Ethnic differences in respiratory impairment

Carlos A Vaz Fragoso,1,2 Gail McAvay,2 Thomas M Gill,2 John Concato,1,2 Philip H Quanjer,3 Peter H Van Ness2

ABSTRACT

Objective Spirometric Z scores by lambda-mu-sigma (LMS) rigorously account for age-related changes in lung function. Recently, the Global Lung Function Initiative (GLI) expanded LMS spirometric Z scores to multiple ethnicities. Hence, in aging populations, the GLI provides an opportunity to rigorously evaluate ethnic differences in respiratory impairment, including airflow limitation and restrictive pattern.

Methods Using data from the Third National Health and Nutrition Examination Survey, including participants aged 40–80, we evaluated ethnic differences in GLI-defined respiratory impairment, including prevalence and associations with mortality and respiratory symptoms.

Results Among 3506 white Americans, 1860 African Americans and 1749 Mexican Americans, the prevalence of airflow limitation was 15.1% (13.9% to 16.4%), 12.4% (10.7% to 14.0%) and 8.2% (6.7% to 9.8%), and restrictive pattern was 5.6% (4.6% to 6.5%), 8.0% (6.9% to 9.0%) and 5.7% (4.5% to 6.9%), respectively. Airflow limitation was associated with mortality in white Americans, African Americans and Mexican Americans—adjusted HR (aHR) 1.66 (1.23 to 2.25), 1.60 (1.09 to 2.36) and 1.80 (1.17 to 2.76), respectively, but associated with respiratory symptoms only in white Americans—adjusted OR (aOR) 2.15 (1.70 to 2.73). Restrictive pattern was associated with mortality but only in white Americans and African Americans—aHR 2.56 (1.84 to 3.55) and 3.23 (2.06 to 5.05), and associated with respiratory symptoms but only in white Americans and Mexican Americans—aOR 2.16 (1.51 to 3.07) and 2.12 (1.45 to 3.08), respectively.

Conclusions In an aging population, we found ethnic differences in GLI-defined respiratory impairment. In particular, African Americans had high rates of respiratory impairment that were associated with mortality but not respiratory symptoms.

INTRODUCTION

Prior work suggests that ethnic differences exist in respiratory disease.1–3 For example, as reported by the Centers for Disease Control and Prevention (USA), prevalence rates for chronic bronchitis and emphysema are higher in white Americans than in African Americans or Hispanics.1,2 Similarly, age-adjusted death rates for chronic obstructive pulmonary disease (COPD), defined as chronic bronchitis or emphysema, are higher in white Americans than in African Americans or Hispanics.1,2 These epidemiologic data have limitations, however, for at least two reasons.4,5 First, confirmation of airway obstruction as a criterion for diagnosing COPD is underutilised in clinical practice—that is, chronic bronchitis and emphysema may occur in the absence of airway obstruction and vice versa.4,5 Second, death certificates in patients with respiratory disease may misclassify the cause of death.6

Spirometry provides an objective evaluation of respiratory disease, including potential ethnic differences.8–9 In particular, respiratory disease is often established by a reduction in spirometric function, heretofore termed a respiratory impairment, and is subsequently categorised as airflow limitation (airway obstruction) or restrictive pattern.1,5,9 Importantly, because respiratory disease occurs more frequently in aging populations (≥40 years),1,2 the spirometric criteria that establish respiratory impairment must account for age-related reductions in lung function and the age-related variability in spirometric performance.8–18

The lambda-mu-sigma (LMS) method rigorously accounts for age-related changes in lung function by using Z-scores that incorporate the mean (mu)—representing how spirometric measures change based on predictor variables (age and height); the coefficient of variation (sigma)—representing the spread of reference values; and skewness (lambda)—

Key messages

What is the key question?

▸ In aging populations, are there ethnic differences in respiratory impairment?

What is the bottom line?

▸ Lambda-mu-sigma (LMS)-calculated spirometric Z scores rigorously account for age-related changes in lung function. Recently, the Global Lung Function Initiative (GLI) expanded the availability of LMS spirometric Z scores to multiple ethnicities. Hence, in aging populations, the GLI provides an opportunity to rigorously evaluate ethnic differences in respiratory impairment, including spirometric airflow limitation and restrictive pattern.

