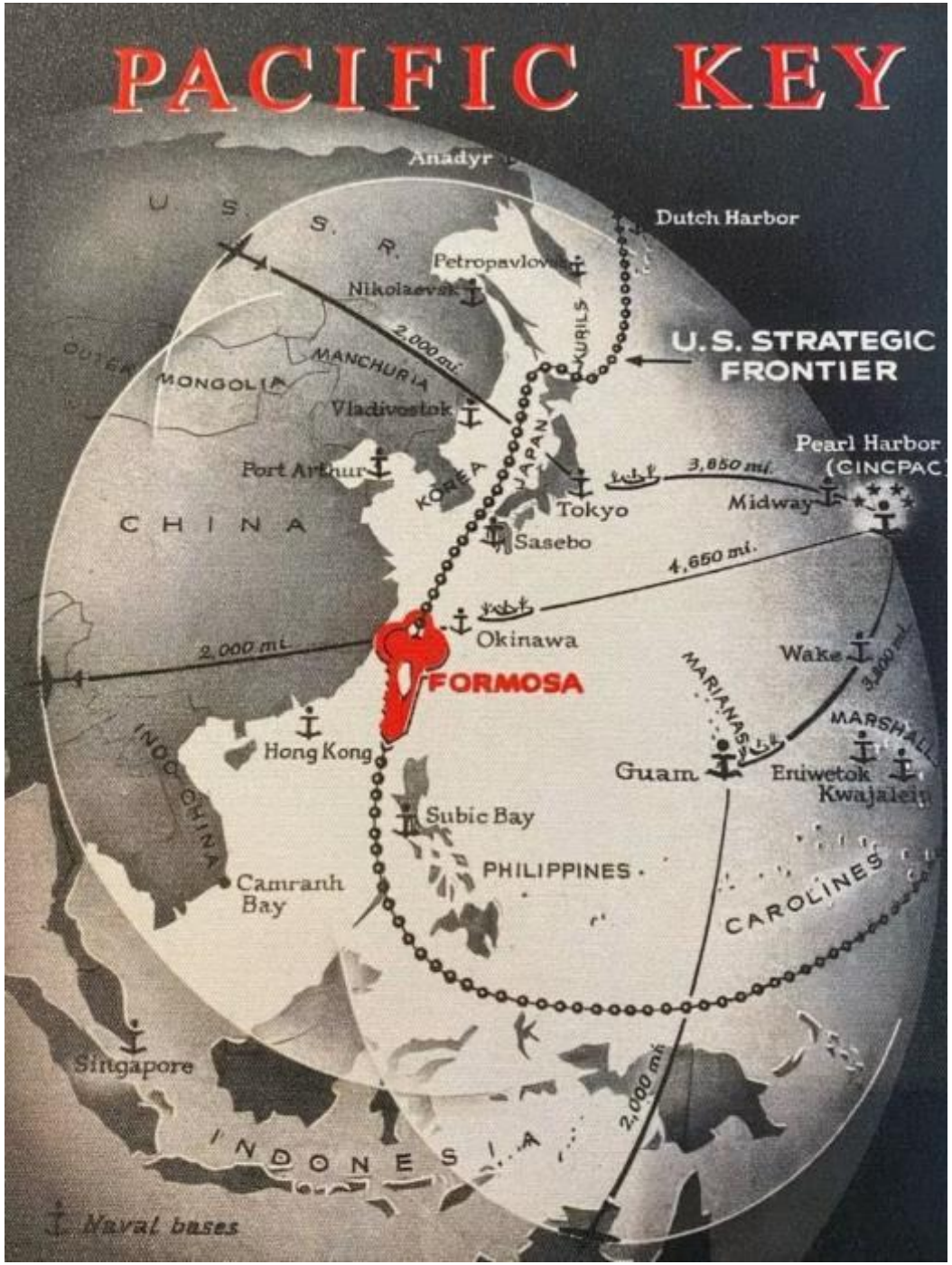
Race-specific or race-neutral: That's the (lung function) question!

D2 Chih-Wei Tseng

APR 9 2025

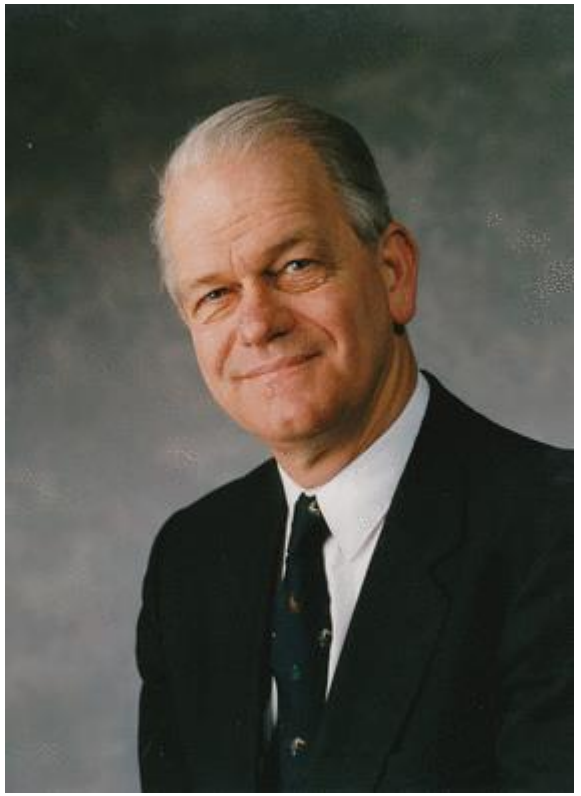


Is Taiwan in Northeast Asia or Southeast Asia?

