

Race/ethnicity and spirometry reference equations: a review of the literature

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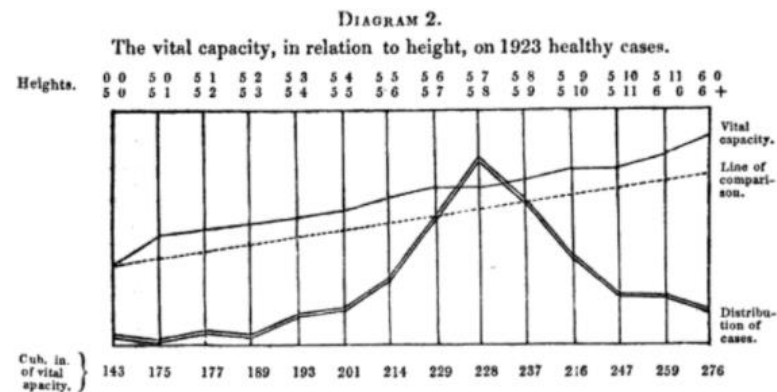
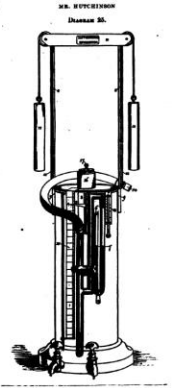
Race Adjustment in Clinical Algorithms

- Race, a social construct, has been used in clinical algorithms, often as a substitute for an observed difference in population variation that is then *assumed* to be due to a genetic or biologic difference.
- However, race is not a reliable proxy for physiologic differences.
- There is greater genetic variation within racial groups than between them.
- Rather, differences observed by racial/ethnic groups in diagnoses and health outcomes may be due to social determinants of health and structural racism.

Collins FS, et al. Science 2003.
Schluger NW, et al. Annals ATS 2021.
Sirugo G, et al. JCI 2021.
Vyas DA, et al. N Engl J Med 2020.

Background

- The spirometer was invented in 1844 by John Hutchinson to assess lung function.
- He described the vital capacity as “the greatest voluntary expiration, following the deepest inspiration.”
- Using a cohort of 1,923 healthy cases, he compared vital capacity to height, establishing “normal” versus “abnormal” lungs.
- Hutchinson noted variations in average lung functions based on gender, age, occupation, and social class.



Hutchinson J. Med Chir Trans 1846.
Bhakta NR et al. Chest 2021.

Background

- In 1869, a large survey found vital capacity was lower in Black individuals when compared to White individuals.
- This idea had also been used to justify the conditions of slavery by Thomas Jefferson.
- Following this, much of the focus on population differences in lung function were attributed to race, using race as a biologic proxy rather than understanding race as a social construct that reflects other social and environmental factors.
- Current spirometry reference equations are calculated based on healthy non-smoker populations, adjust for age, height and sex, and include a term for race/ethnicity.
- For two people with the same absolute measured lung function, of same age, sex and height, a Black individual will have a higher percent-predicted value compared to a White individual based on current equations.

Current guideline recommendations

- The American Thoracic Society currently recommends the use of the Global Lung Function Initiative (GLI) reference equations, developed in 2012.
- Previously the NHANES III reference equations were used with separate equations for White, Black and Hispanic groups, with a correction factor of 0.88 derived later for Asian individuals.
- GLI equations provide separate coefficients for White, African American, North East Asian and South East Asian race/ethnicities.
- These are used to calculate the percent-predicted forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC).
- With the reference equations, there is higher mean percent-predicted lung volumes among Black compared to White adults, when holding all else constant, despite having the same absolute volumes measured – leading to underdiagnosis of respiratory disease in Black patients.

Culver BH et al. AJRCCM 2017.

Hankinson JL, et al. AJRCCM 1999.

Hankinson JL, et al. Chest 2010.

Quanjer PH, et al. Eur Respir J 2012.

Factors that affect lung function

- Lung growth is impacted by developmental and childhood exposures, including
 - Nutritional deficiencies, prematurity and low birth weight
 - Childhood respiratory infections
 - Second-hand smoke
 - Air pollution exposure, such as PM 2.5, ozone, traffic
 - Lower socioeconomic status
- There is unfair and unequal distribution of these exposures with marginalized racial and ethnic groups being more unfairly exposed.
- These factors have not been accounted for in race-based adjustments nor in interpretation.

Schluger NW, et al. *Annals ATS* 2021.
Gaffney A, et al. *Eclinical Medicine* 2021.
Barker DJ, et al. *BMJ* 1991.
Ejike CO, et al. *Am J Respir Crit Care Med* 2019.
Lovasi GS, et al. *Am J Epidemiol* 2010.
Martinez FD. *N Engl J Med* 2016.
Gaffney AW et al. *JAMA Internal Medicine* 2021.