Why read on?

▸ In a large sample of people aged 40–80, we found ethnic differences in GLI-defined respiratory impairment, including prevalence rates and associations with health outcomes. In particular, African Americans present a unique public health challenge, with high rates of respiratory impairment being associated with increased mortality but not respiratory symptoms.
inform public health policy and clinical practice regarding ethnic
the associations of interest. The results of the present study may
questions19:
mortality and respiratory symptoms. As a secondary aim, we also

pattern, and their corresponding associations with 5-year all-cause

mortality are unusual in younger people.13 W e excluded partici-
pants who had self-reported asthma to focus on COPD as the

Spirometry
At the baseline visit, spirometry was performed using ATS pro-
tocols.19 21 The measures of interest included the forced vital
capacity (FVC) and forced expiratory volume in 1 s (FEV1).

Lung Function Initiative (GLI) has recently published equations
LMS-calculated spirometric Z

scores, allowing respiratory impairment to be established across
multiple ethnicities (see Methods).12

Whether ethnic differences exist in GLI-defined respiratory
impairment has not yet been evaluated. Therefore, using
GLI-based spirometric criteria and data from the Third National
Health and Nutrition Examination Survey (NHANES III)19—
including participants aged 40–80 who were specifically identified
as white Americans, African Americans and Mexican Americans—
we calculated prevalence rates for airflow limitation and restrictive
pattern, and their corresponding associations with 5-year all-cause
mortality and respiratory symptoms. As a secondary aim, we also

evaluated sex and smoking history as potential effect modifiers of
the associations of interest. The results of the present study may
inform public health policy and clinical practice regarding ethnic
differences in respiratory impairment.

METHODS
Study population
NHANES III is a national probability sample of Americans aged
8–80, assembled in 1988–1994, with white Americans, African
Americans and Mexican Americans representing the three
largest ethnic groups. A separate Hispanic category was also
identified but comprised only 2.4% of the NHANES III
cohort.19 Given our specific aims, our analytical sample there-
fore included participants aged 40–80 who were white
Americans, African Americans or Mexican Americans and who,
at baseline, had no self-reported asthma and had completed at
least two American Thoracic Society (ATS) acceptable spiromet-
ic manoeuvres (the maximal exhalation manoeuvre contin-
ued for at least 6 s, with a minimum 2 s terminal plateau).19 We
selected age ≥40 because respiratory impairment and its related
mortality are unusual in younger people.1 3 We excluded partici-
pants who had self-reported asthma to focus on COPD as the
cause of airflow limitation (see online supplementary appendix
A1, regarding frequency distributions of self-reported

asthma, stratified by ethnicity and spirometric categories).

The institutional review boards from the Veterans Affairs
Connecticut Healthcare System and Yale University approved
the study, granting exemption from participant consent because
it involved de-identified data that were publicly available.

Clinical measures
NHANES III recorded all-cause mortality, ascertained from a
public use linked mortality file that contained information based
on the National Death Index.20 For the present study, mortality
surveillance occurred over 5 years.

NHANES III also recorded respiratory symptoms at the base-
line visit, including chronic bronchitis, wheezing and dyspnoea.
Specifically, participants were classified as having respiratory
symptoms if they answered ‘yes’ to any of the following four
questions19: ‘Do you usually cough on most days for three con-
secutive months or more during the year?’; ‘Do you bring up
phlegm on most days for three consecutive months or more
during the year?’; ‘Have you had wheezing or whistling in your
chest at any time in the past 12 months?’; or ‘Are you troubled
by shortness of breath when hurrying on level ground or
walking up a slight hill?’.

Other clinical data included age, sex, height, body mass index
(BMI), ethnicity, health status, chronic conditions and smoking

history.21 Reduced health status was defined as a self-reported
rating of ‘fair-to-poor’. Chronic conditions included self-
reported, physician-diagnosed hypertension, COPD, diabetes,
stroke, myocardial infarction and heart failure. For a smoking
history to be established, ≥10 pack-years of cigarette consump-
tion was required. Participants were also classified as having
high cardiovascular (CV) risk based on BMI ≥30 or having a
history of hypertension, diabetes, stroke, myocardial infarction
or heart failure.

