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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.

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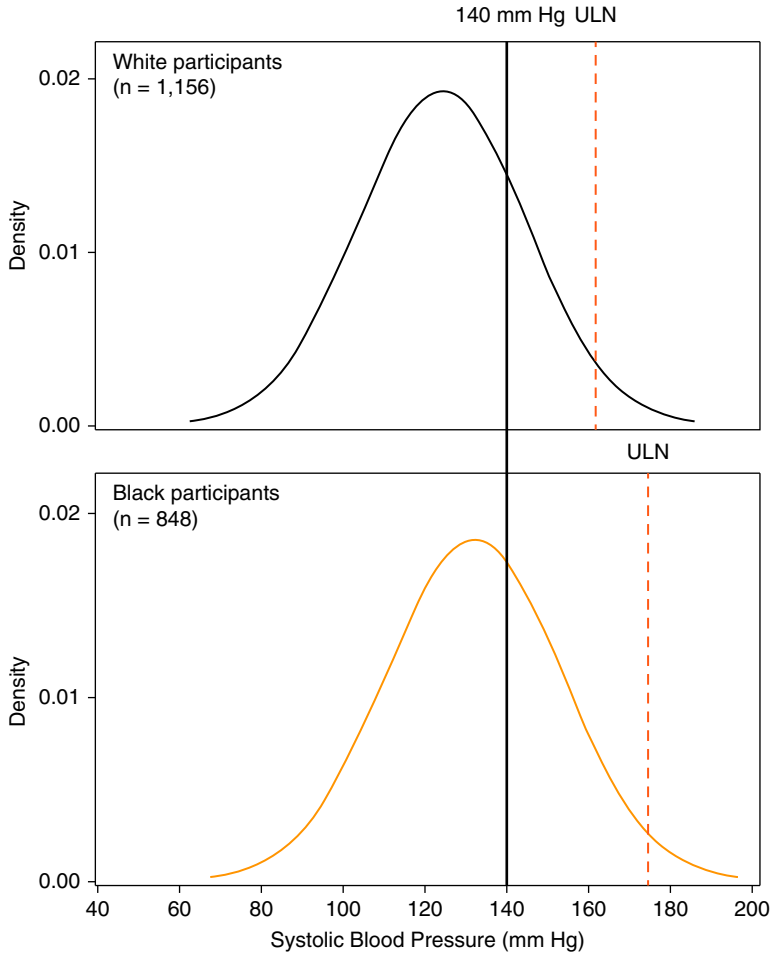

Figure 1. Systolic blood pressure density distributions among never-smoking White and Black participants free of clinical cardiovascular disease in the Multi-Ethnic Study of Atherosclerosis. The mean blood pressure was 124 mm Hg among White and 132 mm Hg among Black participants (8 mm Hg mean difference, $P < 0.001$). The dashed lines show the upper limits of normal (ULN) calculated in these data, which were 162 mm Hg for White participants and 174 mm Hg for Black participants. The solid line shows the recommended threshold of 140 mm Hg for the diagnosis and treatment of hypertension in patients without clinical cardiovascular disease (6). Differences of mean systolic blood pressure and ULN were similar in an analysis of participants without reported hypertension (data not shown). Classification of systolic hypertension was based on a blood pressure of 160 mm Hg until 1993 and 140 mm Hg thereafter (12).

We used percentage predicted FEV_1 as our primary exposure given that treatment of COPD and asthma is based in part on the percentage predicted FEV_1 (9, 10). Re-analysis of our results using a *z*-score approach also found that there was no improvement in the prediction of events with the race/ethnicity-based equations compared with the race/ethnicity-neutral equations (Table 1). Restriction to participants ages 65 and over on Medicare and additional adjustment for educational attainment, smoking status, pack-years, body mass index, blood pressure, high-density lipoprotein, low-density lipoprotein, total cholesterol, and history of hypertension and diabetes also yielded similar results (Table 1).

We believe that it is time to use contemporary, prospective designs with clinically relevant gold standard events to define normality and thresholds for the treatment of lung diseases instead of an approach first published in 1846 (11). Using a prospective design with clinical endpoints, we find no evidence to suggest that the inclusion of terms for race/ethnicity improves the accuracy of the reference equations. The harms of the cross-sectional approach, including underdiagnosis of respiratory symptoms and obstructive lung disease for Black patients, are reported separately (8), and this approach would be unacceptable in other diseases like hypertension. We look forward to the further development of precise and accurate spirometry reference equations to predict and diagnose clinical events for all patients and recommend the use of prospective data to identify risk across populations. ■

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Table 1. Discriminative Accuracy of *Z*-scores for the FEV_1 and FVC Using Race/Ethnicity-based and Race/Ethnicity-Neutral Equations for Chronic Lower Respiratory Disease–related Events and All-Cause Mortality in the Multi-Ethnic Study of Atherosclerosis Lung Study Overall and Restricted to Participants Ages 65 and Over on Medicare

