD Study.
Bolded values indicate point estimates cross MCID threshold.
*Difference in mean predicted value as compared with race-specific equation.

We did not find evidence that GLI-O performed better than NHW-H equations. This likely results from the current GLI-O equation's weighting toward non-Hispanic White populations, while excluding major portions of the world population including continental Africans and Indians (14). However, as described in our introduction, universal application of the NHW-H prediction equation is inappropriate. Consequently, more representative multiethnic equations are an urgent priority (14). In addition, the contribution of environmental exposures and SES to lung function deserves detailed exploration. Previous work indicates that <10% of lung function is attributable to SES factors;

Table 3. Mean Difference in Absolute FEV_1 (in milliliters) for African American Race Compared with Non-Hispanic White Race among Smokers in SPIROMICS

	Unadjusted	Model 1: Anthropometrics	Model 2: Present Day Comorbidity	Model 3: 1 + AOI and Area Deprivation Index	Model 3b: 2 with Race × AOI Interaction
Race	**−90 (−180 to −1)**	**−293 (−374 to −213)**	**−293 (−374 to −213)**	**−222 (−303 to −141)**	−18 (−230 to 194)
Age	—	**−153 (−196 to −111)**	**−153 (−191 to −110)**	**−154 (−195 to −114)**	**−154 (−195 to −113)**
Age squared	—	**1 (0.7 to 1.3)**	**1 (0.7 to 1.3)**	**1 (0.7 to 1.3)**	**1 (0.7 to 1.3)**
Height squared	—	**0.1 (0.1 to 0.1)**	**0.1 (0.1 to 0.1)**	**0.1 (0.1 to 0.1)**	**0.1 (0.1 to 0.1)**
BMI	—	—	**20 (15 to 26)**	**20 (15 to 26)**	**20 (15 to 26)**
Smoking pack-years	—	—	**−3.2 (−4 to −2)**	**−2.7 (−3.9 to −1.6)**	**−3 (−4 to −2)**
Asthma					
No history	—	—	Ref	Ref	Ref
Current asthma	—	—	**−270 (−347 to −193)**	**−265 (−340 to −189)**	**−268 (−343 to −192)**
Don't know	—	—	**−260 (−423 to −97)**	**−243 (−404 to −82)**	**−244 (−405 to −84)**
Childhood pneumonia	—	—	−56 (−141 to 29)	−55 (−139 to 29)	−54 (−138 to 30)
AOI	—	—	—	**52 (36 to 67)**	**58 (42 to 75)**
Area Deprivation Index	—	—	—	**−2 (−3 to −1)**	**−2 (−3 to −1)**
African American × AOI	—	—	—	—	**−41 (−81 to −2)**

Definition of abbreviations: AOI = Adversity–Opportunity Index; BMI = body mass index; COPD = chronic obstructive pulmonary disease; Ref = reference; SPIROMICS = Sub-Populations and InteRmediate Outcome Measures In COPD Study.
Bolded values are statistically significant.

however, these studies fail to account for cumulative, intergenerational, or interactive effects with environmental exposures, which deserve further study (55). Further study of SES and lung disease may also clarify why, in both this and previous reports (56), the gaps in symptom severity between low- and high-status individuals are not more directly proportional to their observed social disparities. Mechanistic studies are also helpful. Like our own finding of lower FVC with preserved FEV_1/FVC ratio, previous work suggests that the sort of subclinical injury we postulate may manifest as stunted lung growth or lower maximal potential rather than accelerated decline (57). A third major direction is exploring the implications of our findings, such as on spirometry-based criteria for thoracic surgery, employment, and disability. In employment and surgery especially, there are already significant racial disparities that might be further exacerbated by moving away from race-specific equations (58–60). Atop these complexities are the uncertain effects of, on the one hand, raising the reference standard for many populations and, on the other, widening the SD—both