Statistical analysis
Baseline characteristics and the frequency distributions of
respiratory impairment, including air

flow limitation and restrictive

pattern were treated as nominal categories, with the reference
category representing departure from normality.11 12 A Z score of −1.64
defines the lower limit of normal (LLN) as the fifth percentile
of the distribution.11 12 Notably, using data from large reference
populations of asymptomatic lifelong non-smokers, the Global
Lung Function Initiative (GLI) has recently published equations
that expand the availability of LMS-calculated spirometric Z
scores, allowing respiratory impairment to be established across
multiple ethnicities (see Methods).12

As per recommendations from the ATS and European
Respiratory Society, the diagnostic threshold for spirometric
measures was set at the fifth percentile of distribution, defining
the LLN.9 In addition, because a substantial proportion of partic-

ipants had risk factors for respiratory impairment, including
smoking history, respiratory symptoms, and high cardiovascular
risk, the LLN at the 5th percentile was also deemed more clinically
appropriate than the 2.5th percentile, which is otherwise
recommended for screening only.9 11 12 In the present study, the
LLN was thus defined by a Z score of −1.64, corresponding to
the fifth percentile of the distribution of Z scores.10–18 The
respiratory status of each participant was then categorised as
normal spirometry (FEV1/FVC and FVC, both ≥LLN) or
respiratory impairment, including airflow limitation (FEV1/FVC
<LLN) or restrictive pattern (FEV1/FVC≥LLN but FVC<LLN).

The association between respiratory impairment and death
was then evaluated using Cox regression models. The following
covariates, identified a priori as clinically plausible confounders,
were entered into the adjusted model (regardless of their level
of statistical significance): age, sex, smoking history, high CV
risk and reduced health status. Airflow limitation and restrictive
pattern were treated as nominal categories, with the reference
group including participants who had normal spirometry. Each
model’s goodness of fit was assessed by model-fitting procedures
and by the analysis of residuals. The proportional hazards
assumption was tested by using interaction terms for the
time-to-event outcome and each variable in the multivariable
model; the terms were retained if p<0.05 after adjusting for the
multiplicity of comparisons. Higher-order effects were tested
for the continuous covariates and included in the final model if
they met a forward selection criterion of p<0.20.

Similarly, the association between respiratory impairment and
respiratory symptoms at baseline was evaluated by calculating

ORs, using logistic regression models. Covariates in the adjusted model were as described previously. Lastly, potential effect modifiers of associations with health outcomes were assessed. In these analyses, interactions for each ethnic group were evaluated and involved ‘crossing’ sex and smoking history, with airflow limitation and restrictive pattern. HRs for death and ORs for respiratory symptoms were estimated according to sex and smoking history, using separate regression models for each ethnic group and combinations of effect modifiers. In tests of potential effect modification, p values for interaction terms were not adjusted for the multiplicity of comparisons, because the clinical interest was toward avoiding type II errors, rather than type I errors. Covariates included age, sex, smoking history, high CV risk and reduced health status. African Americans had the highest rate of reduced health status, n (%) 672 (19.2) 609 (32.8) 731 (41.8) <0.001 <0.001 <0.001

RESULTS
Table 1 summarises baseline characteristics according to ethnicity. Significant differences were as follows: white Americans were older and had the highest rates of having a smoking history and (self-reported, physician-diagnosed) COPD or myocardial infarction, but the lowest rates of obesity (BMI≥30) and reduced health status. African Americans had the highest rate of CV risk, including hypertension. Mexican Americans had the highest rates of diabetes and reduced health status, but the lowest rates of having a smoking history, hypertension or stroke.

Table 2 summarises respiratory impairment, respiratory symptoms and mortality according to ethnicity. Overall, the prevalence of airflow limitation varied in a progression of white