Potential impacts of race adjustment

- Pulmonary Function Tests (PFTs) are used in the pre-operative evaluation for thoracic surgeries.
- PFTs are also used in pre-employment testing and disability.
- Black patients are less likely to be listed for lung transplantation.
 - In a study of patients with idiopathic pulmonary fibrosis, Black and Hispanic patients were found to have increased risk of death compared to White patients after being listed for lung transplant.
- Black, Hispanic, and American Indian or Alaska Native individuals have had higher risk of COVID-19 infection compared to White individuals.
 - Use of current equations could lead to underdiagnosis of restrictive disease in follow-up PFTs for COVID-19 patients.

Schluger NW et al. Annals of ATS [In press] 2021.

Lederer et al. Am J Transplant 2006.

CDC 2021.

Anderson MA, et al. Lancet Resp Med 2021.

Racial disparities in COPD

- Delayed diagnosis of pulmonary diseases:
 - Black individuals are less likely to have a prior diagnosis of COPD when compared to White individuals.
 - At UPenn, in an analysis of 14,080 Black patients who had undergone PFTs, use of White race/ethnic-based reference equations led to an additional diagnosis of obstructive lung disease by 1.7% and of restrictive disease by 4.7%.
- Black patients with COPD are less likely to be on treatment, and to participate in guideline-recommended pulmonary rehabilitation programs.
- Black patients with COPD have higher rates of ED visits and hospitalizations.

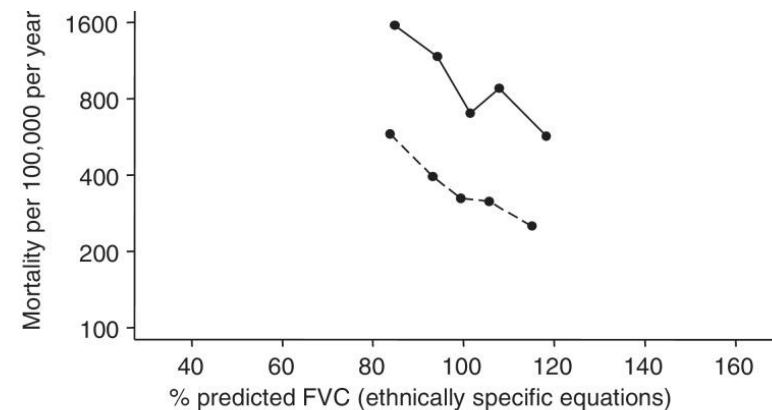
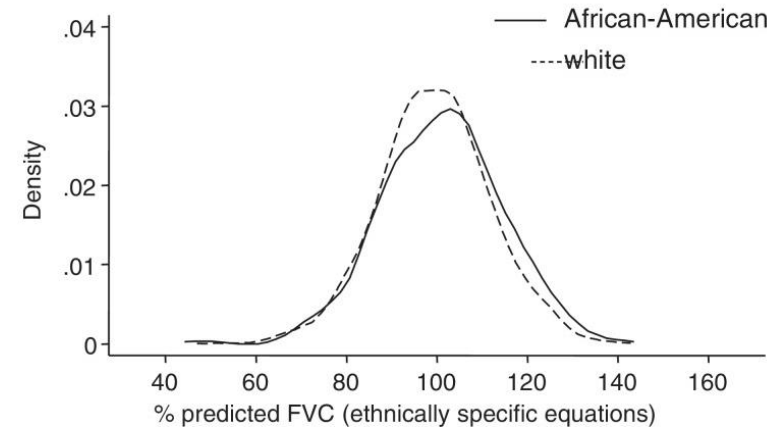
Moffett A, et al. AJRCCM [Abstract] 2021.
Bhakta NR, et al. Chest 2021.
Martinez CH, et al. Ann Am Thorac Soc 2015.
Han MK, et al. Chest 2011.
Martin A, et al. Br J Gen Pract 2012.
Spitzer KA, et al. Chest 2020.
Ejike CO, et al. AJRCCM 2019.