What's your answer?

Why Global Lung Function Initiative (GLI) is Needed

- In the past (1960), lung function reference values were primarily established based on specific populations (e.g., European Caucasians Male coal workers).
- For other ethnic groups, adjustments were commonly applied using 'correction factors.'
- For example, lung function values for **African Americans were typically set around 15% lower than those for Caucasians**.



Philip Quanjer 1936-2017

In memoriam: Professor Philip H. Quanjer
Janet Stocks, Irene Steenbruggen
European Respiratory Journal 2017 50(3): 1701660

Modelling lung function

Until very recently regression equations for lung function were based on simple additive linear regression techniques. The by far most popular models had the following form:

$$Y = a + b \bullet height + c \bullet age + error \text{ (adults)}$$
$$\log(Y) = a + b \bullet \log(height) + error \text{ (children)}$$

for capturing non-linear curves is by adding a "spline" to a linear relationship:

$$\log(Y) = a + b \bullet \log(height) + c \bullet \log(age) + spline + error$$

$$\log(Y) = a + b \bullet \log(height) + c \bullet \log(age) + d \bullet Ethn + spline + error$$

Philip Quanjer 1936-2017
Born in Pontianak (now Indonesia) -> Netherlands

In memoriam: Professor Philip H. Quanjer
Janet Stocks Irene Steenbruggen
European Respiratory Journal 2017 50(3): 1701660

Importance of Ethnicity in Lung Function Interpretation

- **Ethnicity significantly influences lung volumes (such as FVC):**
  - Normal lung function reference values differ among ethnic groups, impacting the interpretation of measurements.
  - Using inappropriate standards can result in misclassification.
- **Incorrect ethnicity references lead to diagnostic inaccuracies:**
  - Applying standards derived from one ethnic group to another can falsely indicate lung disease (false-positive) or incorrectly suggest normal function (false-negative), emphasizing the necessity of ethnicity-specific standards.

Datasets used in final analyses

Country	N	Country	N
Algeria	273	Netherlands	3319
Australia	982	Norway	1535
Austria	333	Poland	220
Brazil	178	Portugal	137
Canada	329	Sweden	123
Chile	102	Switzerland	11756
China	5114	Taiwan	2806
Germany	4708	Thailand	3262
Iceland	164	Tunisia	870
Israel	124	UK	16888
Italy	1818	Uruguay	156
Korea	2252	USA	18212
Mexico	4236	Venezuela	243
Total			80140

Datasets not used in final analyses

Country	N
China	3483
France	63376
India	2548
Iran	6137
Oman	1256
Pakistan	2928
Philippines	316
South Africa	146
Total	80190

Table E2 – Number of subjects that could not be included in the final analyses for reasons delineated in the printed manuscript.