### Table 1 Baseline characteristics according to ethnicity

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>White Americans N=3506</th>
<th>African Americans N=1860</th>
<th>Mexican Americans N=1749</th>
<th>Adjusted p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>W vs A</td>
</tr>
<tr>
<td>Age (years, mean (SE))</td>
<td>60.7 (0.4)</td>
<td>56.0 (0.5)</td>
<td>56.0 (0.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>1830 (52.2)</td>
<td>968 (52.0)</td>
<td>847 (48.4)</td>
<td>0.923</td>
</tr>
<tr>
<td>BMI (kg/m²), mean (SE)</td>
<td>27.2 (0.1)</td>
<td>28.5 (0.2)</td>
<td>28.6 (0.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking history, n (%)</td>
<td>878 (25.0)</td>
<td>636 (34.2)</td>
<td>589 (33.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic conditions, n (%)†</td>
<td>1950 (56.1)</td>
<td>1183 (64.9)</td>
<td>1265 (73.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart failure</td>
<td>127 (3.6)</td>
<td>89 (4.8)</td>
<td>105 (6.0)</td>
<td>0.065</td>
</tr>
<tr>
<td>High CV risk, n (%)‡</td>
<td>1885 (53.8)</td>
<td>1233 (66.3)</td>
<td>1021 (58.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Reduced health status, n (%)</td>
<td>672 (19.2)</td>
<td>609 (32.8)</td>
<td>731 (41.8)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Self-reported, physician diagnosed.
† Included chronic bronchitis or emphysema.
‡ Included the presence of any of the following: BMI≥30, hypertension, diabetes, heart failure, stroke or myocardial infarction. A, African Americans; BMI, body mass index (weight in kg divided by height in m²); COPD, chronic obstructive pulmonary disease; CV, cardiovascular; M, Mexican Americans; W, white Americans.

### Table 2 Spirometry and health outcomes according to ethnicity

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>White Americans N=3506</th>
<th>African Americans N=1860</th>
<th>Mexican Americans N=1749</th>
<th>Adjusted p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>W vs A</td>
</tr>
<tr>
<td>Spirometry*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>2778 79.3 (77.8 to 80.7)</td>
<td>1482 79.7 (77.7 to 81.7)</td>
<td>1504 86.0 (84.3 to 87.8)</td>
<td>0.780 &lt;0.001 &lt;0.001</td>
</tr>
<tr>
<td>Airflow limitation</td>
<td>531 15.1 (13.9 to 16.4)</td>
<td>230 12.4 (10.7 to 14.0)</td>
<td>144 8.2 (6.7 to 9.8)</td>
<td>0.014 &lt;0.001 0.002</td>
</tr>
<tr>
<td>Restrictive pattern</td>
<td>196 5.6 (4.6 to 6.5)</td>
<td>148 8.0 (6.9 to 9.0)</td>
<td>100 5.7 (4.5 to 6.9)</td>
<td>0.002 0.863 0.016</td>
</tr>
<tr>
<td>Health outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory symptoms†</td>
<td>1452 41.5 (39.2 to 43.8)</td>
<td>668 36.0 (33.5 to 38.5)</td>
<td>604 34.6 (31.9 to 37.3)</td>
<td>&lt;0.001 &lt;0.001 0.541</td>
</tr>
<tr>
<td>Deaths, n (%)</td>
<td>308 8.8 (7.6 to 10.0)</td>
<td>173 9.3 (8.0 to 10.6)</td>
<td>121 6.9 (5.4 to 8.4)</td>
<td>0.632 0.063 0.039</td>
</tr>
</tbody>
</table>

*Recorded at baseline: normal spirometry was defined by FEV₁/FVC and FVC, both >LLN; airflow limitation by FEV₁/FVC<LLN; and restrictive pattern by FEV₁/FVC<LLN and FVC<LLN. Missing data: white Americans (n=1); Mexican Americans (n=1).
†Recorded at baseline: chronic cough or sputum production, dyspnoea on exertion, or wheezing. Missing data: white Americans (n=6); Mexican Americans (n=3); African Americans (n=4).
‡ Over 5 years of follow-up. Vital status was missing for three white Americans and two Mexican Americans. A, African Americans; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; LLN, lower limit of normal; M, Mexican Americans; W, white Americans.
Americans>African Americans>Mexican Americans, whereas restrictive pattern varied in a progression of African Americans>Mexican Americans and White Americans. Whereas airflow limitation exceeded the 5% prevalence level that is expected for a normal population (using our LLN threshold) across the three ethnicities, restrictive pattern exceeded the 5% prevalence level only in African Americans. The frequency of respiratory symptoms varied in a progression of White Americans>Mexican Americans and African Americans. The frequency of deaths over 5 years varied in a progression of Mexican Americans>African Americans and White Americans.

