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⊙ Check for updates

Race/Ethnicity and Reference Equations for Spirometry

To the Editor:

We read with interest two papers in the *Journal* arguing that lung-function prediction equations should be neutral with regard to race and ethnicity. We agree that race is a socio-political construct and we must eliminate racial biases in health care, but we disagree with the approach of McCormack and colleagues (1) and of Elmaleh-Sachs and colleagues (2) who redefine normal values for spirometry to address this issue.

By ignoring a subject's ancestry when evaluating lung function, McCormack and colleagues (1) found spirometry better correlated with subsequent overall mortality in National Health and Nutrition Examination Survey (NHANES) III data. In NHANES III, those of African ancestry were on average younger but had an age-adjusted mortality that was worse than that for people of European ancestry, which fits with Centers for Disease Control and Prevention data (3). In the United States, the small proportion of total deaths related to chronic lower respiratory disease differ significantly between people of African versus European ancestry (3.3% vs. 6.4%, respectively) (4), but the authors attempt to account for all of the difference in all-cause mortality by manipulating lung function data. Using global prediction equations (Global Lung Function Initiative "other" [5]) that combine all ancestries makes the lung function for those of African ancestry appear worse and for those of European ancestry appear better. The resultant improvement in the correlation of FEV_1 z-score with overall mortality is used to justify using global prediction equations. However, the great majority of overall mortality differences are not related to lung function. The different disease spectrum and limitations in both the access to and the delivery of health care for people of African ancestry, that are not accounted for by socio-economic adjustments (6), are not addressed by the authors. Because there are different numbers in the two groups being compared in the study, the probability distribution graphs in the study should use percentage of people rather than numbers of people, as demonstrated in Figure 1, which shows both groups had z-scores approximately centered around unity, which is to be expected from a general population cohort compared with a healthy reference population. Using geographic ancestry-specific equations (5) does not produce a bias between the two groups with the distributions of initial z-scores for FEV_1 in the two groups being remarkably similar.

However, using globally based z-scores that combine all geographic ancestries skews the two groups in different directions. The European ancestry group are shifted to higher and the African ancestry group are shifted to lower FEV_1 z-scores, making the general population of African ancestry cohort appear to have FEV_1 lower than the reference African ancestry cohort (suiting the authors' thesis), while the general population of European ancestry cohort then appear to have FEV_1 higher than the reference European ancestry cohort, which is highly improbable. As the authors note, using global reference equations for spirometry is potentially prejudicial to patient care for both people of African ancestry and European ancestry with a risk of overdiagnosis of respiratory disease in the former and underdiagnosis in the latter.

Elmaleh-Sachs and colleagues (2) also looked at survival- and event-related data in NHANES III data to make a conclusion that race–neutral lung-function prediction equations are the best way forward. Their analysis not only suffers from the problems outlined above, but they also used percentage of predicted lung function values in their analysis. This is a flawed methodology that is not supported by the American Thoracic Society or European Respiratory Society in making assessments about lung function (7). It retains sex, age and size bias and assumes a proportionality in severity which is not proven. Because it retains a size bias, it will include a geographic ancestry bias. Percentage of predicted also ignores the degree of scatter found in normal subjects which varies with sex and geographic ancestry (8).
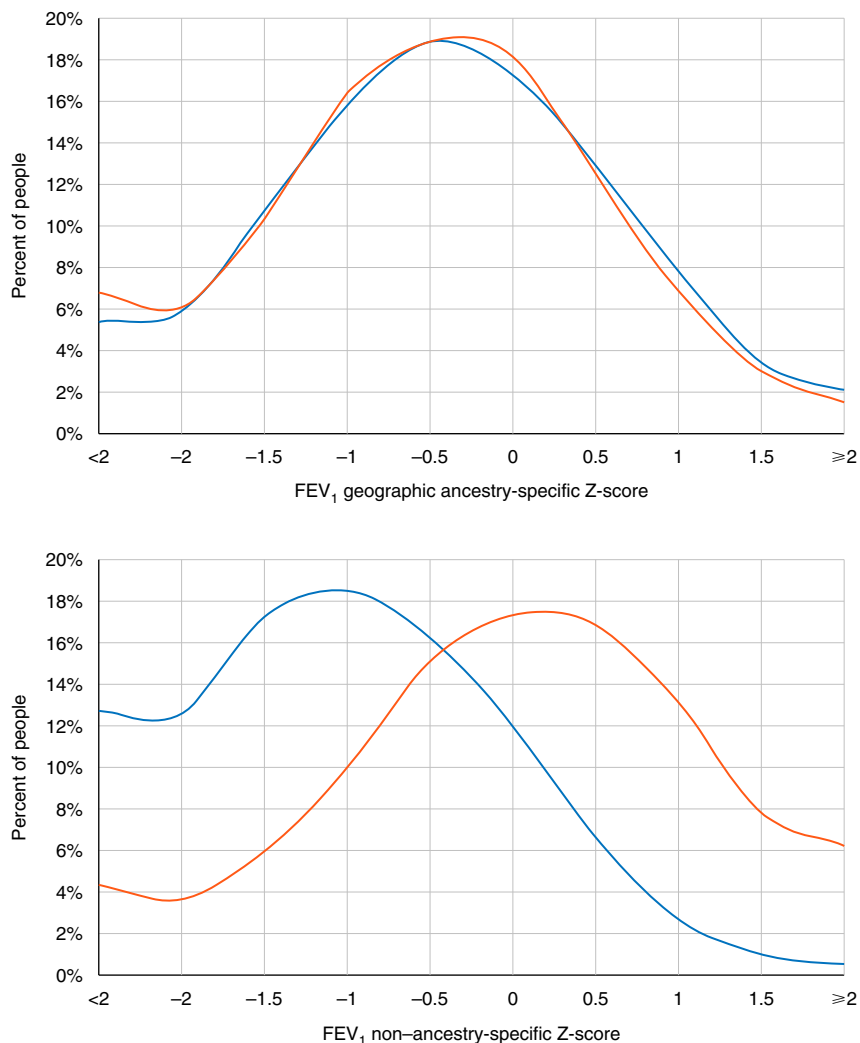
Figure 1. Data replotted from McCormack *et al.* (1) as percentage of the group rather than the number of people for African ancestry (blue lines) and European ancestry (orange lines).