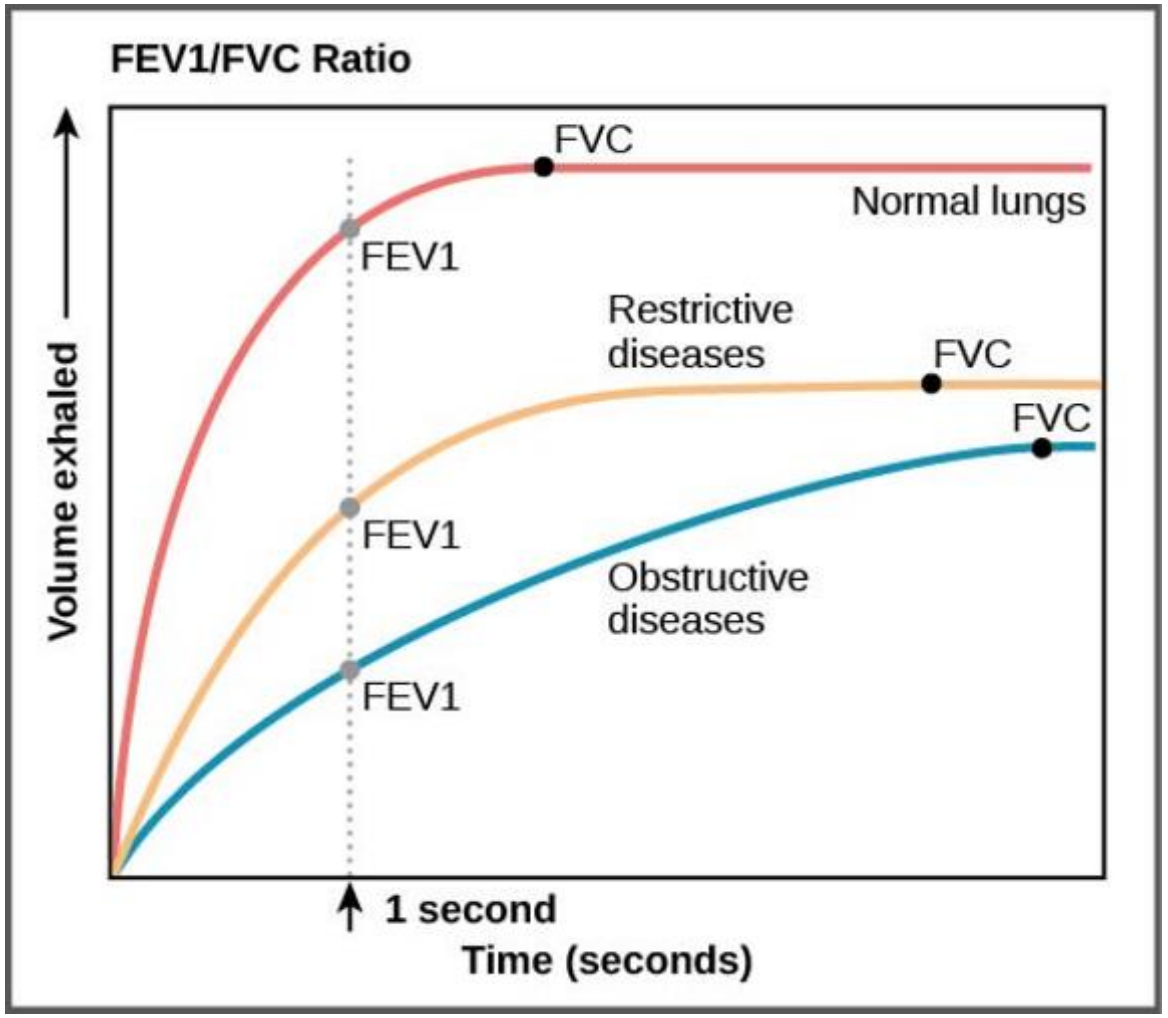
Data submitted	160,330	
Unknown ethnicity		63,865
Suspected asthma		805
Forced expiratory time < 1 s		123
Cannot be fitted in groups		
Indian and Pakistani		5,476
Omani		1,256
South African		146
Philippino		316
Mexico City		4,009
Iran		6,137
No permission to publish		3,483
Outliers		527
Remaining data		74,187

Why Precise Ethnicity-Specific Models Are Crucial for ILD.
That's my question for research!

- Interstitial lung diseases (ILDs) rely heavily on the accurate interpretation of restrictive ventilatory impairments (e.g., reduced FVC, TLC, and DLco).
- Because normal lung volumes vary significantly by ethnicity, employing an inappropriate ethnic reference model can lead to inaccurate severity assessments.
- COPD diagnosis mainly relies on the FEV1/FVC ratio, , which is relatively consistent across ethnic groups

Vocabularies

- FVC: The total amount of air exhaled during a forced breath-out
- FEV1: Forced expiratory volume in one second- the volume of air exhaled during the first second of a forced exhalation
- FVC pred: actual FVC/expected FVC
- LLN: LLN is statistically defined as the value below which only 5% of healthy, non-smoking individuals fall.

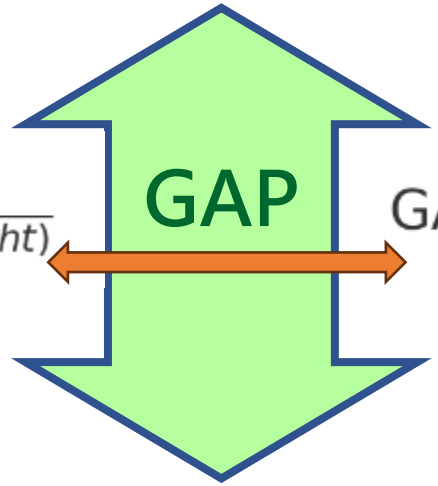


Applying David Hume's law

Ought

FVC and FEV1 references
RACE-SPECIFIC vs. RACE-NEUTRAL…

$$GAP_{race\ neutral} = \frac{Actual\ Value\ (Is)}{Race\ Neutral\ Reference\ (Ought)}$$



$$GAP_{race\ specific} = \frac{Actual\ Value\ (Is)}{Race\ Specific\ Reference\ (Ought)}$$

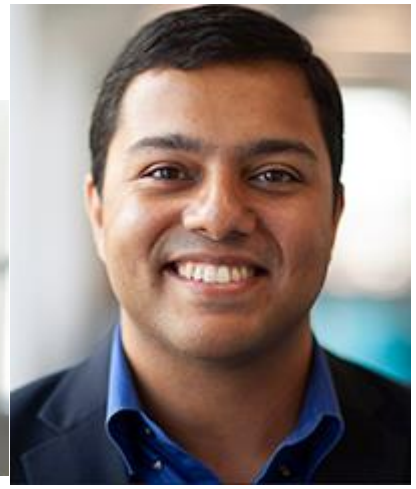
IS

Actual FVC and FEV1…

Taiwan local reference?