Table 3 shows adjusted HRs (aHRs) for death, according to spirometric category and ethnicity. Relative to normal spirometry, airflow limitation was associated with mortality in White Americans and Mexican Americans—aHR 1.66 (1.23 to 2.25) and 1.60 (1.09 to 2.36), respectively. Restrictive pattern was associated with mortality in White Americans and African Americans—aHR 2.56 (1.84 to 3.55) and 3.23 (2.06 to 5.05), respectively. Mexican Americans also had an increased aHR but this was not statistically significant—aHR 2.09 (0.89 to 4.90). In these analyses of mortality, there were no significant interactions between respiratory impairment and ethnicity (ie, HRs were similar).

Table 4 shows adjusted ORs (aORs) for respiratory symptoms, according to spirometric category and ethnicity. Relative to normal spirometry, airflow limitation was associated with respiratory symptoms in White Americans, but had only borderline statistical significance in African Americans and was not associated in Mexican Americans—aOR 2.15 (1.70 to 2.73), 1.38 (0.99 to 1.92) and 1.26 (0.90 to 1.76), respectively. Restrictive pattern was associated with respiratory symptoms in White Americans and Mexican Americans but not African Americans—aOR 2.16 (1.51 to 3.07), 2.12 (1.45 to 3.08) and 1.08 (0.70 to 1.67), respectively. In these analyses of respiratory symptoms, there were significant interactions between respiratory impairment and ethnicity, with African Americans in particular having weak to no associations (ie, ORs were significantly lower, relative to White Americans).

Effect modification by sex and smoking history of the association between respiratory impairment and mortality were not significant (data not shown). In contrast, and as shown in figures 1 and 2, the aOR for respiratory symptoms was significantly modified in several situations: sex, among African Americans who had airflow limitation—aOR 0.86 (0.55 to 1.34) and 1.93 (1.18 to 3.17) for women and men, respectively (p=0.010), and among African Americans who had restrictive pattern—aOR 0.83 (0.53 to 1.31) and 1.66 (0.90 to 3.07) for women and men, respectively (p=0.024); and (2) smoking history, among White Americans who had airflow limitation—aOR 1.48 (0.96 to 2.30) and 2.57 (1.94 to 3.41) for < and ≥10 pack-years, respectively (p=0.025).

**DISCUSSION**

In a large sample of people aged 40–80, we found that GLI-defined respiratory impairment differed in the following: prevalence: airflow limitation was more common in White Americans and African Americans than Mexican Americans, while restrictive pattern was more common in African Americans>Mexican Americans>African Americans.

**Table 3** HRs for 5-year mortality, according to spirometric category and stratified by ethnicity*

<table>
<thead>
<tr>
<th>Spirometric category</th>
<th>White Americans N=3467</th>
<th>African Americans N=1821</th>
<th>Mexican Americans N=1717</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HRs for 5-year mortality (95% CI)‡§</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unadjusted</td>
<td>Adjusted</td>
<td>Unadjusted</td>
</tr>
<tr>
<td>Normal</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Airflow limitation</td>
<td>2.31 (1.75 to 3.06)</td>
<td>1.66 (1.23 to 2.25)</td>
<td>2.58 (1.91 to 3.50)</td>
</tr>
<tr>
<td>Restrictive pattern</td>
<td>3.10 (2.30 to 4.17)</td>
<td>2.56 (1.84 to 3.55)</td>
<td>2.91 (1.88 to 4.50)</td>
</tr>
</tbody>
</table>

*Missing data: white Americans—37 missing covariates, 2 missing mortality; African Americans—39 missing covariates; Mexican Americans—30 missing covariates, 2 missing mortality.
†See footnote to table 2 for description of spirometric category.
‡Relative to white Americans, there were no significant interactions in African American×airflow limitation (p=0.673), African American×restrictive pattern (p=0.973), Mexican American×airflow limitation (p=0.253) and Mexican American×restrictive pattern (p=0.189). These results suggest that the adjusted HRs did not differ significantly by ethnicity.
§Relative to white Americans, there were significant interactions in African American×airflow limitation (p=0.003), African American×restrictive pattern (p=0.012) and Mexican American×airflow limitation (p=0.001), but no significant interaction in Mexican American×restrictive pattern (p=0.669).