Improving the chance that people of African-American ancestry will receive equitable health care is unlikely to be achieved by reducing the precision of spirometry reference values. It is important to distinguish between genuine racism in healthcare and the effects of geographic ancestry on lung function. Anthropomorphic differences in sitting height to standing height account for at least 35% of the discrepancy in lung function between African Americans and White subjects with a further 2.5% to 7.5% relating to poverty and 2.0% to 4.7% to education (9). A better account and understanding of these substantial anthropomorphic differences is needed. We believe that the above authors' conclusions to ignore the differences in the relation between lung function and the sex, age, and standing height for people of different geographic ancestry is not justified from their findings. Neither paper has shown an improvement for individual patients, and their approach could lead to racism from prejudicial judgments being made about whether an individual's lung function is within the range expected for someone of the same geographic ancestry. This will obscure the true causes for the worse overall mortality for people of African ancestry, which must be addressed so that worse prejudicial outcomes do not continue. ■

Martin R. Miller, M.D.*
University of Birmingham
Birmingham, United Kingdom

Brian L. Graham, Ph.D.
University of Saskatchewan
Saskatoon, Saskatchewan, Canada

Bruce R. Thompson, Ph.D.
The University of Melbourne
Melbourne, Victoria, Australia

ORCID ID: 0000-0001-9971-5759 (M.R.M.).

*Corresponding author (e-mail: martin@drmiller.uk).

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Reply by Elmaleh-Sachs *et al.* to Townsend and Cowl, and to Miller *et al.*

From the Authors:

We thank Professor Miller and colleagues and Drs. Townsend and Cowl for their letters in response to our paper (1) and believe we all share the goals of reduced race/ethnicity disparities. However, we disagree with Professor Miller and colleagues that our suggestion to use modern, prospective cohort designs to help define "normal" lung function instead of the current cross-sectional approach will lessen "the chance that people of African American ancestry will receive equitable health care … by reducing the precision of spirometry reference values."

Spirometry should be measured both precisely (reproducibly) and accurately (2, 3), and we argue that criteria for selection of reference equations should also include both precision and accuracy, with the latter assessed in comparison to a gold standard such as incident clinical events. Yet current cross-sectional approaches (3) assess precision but do not consider the prediction of clinically meaningful outcomes to assess accuracy.

Our paper uses prospectively ascertained and validated incident clinical events of chronic lower respiratory disease (CLRD) hospitalizations and deaths (4) to test the predictive accuracy of reference equations. Using this approach, we find no evidence that race/ethnicity-based equations are more accurate for the prediction of incident CLRD events than race/ethnicity- neutral equations, which we and others (5) believe call into question the benefit of including race/ethnicity in spirometry reference equations.

A prospective design to define clinical thresholds based upon incident clinical events is common for other diseases including hypertension (6, 7), rather than cross-sectional designs. Cross-sectional analyses in multi-ethnic prospective cohorts such as the Multi-Ethnic Study of Atherosclerosis (MESA), in which our report (1) is based, demonstrate significant differences in mean blood pressures and upper limits of normal among never-smoking White and Black participants free of clinical cardiovascular disease (Figure 1). Indeed, the use of a race-based "upper" limit of normal approach to define hypertension, analogous to the approach that the European Respiratory Society and American Thoracic Society (ERS/ATS) recommends to define abnormal spirometry (3), would classify 75% of White participants and 84% of Black participants with hypertension (diagnosed based upon the recommended threshold of 140 mm Hg [6]) as having "normal" blood pressure. This cross-sectional approach would underestimate the risk of incident clinical events among Black participants and significantly increase race/ethnicity disparities in cardiovascular disease compared with the recommended, prospective approach (6).

In chronic lung disease, the current ERS/ATS-based approach based on cross-sectional reference equations do define higher percentage predicted values in the FEV_1 for Black individuals with the same degree of respiratory symptoms and chronic obstructive pulmonary disease (COPD) severity as White individuals, which may be one of multiple causes of clinically significant race/ethnicity disparities in COPD (8)—and one that we can address.

Drs. Townsend and Cowl importantly point out that there are two sides to every threshold, and race/ethnicity-neutral equations may increase some race/ethnicity disparities in occupational settings; however, defining individuals at higher risk of CLRD to have "normal" lung function and allowing them to work in high-risk occupational settings may increase their risk further.

Miller and colleagues also suggest that better measurement and understanding of the "substantial anthropomorphic differences" between races is needed to reduce race/ethnicity disparities. We take issue with this suggestion given the long and dubious history of using anthropometry purportedly to explain perceived functional differences by race/ethnicity, the large number of average differences by race/ethnicity that are mostly irrelevant to disease pathobiology and "normality" (mean height, skin color, etc.), and our current findings that suggest that incorporation of additional anthropometric measures to explain perceived functional differences is likely to be clinically irrelevant.