	Events/ Person-years of Follow-Up	Incidence Rate per 10,000 Person-Years	*Z*-Score	Harrell C Statistic (95% CI)			*P* Value
				Race/ Ethnicity-based Equations*	Race/ Ethnicity-Neutral Equations†	Difference	
Chronic lower respiratory disease-related events‡							
Overall (unadjusted): n = 3,344	181/34,987	52	FEV_1	0.70 (0.66, 0.74)	0.71 (0.66, 0.75)	−0.009 (−0.02, 0.007)	0.28
			FVC	0.59 (0.55, 0.64)	0.61 (0.57, 0.65)	−0.02 (−0.04, 0.0003)	0.05
Restricted to ages 65 and over on Medicare (adjusted): n = 1,317	103/13,096	79	FEV_1	0.69 (0.63, 0.75)	0.69 (0.63, 0.75)	0.0008 (−0.01, 0.02)	0.91
			FVC	0.67 (0.61, 0.73)	0.67 (0.61, 0.72)	0.001 (−0.01, 0.01)	0.83
All-cause mortality							
Overall (unadjusted): n = 3,344	547/35,655	153	FEV_1	0.55 (0.53, 0.58)	0.56 (0.53, 0.58)	−0.008 (−0.02, 0.002)	0.12
			FVC	0.52 (0.50, 0.55)	0.54 (0.51, 0.56)	−0.01 (−0.02, −0.002)	0.02
Restricted to ages 65 and over on Medicare (adjusted): n = 1,317	346/13,449	257	FEV_1	0.65 (0.62, 0.68)	0.65 (0.62, 0.68)	−0.0009 (−0.005, 0.003)	0.65
			FVC	0.65 (0.62, 0.68)	0.65 (0.62, 0.68)	−0.0007 (−0.004, 0.003)	0.70

Definition of abbreviations: CI = confidence interval; GLI = Global Lung Function Initiative.
Unadjusted analyses from Cox proportional hazards regression models.
Adjusted analyses from Cox proportional hazards regression models including body mass index, educational attainment, smoking status, pack-years, blood pressure, high-density lipoprotein, low-density lipoprotein, total cholesterol, self-reported diabetes and hypertension, and use of medications for diabetes and hypertension.
*Guideline-based application of GLI race/ethnicity-based reference equations. GLI equations are not available for Hispanic individuals; the GLI equation for White individuals was therefore used. GLI equations include two equations for Asian individuals; the one for North East Asians was used.
†Race/ethnicity-neutral approach applying GLI "Other" reference equations to all groups.
‡Chronic lower respiratory disease–related events defined as hospitalizations or deaths for which chronic lower respiratory disease was classified as a primary, underlying, or contributing cause by adjudication or administrative criteria following a previously validated protocol (4).

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Reply by McCormack *et al.* to Townsend and Cowl, and to Miller *et al.*

From the Authors:

We appreciate the opportunity to respond to the points raised by Drs. Miller, Graham and Thompson and Drs. Townsend and Cowl regarding our publication "Race, Lung Function, and Long-Term Mortality in the National Health and Examination Survey III" (1). Our findings caution that integrating the lower lung function observed among Black Americans in a definition of normal may have the potential to obscure adverse health implications. Miller and colleagues argue for the use of race-specific reference equations for interpretation of lung function by arguing that using all-cause mortality as an outcome lacks validity and that categories defined by the Global Lung Function Initiative (GLI) reference equations represent the effects of "geographic ancestry" on lung function. We agree that studying overall mortality has inherent limitations. However, lung function has consistently been linked to all cause mortality, and poor lung function affects not only respiratory mortality but also cardiovascular mortality (2), the leading cause of death in the United States. Further, Elmaleh-Sachs and colleagues, and others, have recently shown similar results for chronic lung related events and mortality (3, 4).

Miller uses the term "geographic ancestry," a term which has unclear meaning. The concept of geography in lung function seems to harken back to recommendations that existed before the availability of large datasets of normative values to gather data from local populations to develop normal values for individual labs (5). A perceived benefit of such an approach was that geographic conditions that may affect lung function, such as living at altitude, would be addressed by local norms. However, a major limitation was the lack of standardization between labs, a problem addressed by the use of much larger datasets such as National Health and Nutrition Examination Survey (NHANES) and GLI reference equations.

It is not correct to state that GLI subgroups from which reference equations are based represent "geographic ancestry." Reference data for Black/African American populations were drawn solely from U.S. cohorts, including NHANES and Multi-Ethnic Study of Atherosclerosis, where race was self-reported. Data from other groups was also based on a concept of race rather than geography resulting in vast heterogeneity in geography within subgroups. For example, the GLI Caucasian subgroup includes individuals of various ethnicities in Northern Africa, North America, South America, Europe, Asia, the Middle East, and Australia (6).

Further, the concept of ancestry often implies genetic data, and it is important to note that neither the GLI nor NHANES include genetic data. There is ongoing work to define the extent to which genetic ancestry contributes to the observed variation in lung function and may be applied to improve precision of GLI equations, as well as the practical limitations of implementing such approaches (7, 8). These questions are beyond the scope of our work. Further, focus on "geographic ancestry" has the potential to distract from the possible harms that may stem from classifying groups according to race, which Miller and colleagues agree is a social rather than biologic construct.

A strength of the NHANES data is that this is a publicly available resource, providing the opportunity to ensure reproducibility. Miller and colleagues recapitulate the figure in our manuscript, replicating our finding that that race-specific comparisons normalize the lower lung function among Black (African American) individuals apparent when using a universal, multi-racial approach. Miller and colleagues argue that "the probability distribution graphs in the study should use percent of people rather than numbers of people"; our goal in showing the raw numbers of individuals was not only to show the distribution of lung function outcomes but also to allow the reader to see how much data was contributing to our mortality estimates at each strata of lung function.

Both Miller, Townsend, and their colleagues note the potential contribution of anthropomorphic differences to the observed differences in lung function by race. They also note that there is reduced precision with a multiracial approach compared with race-specific, demonstrated by the wider confidence intervals surrounding the curves estimating normal lung function. Future steps, including anthropometric measurements for those being tested, would increase precision without the negative impact of including race in medical decision-making. However, we would emphasize that a more important goal is to improve accuracy and that the goal of measuring lung function is to quantify

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