Paper 1 from NEJM
Paper 2 from AJRCCM

Paper 1 NEJM June 13, 2024



The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Implications of Race Adjustment in Lung-Function Equations

J.A. Diao, Y. He, R. Khazanchi, M.J. Nguemeni Tiako, J.I. Witonsky, E. Pierson, P. Rajpurkar, J.R. Elhawary, L. Melas-Kyriazi, A. Yen, A.R. Martin, S. Levy, C.J. Patel, M. Farhat, L.N. Borrell, M.H. Cho, E.K. Silverman, E.G. Burchard, and A.K. Manrai

Background: Spirometry and the Shift to Race-Neutral Equations

- Spirometry is essential for diagnosing and monitoring lung diseases such as COPD.
- Predicted normal values are typically based on age, sex, height, and historically, race.
- Race-based reference equations (e.g., GLI-2012) have been criticized for reinforcing outdated racial assumptions and inequities.
- In 2022, the GLI-Global equations were introduced as race-neutral alternatives, endorsed by ATS/ERS in 2024.
- This study quantifies the clinical, social, and economic impacts.

Method

- Study Design: Cross-sectional and retrospective analysis using 5 large cohorts to evaluate the impact on classification and clinical/policy outcomes
- Data source:
  - NHANES III (1988–1994): general U.S. population
  - NHANES IV (2007–2012): general U.S. population
  - MESA: Multi-Ethnic Study of Atherosclerosis
  - UK Biobank: large, predominantly White cohort
  - OPTN: 2020 U.S. lung transplant waiting list

Table 2. Criteria for Assessing Clinical, Occupational, and Financial Outcomes.*

Outcome	Spirometric Criteria†	Age Criteria	Other Criteria	Source
Ventilatory impairment		6–79 yr	None	ERS–ATS (2021)[2]
Obstructive	FEV_1:FVC <LLN			
Nonobstructive	FEV_1 or FVC <LLN and FEV_1:FVC >LLN			
COPD severity		6–79 yr	None	GOLD (2023)[3]
Grade 1 (least severe)	FEV_1:FVC <0.70 and FEV_1 ≥80% of predicted			
Grade 2	FEV_1:FVC <0.70 and FEV_1 50–79% of predicted			
Grade 3	FEV_1:FVC <0.70 and FEV_1 30–49% of predicted			
Grade 4 (most severe)	FEV_1:FVC <0.70 and FEV_1 <30% of predicted			
Occupational disqualification from firefighting	FEV_1 or FVC <70% of predicted, *or* FEV_1 or FVC <80% of predicted and FEV_1:FVC <0.75, *or* FEV_1 or FVC <90% of predicted and previous diagnosis of asthma	18–65 yr	Work exposure to dust or fumes	NFPA (2007)[23]
Medical impairment ratings		18–79 yr	Work exposure to dust or fumes	AMA (2008)[24]
Class 1 (least severe)	FEV_1 65–79% of predicted or FVC 70–79% of predicted			
Class 2	FEV_1 55–64% of predicted or FVC 60–69% of predicted			
Class 3	FEV_1 45–54% of predicted or FVC 50–59% of predicted			
Class 4 (most severe)	FEV_1 <45% of predicted or FVC <50% of predicted			
VA disability ratings		18–79 yr	Served in the U.S. Armed Forces	VA (2023)[25,26]
10% (least severe)	FEV_1 71–80% of predicted or FEV1:FVC 0.71–0.80			
30%	FEV_1 56–70% of predicted or FEV1:FVC 0.56–0.70			
60%	FEV_1 40–55% of predicted or FEV1:FVC 0.40–0.55			
100% (most severe)	FEV_1 <40% of predicted or FEV1:FVC <0.40			

1

2

3

4

5

6 Lung transplant priority

7 Not in Table 2:

clinical outcome prediction (e.g., respiratory symptoms, hospitalization, new-onset disease, mortality)

7 Outcomes

1. Ventilator impairment
   a. Obstructive: asthma/COPD
   b. Non-obstructive
2. COPD severity grading
3. Occupational eligibility
4. Medical impairment ratings
5. Disability compensation
6. Lung transplant priority
7. Associations with respiratory outcomes