**Table 4** ORs for respiratory symptoms, according to spirometric category and stratified by ethnicity*

<table>
<thead>
<tr>
<th>Spirometric category</th>
<th>White Americans N=3465</th>
<th>African Americans N=1821</th>
<th>Mexican Americans N=1716</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ORs for respiratory symptoms (95% CI)‡§</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Un adjusted</td>
<td>Adjusted</td>
<td>Un adjusted</td>
</tr>
<tr>
<td>Normal</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Airflow limitation</td>
<td>2.70 (2.20 to 3.32)</td>
<td>2.15 (1.70 to 2.73)</td>
<td>1.41 (1.02 to 1.94)</td>
</tr>
<tr>
<td>Restrictive pattern</td>
<td>2.67 (1.90 to 3.76)</td>
<td>2.16 (1.51 to 3.07)</td>
<td>1.41 (0.96 to 2.08)</td>
</tr>
</tbody>
</table>

*Missing data: white Americans—37 missing covariates, 4 missing respiratory symptoms; African Americans—39 missing covariates, 4 missing respiratory symptoms; Mexican Americans—30 missing covariates, 3 missing respiratory symptoms.
†See footnote to table 2 for description of spirometric category.
‡ORs were calculated using three separate logistic regression models for each ethnic group. In the adjusted models, covariates included age, sex, smoking history, high cardiovascular risk and health status.
§Relative to white Americans, there were significant interactions in African American×airflow limitation (p=0.001), African American×restrictive pattern (p=0.12) and Mexican American×airflow limitation (p=0.001), but no significant interaction in Mexican American×restrictive pattern (p=0.669).
Americans than white Americans or Mexican Americans; (2) all-cause mortality: airflow limitation was associated with mortality in all three ethnic groups, while restrictive pattern was associated with mortality only in white Americans and African Americans—furthermore, the magnitude of these associations did not differ by ethnicity; respiratory symptoms: airflow limitation was associated with respiratory symptoms but only in white Americans, while restrictive pattern was associated with respiratory symptoms but only in white Americans and Mexican Americans—furthermore, the magnitude of these associations did not differ by ethnicity.

Figure 1  Adjusted OR (95% CI) for respiratory symptoms among participants who had airflow limitation, stratified by effect modifier—sex (A) and smoking history (B). Separate logistic regression models were used for each ethnic group and effect modifier combination, with normal spirometry as the reference group. Covariates included age, sex, smoking history, high CV risk and reduced health status, without the variable that was the effect modifier of interest. (A) Airflow limitation×sex (significant interaction in African Americans, p=0.010). (B) Airflow limitation×smoking history (significant interaction in white Americans, p=0.025). CV, cardiovascular.
differed by ethnicity, with African Americans in particular having weak to no associations; and effect modification: female sex decreased the association of airflow limitation and restrictive pattern with respiratory symptoms but only in African Americans, while smoking history increased the association of airflow limitation with respiratory symptoms but only in white Americans.
Americans—otherwise, there was no effect modification for the mortality outcome.

These results indicate that ethnic differences exist in GLI-defined respiratory impairment, including prevalence rates, associations with health outcomes, and effect modification. In particular, African Americans present a unique public health challenge, with higher rates of respiratory impairment being associated with mortality but not respiratory symptoms.

Our approach for evaluating ethnic differences in respiratory impairment has a strong mathematical and clinical rationale. As discussed earlier, GLI-defined respiratory impairment is based on LMS-calculated spirometric Z scores that rigorously account for age-related changes in lung function, including variability in spirometric performance and skewness of reference data. As additional evidence supporting this approach in clinical practice, Z scores are routinely used to diagnose osteoporosis (bone mineral density) and the LMS method is widely applied to construct growth charts. In the current context, ethnic differences were also evaluated based on associations between respiratory impairment and health outcomes. All-cause mortality is a definitive outcome that is resistant to miscoding and has been the primary endpoint in clinical trials. Respiratory symptoms, including dyspnoea, chronic bronchitis and wheezing, are often the bases for pursuing healthcare.