Underestimation of symptoms in COPD

- In a study of 2,652 current or former smokers from SPIROMICS with or at risk for COPD, comparing NHANES race-specific, NHANES White-race, and GLI-Other reference equations, they found:
 - Correlation between percent-predicted FEV1 and respiratory symptoms differed between Black and White participants with the use of race-adjusted equations but were identical when no race-adjustment used.
 - The use of universally-applied White-race equations or GLI Other equations performed better in reflecting symptom burden on COPD Assessment Test (CAT) and St George's Respiratory Questionnaire (SGRQ) scores, 6-minute walk test for functional outcomes, and radiographic airway disease.
 - The inclusion of an adversity opportunity index, neighborhood deprivation, smoking pack-years, asthma, and BMI reduced the effect size of the race term in a multivariable model of lung function.
 - **Race adjustment can underestimate impaired lung function and symptoms in Black patients.**

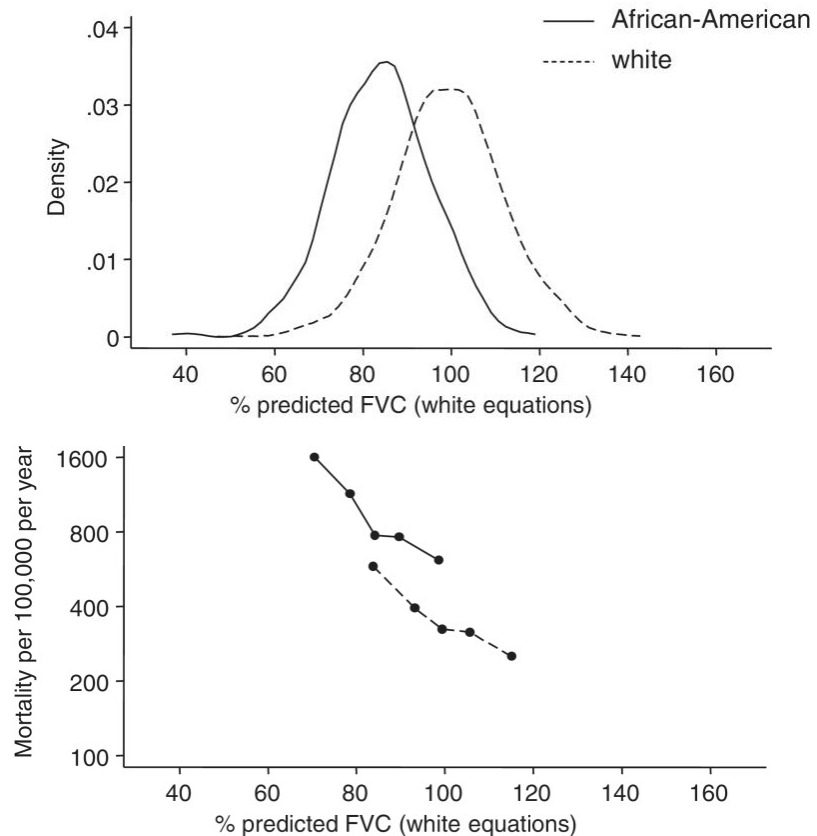
Consequences of race-adjustment in spirometry interpretation on mortality

- This shows the distribution of the percent-predicted forced vital capacity (FVC) for Black and White men with the use of the NHANES III race-specific equations
- This shows the mortality rates based on the calculated percent-predicted FVC, and the mortality rate among Black men is higher at any given value of percent-predicted FVC compared to White men.



Consequences of race-adjustment in spirometry interpretation on mortality

- This shows the distribution of the percent-predicted FVC for Black and White men with the use of the NHANES III race-neutral equation
- This shows the mortality rates based on the calculated percent-predicted FVC, and while the mortality rate among Black men is still higher, the mortality rates increase linearly as FVC decreases.



Follow up studies

- After adjusting for age, sex, and height, Black and White individuals with the same FVC in liters have similar mortality rates.
- **Thus, it suggested that predicted values from current race-adjusted reference equations underestimate the risk of mortality in Black patients.**
- Two new studies published in 2021 to further investigate the Black-White differences in FVC.
 - In an analysis of 9,034 White and Black participants ages 20 – 80
 - Calculated percent-predicted FVC among Black and White participants with:
 - The NHANES III race-specific prediction equations;
 - The NHANES III White prediction equation applied to all persons.

Distribution of FVC among participants by the different equations

Measures of forced vital capacity (FVC) of White and Black participants ($n = 9037$) ages 20–80, NHANES III.

	White ($n = 5294$)	Black ($n = 3743$)	p -value
Mean FVC (\pm SE)			
FVC (Liters)	4.3 ± 0.03	3.7 ± 0.02	<0.001
FVC, percent predicted (White equation)	98.3 ± 0.36	84.5 ± 0.28	<0.001
FVC, percent predicted (race-specific equation)	98.3 ± 0.36	101.1 ± 0.34	<0.001
Proportion with reduced ($<$ LLN) FVC (\pm SE)			
Using White prediction equation (%)	8.8 ± 0.6	39.9 ± 1.2	<0.001
Using race-specific prediction equation (%)	8.8 ± 0.6	4.8 ± 0.4	<0.001

p -values calculated using uni-variate linear regression (Mean FVC) or Pearson chi-square (Proportion with reduced FVC).

Note: FVC=forced vital capacity; SE=standard error; LLN = lower limit of normal. Percent predicted and LLN calculated using NHANES III prediction equations.¹.