Statistical Analysis

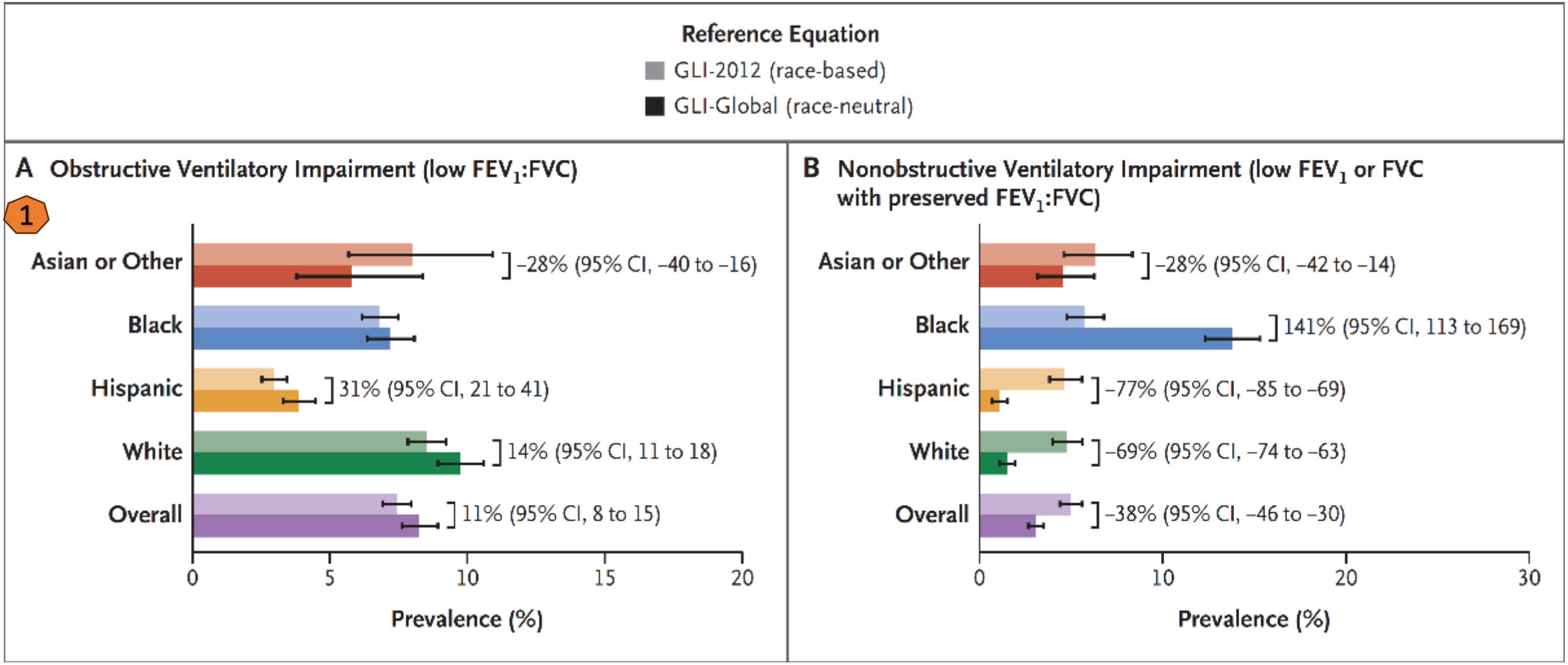
- Calculated predicted values & LLN using GLI-2012 and GLI-Global
- Derived % predicted
- Used NHANES IV weights for national projections
- Assessed predictive accuracy using Harrell's C-statistic
- Conducted secondary analyses of sensitivity/specificity at z = −1.645 (5th percentile)

Results

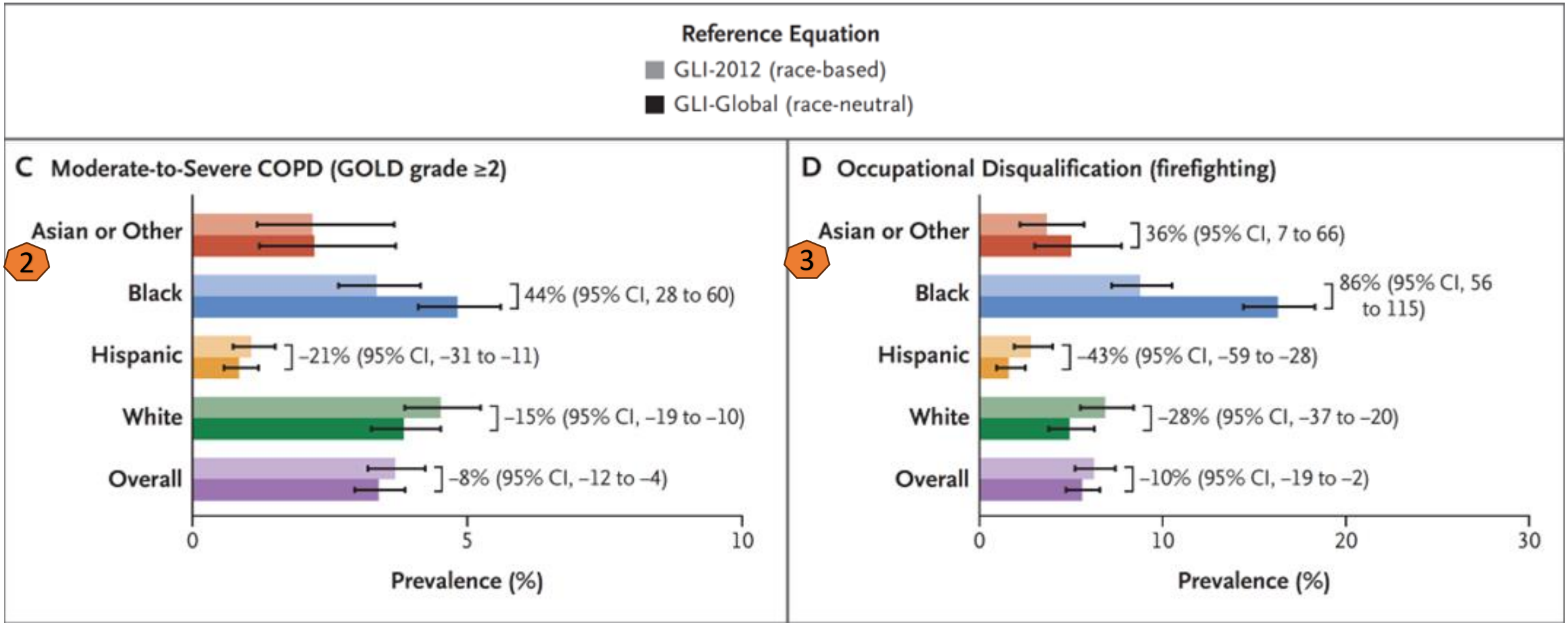
Table 1. Demographic Characteristics, Spirometric Measurements, and Respiratory Conditions.*