Because we excluded participants who had self-reported asthma, the spirometric diagnosis of airflow limitation in the present study was likely due to airway obstruction from COPD. Hence, our results suggest that white Americans and African Americans have significantly higher rates of spirometry-confirmed COPD than Mexican Americans (table 2). These higher rates may be due to a greater smoking exposure in white Americans and African Americans, along with a possible ethnicity-specific protection in Mexican Americans.

Restricted spirometry was associated with the metabolic syndrome, coronary heart disease and sudden cardiac death, and because a reduced FVC is a required criterion for establishing restrictive pattern, we postulate that a CV mechanism may have been an important contributor to restrictive pattern in our study population, including its association with health outcomes. This is especially relevant to African Americans. The latter group had the highest rates of CV risk and restrictive pattern, whereas white Americans and Mexican Americans had lower rates of CV risk and restrictive pattern (tables 1 and 2, respectively).

The present study also demonstrated a differential impact of ethnicity on associations with death and respiratory symptoms (tables 3 and 4, respectively). For example, in adjusted analyses, we found that white Americans who had airflow limitation or restrictive pattern had a significant increase in the risk of death and odds of having respiratory symptoms. In contrast, African Americans who had restrictive pattern had a significant increase in the risk of death but not in the odds of having respiratory symptoms. Similarly, Mexican Americans who had airflow limitation had a significant increase in the risk of death but not in the odds of having respiratory symptoms. Lastly, ethnic differences on associations with respiratory symptoms, but not death, were also seen regarding effect modification by female sex, being significant only in African Americans, and by smoking history, being significant only in white Americans (figures 1 and 2).

The differential impact of ethnicity on associations with respiratory symptoms may affect prevalence rates for respiratory disease. In particular, we found that the rate of airflow limitation (spirometry-confirmed COPD) relative to self-reported, physician-diagnosed COPD was higher in white Americans (15.1% vs 9.1%, respectively), yet more than doubled in African Americans (12.4% vs 5.0%, respectively) and Mexican Americans (8.2% vs 3.8%, respectively) (tables 1 and 2). We postulate that the lower rates of self-reported, physician-diagnosed COPD occurred because spirometry is not routinely applied in clinical practice, or participants may not have sought medical care, and because respiratory symptoms are neither sufficient nor necessary to establish clinically meaningful respiratory disease. Prior work by our own group has shown, for example, that 31% of participants who had moderate-to-severe spirometry-confirmed COPD (based on FEV1 Z scores) had no respiratory symptoms. In addition, the designation of self-reported, physician-diagnosed COPD may have limited diagnostic accuracy. In the present study, more than half of the participants who had self-reported, physician-diagnosed COPD had normal spirometry (see online supplementary appendix table A2).

In light of the above discussion, future work should evaluate additional health outcomes, including other verbal descriptors of dyspnoea, measures of health-related quality of life, and exercise capacity (6 min walk test), across multiple ethnicities. Moreover, because preventive healthcare is available (smoking cessation, vaccinations, CV risk modification, and reduction of indoor and outdoor air pollutants), health outcomes should also be evaluated in people aged ≥40 who at baseline have a spirometric respiratory impairment but no respiratory symptoms (as defined in the present study). The latter assessment has precedence, given that the Framingham Risk Score is currently recommended in all asymptomatic people aged ≥40, including those without a clinical history of coronary heart disease.

Although the present study used rigorous spirometric criteria, at least three potential limitations are noted. First, NHANES III does not provide sufficient data to confirm the pathophysiology of respiratory impairment. For example, in addition to COPD, airflow limitation could be due to asthma, given that spirometry in NHANES III was not specifically obtained after a bronchodilator, that self-reported asthma (a key exclusion criterion) may have been underreported by participants, and that longstanding asthma may lead to irreversible airflow limitation. Similarly, restrictive pattern as a basis for establishing pulmonary restriction requires confirmation by a reduced total lung capacity, and may have included several non-CV aetiologies. Second, self-reported ethnicity may not be entirely accurate, potentially leading to misclassification in the ethnic-specific reference equations that were used to calculate spirometric Z scores. Moreover, because pulmonary function like many clinical phenomena occurs along a continuum, spirometric Z scores that are just above or below the LLN may have limited diagnostic accuracy when evaluating a respiratory impairment. A potential related limitation is that establishing the LLN at the 5th percentile, rather than the 2.5th percentile (see methods), may increase false-positive designations for respiratory impairment. Nonetheless, the 2.5th percentile threshold may substantially increase false-negative designations, particularly given that NHANES III participants aged 40-80 frequently had a smoking history, respiratory symptoms and high cardiovascular risk. Third, there may be differences in cultural, geographical and socioeconomic factors between and within the three ethnic categories. In particular, differences in sedentary behaviour could alter the association between respiratory impairment and symptoms (exertional dyspnoea). To address these limitations, future studies should include comprehensive tests of cardiopulmonary function and an assessment of genetic, cultural, geographical and socioeconomic factors.
CONCLUSION
In a large sample of people aged 40–80, we found that significant ethnic differences existed in GLI-defined respiratory impairment, including prevalence rates, associations with health outcomes and the presence of effect modifiers. In particular, African Americans present a unique public health challenge, with high rates of airflow limitation and restrictive pattern being associated with increased mortality but not respiratory symptoms. These results may inform future research and public health policy regarding ethnic differences in respiratory impairment.