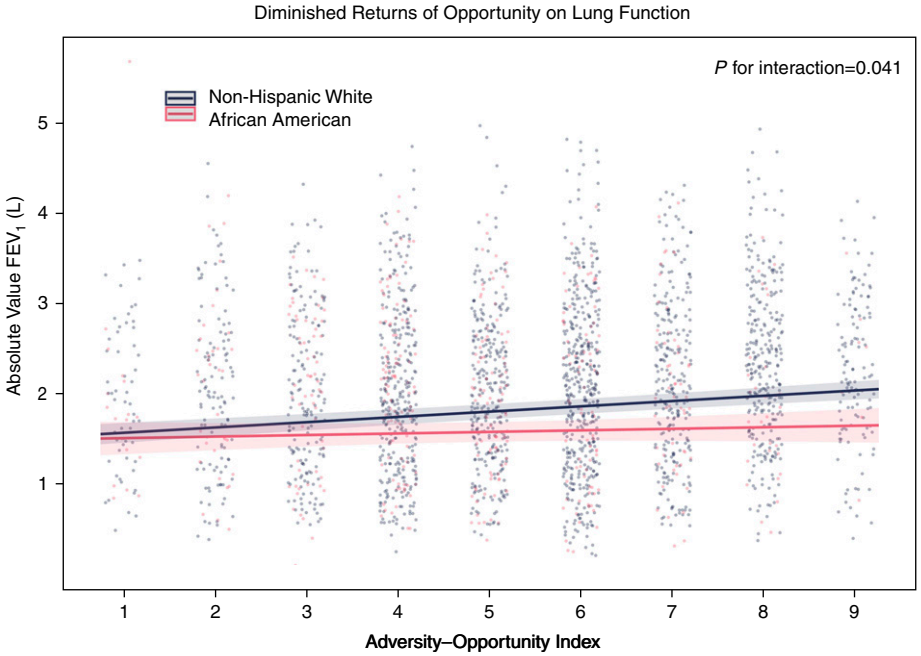

Figure 3. Absolute FEV_1 in milliliters for African American and Non-Hispanic White participants from SPIROMICS at each level of the Adversity–Opportunity Index (AOI). Overlying are the multivariable linear regressions of FEV_1 by AOI, stratified by self-reported race. *P* for interaction = 0.041 indicating that African American participants do not manifest the same increased FEV_1 with increasing AOI as seen for non-Hispanic White participants. COPD = chronic obstructive pulmonary disease; SPIROMICS = Sub-Populations and InteRmediate Outcome Measures In COPD Study.

expected results of moving toward multiethnic equations. The correlation of lung function to the most relevant, particular symptoms in each domain must be understood to ensure an equitable system. Different racial groups have been found to respond divergently to self-report survey language in ways that influence results, but this possibility remains incompletely explored in COPD instruments (61).

This work's principal strengths are its large sample size, measurement of multiple disease-specific outcomes, and the incorporation of SES through individual, neighborhood, and early childhood data. There are multiple limitations. Truncal height, which was unavailable in our data set, better predicts lung function than total height (18) and may explain part of the observed racial disparities. Early life factors like birth weight are important to the trajectory of lung function but were not queried in SPIROMICS (62, 63). Our metrics of adversity were measured at a single time point rather than across the lifespan, let alone accounting for suggested intergenerational effects (64). Recall bias is a major limitation regardless of the frequency of ascertainment. Cohorts prospective to adverse childhood events might better model their impact. Greater recruitment among affluent African American individuals would help confirm the observed interactions between race, inequity, and lung function. Further validation of our novel AOI would also be helpful. Minimal enrollment of self-identified racial groups beyond the two examined here (African American and non-Hispanic White) limits our ability to discuss racial adjustment in those populations. Greater granularity in racial and/or ethnic classification would also be of benefit.

Lastly, consideration of limitations of the present study would be incomplete without acknowledging the potential role of genetic ancestry. Ancestry is both distinct from the concept of race and superior to it in predicting lung function (65). Although we were eager to investigate how this approach correlated to clinical outcomes, we did not proceed from currently published equations given concerns around poor age overlap with SPIROMICS, the uncertain application to individuals with very low fractions of African ancestry, and the suggestion of cohort-specific effects given the differing values derived even from similarly aged groups (65). The inverse association between African ancestry and lower lung function in minorities of African descent might reflect African genetic variation for a common ancestry, but it is important to consider that ancestry tracks with the geographic, environmental, and historical factors, which could result in gene-by-environment interactions impacting lung function (65). Hence, by deriving expected values only from within a population without considering either social condition or cross-group comparisons, an ancestry-based system may replicate the flaws we critique in the race-based standard. That is, where differential allelic assortment and structural inequities are collinear, such analyses can effectively mislead (66).

Conclusions

Race-specific lung function prediction equations were inferior to universally applied alternatives in explaining symptom burden in an American population of smokers with and at risk for COPD. Although lung function in the lowest quartile of AOI was similarly low between races, on average, only non-Hispanic White participants benefited from better composite life exposures. Collectively, our analysis suggests that race-specific lung function prediction underrecognizes disease burden among individuals, while at the systemic level, it blinds clinicians and policy makers to important and potentially modifiable causes of lung disease. The consistency of the findings across pathology, symptoms, outcomes, and potential contributors to COPD argues for a broad reconsideration of the use of race-specific lung function prediction equations in this population in favor of multiethnic universally applied alternatives (67). ■

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