Characteristic	NHANES III (N=31,311)	NHANES IV (N=30,442)	MESA (N=6814)	U.K. Biobank (N=501,723)	OPTN (N=42,751)
Data-collection period	1988–1994	2007–2012	2005–2007	2006–2010	2005–2023
Participants included — no. (%)†	15,861 (50.7)	17,067 (56.1)	3262 (47.8)	290,136 (57.8)	42,751 (100)
Female sex or gender — %‡	51.2	50.0	53.1	57.2	43.5
Race or ethnic group — %§					
Asian	—	4.4	16.5	2.0	2.6
Black	28.7	21.9	25.0	1.3	9.8
Hispanic	28.5	29.6	11.3	—	8.8
White	38.9	39.6	35.2	95.1	78.2
Multiracial, other race, or unknown	3.9	4.5	—	1.1	0.7
Median age (IQR) — yr	35 (20–54)	33 (16–52)	65 (57–73)	57 (50–63)	59 (49–65)
Median height (IQR) — cm	165 (157–173)	165 (156–173)	165 (158–173)	167 (161–175)	170 (161–177)
Median spirometric values (IQR)					
FEV_1 — liters	2.91 (2.29–3.56)	2.92 (2.23–3.61)	2.30 (1.87–2.83)	2.71 (2.26–3.26)	—
FVC — liters	3.60 (2.90–4.42)	3.62 (2.81–4.48)	3.06 (2.48–3.81)	3.55 (2.99–4.29)	1.82 (1.37–2.38)
FEV_1:FVC	0.81 (0.76–0.86)	0.82 (0.77–0.86)	0.76 (0.71–0.80)	0.77 (0.73–0.80)	—
Respiratory factors — %¶					
Smoking history	41.4	33.9	49.8	21.1	44.1
Respiratory symptoms	24.0	15.5	14.3	22.0	100
Respiratory disease	20.1	16.1	32.1	23.3	100