Contributors CAVF is guarantor of the study. CAVF, GM, TMG, JC, PHQ and PHVN contributed to the study conception and design. CAVF, GM, TMG, JC, PHQ and PHVN contributed to the interpretation and analysis of data. CAVF drafted the manuscript, and all authors revised the manuscript critically for important intellectual content and provided final approval of the version to be published.

Funding The study was conducted at the VA Clinical Epidemiology Research Center and the Yale Claude D Pepper Older Americans Independence Center (P30AG02134). CAVF is a recipient of a Career Development Award from the Department of Veterans Affairs and an RO3 award from the National Institute on Aging (RO3AG037051). TMG is the recipient of K24AG021507 and K07AG043587 from the National Institute on Aging. JC is supported by the Department of Veterans Affairs Cooperative Studies Program.

Competing interests None.

Ethics approval Institutional review boards from the Veterans Affairs Connecticut Healthcare System and Yale University (USA) approved the study.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The NHANES III dataset has been de-identified and is publicly available.

REFERENCES
APPENDIX:

SELF-REPORTED ASTHMA AND SELF-REPORTED COPD

As shown in Table A1, among the 569 participants who were excluded because of self-reported asthma, 50%-57% had normal spirometry. The latter likely occurred because asthma is characterized by reversible airways obstruction (airflow limitation due to asthma may have reverted back to normal spirometry). Otherwise, 28%-40% of those who had self-reported asthma also had airflow limitation at the baseline visit.

As discussed in Methods section of the article, our focus was on chronic obstructive pulmonary disease (COPD) as the cause of airflow-limitation. Accordingly, in our final analytical sample, having excluded participants who had self-reported asthma made it more likely that those who had airflow limitation had COPD, thereby increasing specificity.

Table A1. Frequency distribution of self-reported asthma by ethnicity and spirometric category

<table>
<thead>
<tr>
<th>Spirometric Group</th>
<th>Self-Reported Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>White-Americans N = 311</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
</tr>
<tr>
<td>Normal</td>
<td>167 (54)</td>
</tr>
<tr>
<td>Airflow-limitation</td>
<td>122 (39)</td>
</tr>
<tr>
<td>Restrictive-pattern</td>
<td>22 (7)</td>
</tr>
<tr>
<td>Total</td>
<td>311 (100)</td>
</tr>
</tbody>
</table>

As noted in the Discussion section of the article, we posit that self-reported, physician-diagnosed COPD may have a limited diagnostic accuracy. As shown in Table A2, across the three ethnicities, more than half of the participants who had self-reported, physician-diagnosed COPD had normal spirometry. Unlike asthma, COPD is most often characterized by irreversible airways obstruction.

Table A2. Frequency distribution of self-reported COPD by ethnicity and spirometric category

<table>
<thead>
<tr>
<th>Spirometric Group</th>
<th>Self-Reported COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>White-Americans N = 319</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
</tr>
<tr>
<td>Normal</td>
<td>181 (57)</td>
</tr>
<tr>
<td>Airflow-limitation</td>
<td>120 (38)</td>
</tr>
<tr>
<td>Restrictive-pattern</td>
<td>18 (6)</td>
</tr>
<tr>
<td>Total</td>
<td>319 (100)</td>
</tr>
</tbody>
</table>