Regression analysis based on percent-predicted FVC by different equations

- During 184,206 person-years of follow-up, 3064 deaths occurred.
- The average age at death was 66.4 years among Black individuals and 74.5 years among White individuals.

Hazard ratio (for death), Black vs. White race among US adults ages 20–80 in NHANES III ($n = 9037$).

Model	Covariates	Hazard Ratio, Black vs. White Race	95% Confidence Interval	<i>p</i> -value	
A1	Age and sex	1.46	1.29	1.65	<0.001
A2	Age, sex, and height (cm) plus FVC (L)	1.03	0.91	1.16	0.621
A3	Age plus FVC percent predicted (White equation)	1.05	0.93	1.18	0.445
A4	Age plus FVC percent predicted (race-specific equations)	1.52	1.35	1.70	<0.001

- Black participants' age and sex adjusted mortality was greater than White participants.
- But, with the use of percent-predicted White equations for everyone, Black race was no longer independently predictive of mortality.
- Again, with race-specific equations, Black race showed increased mortality hazard.

Similar results with the GLI equations

- In an analysis of 12,770 Black or White individuals from NHANES III
 - Calculated percent-predicted FEV1, FVC and Z scores among Black and White participants with:
 - The GLI race-ethnic specific equations;
 - The GLI “Other” equation applied to all persons.
- Again, race-specific equations led to lower predicted survival for Black participants at a given FEV1 Z score. However, this diminished with the use of the “Other” equation, finding similar mortality risk between groups.
- The lower average lung function in Black compared to White individuals, with which the race-specific equations is “normalized”, “reinforces a false assumption about “normal” lung volumes in Black populations and the health implications.”

GLI spirometry reference equations

- GLI equations for males and females are:

$$\text{Predicted value of FEV}_1 \text{ or FVC} = \exp(\beta_0 + \beta_1 \log(\text{height}) + \beta_2 \log(\text{age}) + \text{spline}(\text{age}) + \beta_3(\text{Black}) + \beta_4(\text{North East Asian}) + \beta_5(\text{South East Asian}))$$

- The GLI “Other” Equations (or “Mixed Ethnic Origin”), an average of the available data from the four racial/ethnic groups above.
 - Has been proposed as a universal approach, but limitations include that it does not fully represent the global population.

Performance of GLI “Other” equation

- In an analysis of 3,344 participants from the Multi-Ethnic Study of Atherosclerosis (MESA) Lung Study, a prospective, population-based cohort of White, Black, Hispanic and Asian participants from 6 US communities:
 - Calculated percent-predicted FEV1, FVC among all participants with:
 - The GLI “Other” equation applied to all persons (referred to as the “race/ethnic-neutral equations”);
 - The GLI race/ethnic specific reference equations.
 - Tested associations between predicted values and the occurrence of chronic lower respiratory disease events and all cause mortality

Differences at clinically relevant thresholds comparing equations

	White	Black	Hispanic	Asian
Percent-predicted FEV₁ <80%				
Race/ethnic-based equations, %	17%	18%	16%	26%
Race/ethnic-neutral equations, %	11%	33%	8%	18%
Percent-predicted FVC ≤80%				
Race/ethnic-based equations, %	12%	14%	11%	19%
Race/ethnic-neutral equations, %	6%	27%	6%	13%
Moderate-severe airflow limitation				
Race/ethnic-based equations, %	10%	8%	6%	8%
Race/ethnic-neutral equations, %	7%	12%	4%	7%

Discriminative accuracy of percent-predicted lung function comparing equations

Percent-predicted lung function	Harrell C-statistic		P-value
	Race/ethnic-based equations	Race/ethnic-neutral equations	Difference between Race/ethnic-based and Race/ethnic-neutral equations
Chronic Lower Respiratory Disease events			
FEV ₁	0.71	0.72	0.22
FVC	0.61	0.62	0.03
All-cause mortality			
FEV ₁	0.57	0.57	0.44
FVC	0.53	0.54	0.14

Conclusions

- Use of race-based equations in pulmonary function tests is associated has the potential to delay diagnosis and treatment of chronic lung diseases, as well as restrict access to disability, rehabilitation programs and lung transplantation for Black patients.
- Use of race-based equations in pulmonary function tests underestimates mortality for Black patients.
- Current equations also do not take capture racially disparate exposures such as environmental and social mechanisms that are likely related to structural racism and can contribute to lower lung function.
- Given the harms of continued use of race-based equations, the use of the GLI “Other” reference equation could be applied to all patients. It is already available to everyone and could remove barriers to care and underdiagnosis of lung disease.
- There have not yet been any guideline recommendations changes from the American Thoracic Society.

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Thank you!

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Questions or comments?

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