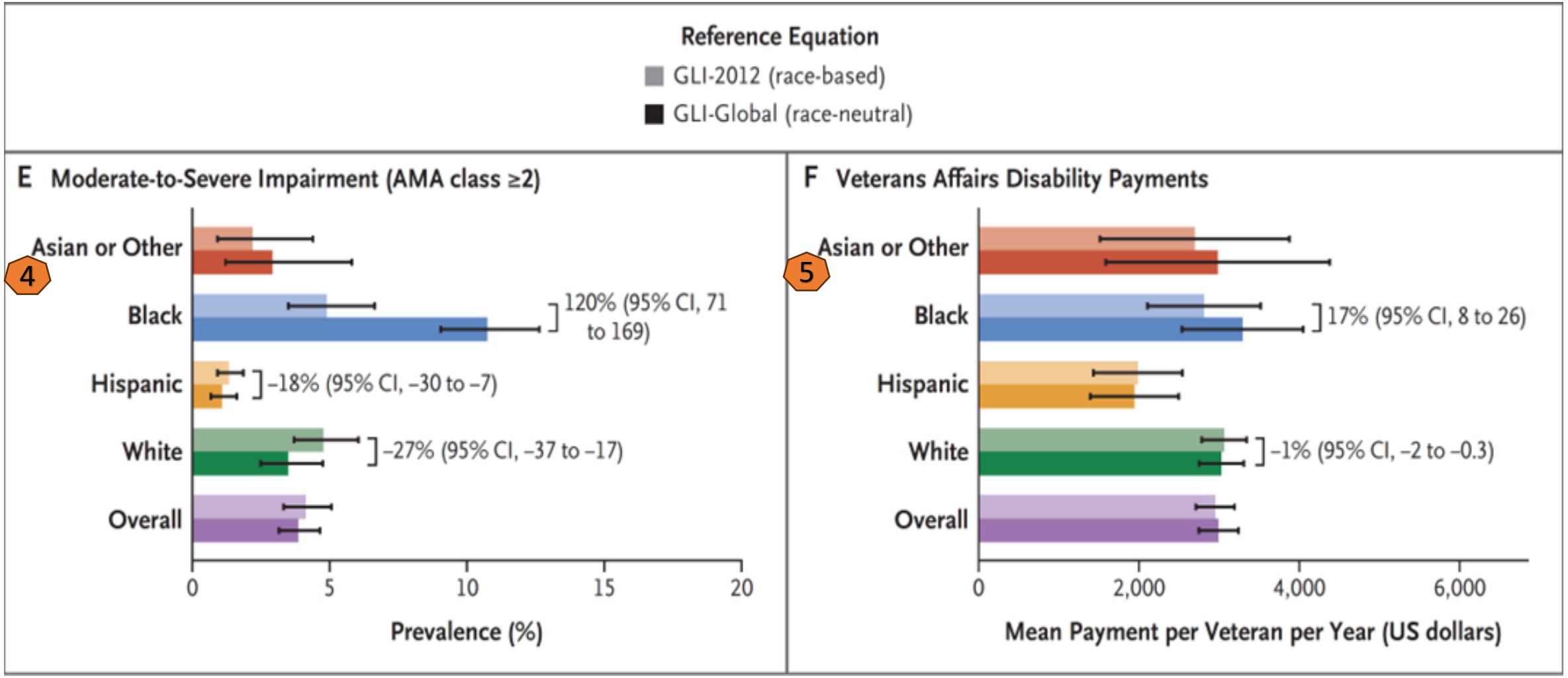
Results-2


Reference Equation
GLI-2012 (race-based)
GLI-Global (race-neutral)
A Obstructive Ventilatory Impairment (low FEV1:FVC)
1
Asian or Other
Black
Hispanic
White
Overall
−28% (95% CI, −40 to −16)
31% (95% CI, 21 to 41)
14% (95% CI, 11 to 18)
11% (95% CI, 8 to 15)
0
5
10
15
20
Prevalence (%)
B Nonobstructive Ventilatory Impairment (low FEV1 or FVC with preserved FEV1:FVC)
Asian or Other
Black
Hispanic
White
Overall
−28% (95% CI, −42 to −14)
141% (95% CI, 113 to 169)
−77% (95% CI, −85 to −69)
−69% (95% CI, −74 to −63)
−38% (95% CI, −46 to −30)
0
10
20
30
Prevalence (%)

Results-3


Reference Equation
GLI-2012 (race-based)
GLI-Global (race-neutral)
C Moderate-to-Severe COPD (GOLD grade ≥2)
Asian or Other
Black
Hispanic
White
Overall
44% (95% CI, 28 to 60)
–21% (95% CI, –31 to –11)
–15% (95% CI, –19 to –10)
–8% (95% CI, –12 to –4)
0
5
10
Prevalence (%)
2
D Occupational Disqualification (firefighting)
Asian or Other
Black
Hispanic
White
Overall
36% (95% CI, 7 to 66)
86% (95% CI, 56 to 115)
–43% (95% CI, –59 to –28)
–28% (95% CI, –37 to –20)
–10% (95% CI, –19 to –2)
0
10
20
30
Prevalence (%)
3

Results-4


Reference Equation
GLI-2012 (race-based)
GLI-Global (race-neutral)
E Moderate-to-Severe Impairment (AMA class ≥2)
Asian or Other
Black
Hispanic
White
Overall
120% (95% CI, 71 to 169)
–18% (95% CI, –30 to –7)
–27% (95% CI, –37 to –17)
0
5
10
15
20
Prevalence (%)
F Veterans Affairs Disability Payments
Asian or Other
Black
Hispanic
White
Overall
17% (95% CI, 8 to 26)
–1% (95% CI, –2 to –0.3)
0
2,000
4,000
6,000
Mean Payment per Veteran per Year (US dollars)

4

5

Results-5

In terms of numbers affected; national projections based on NHANES data with survey weights

Table 3. Extrapolated Changes in Outcomes Calculated from Race-Based and Race-Neutral Lung-Function Equations, According to Persons Affected and Disability Payments in the United States.*

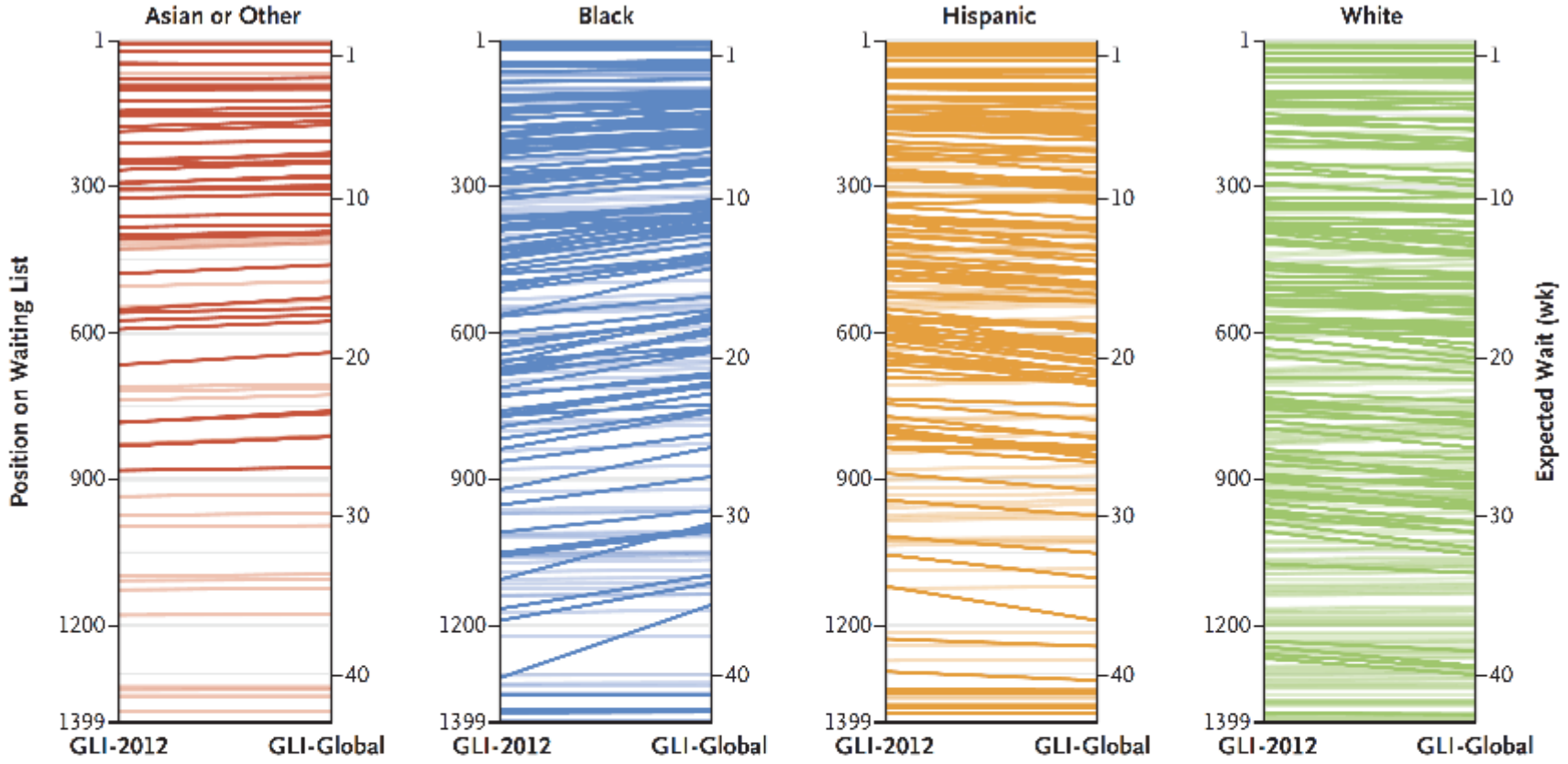
Outcome	Net Change					Total Change		
	Overall	Asian or Other	Black	Hispanic	White	Overall	Newly Classified	No Longer Classified
Persons affected — no., in thousands (95% CI)								
Obstructive impairment	2070 (1330 to 2820)	−392 (−608 to −177)	110 (−17 to 237)	349 (231 to 466)	2010 (1360 to 2650)	3200 (2630 to 3860)	2640 (2080 to 3290)	565 (338 to 884)
Nonobstructive impairment	−4700 (−6140 to −3270)	−304 (−498 to −110)	2340 (1930 to 2750)	−1370 (−1800 to −942)	−5370 (−6550 to −4190)	9620 (8570 to 10,800)	2460 (1960 to 3040)	7160 (6130 to 8320)
Moderate-to-severe COPD: GOLD grade ≥2	−749 (−1180 to −316)	6 (−15 to 27)	428 (300 to 556)	−85 (−139 to −32)	−1100 (−1480 to −715)	1660 (1300 to 2070)	453 (324 to 617)	1200 (857 to 1640)
Occupational disqualification from firefighting	−624 (−1200 to −48)	72 (10 to 135)	754 (540 to 969)	−181 (−262 to −100)	−1270 (−1730 to −809)	2280 (1840 to 2780)	826 (601 to 1110)	1450 (1030 to 1980)
Moderate-to-severe impairment: AMA class ≥2	−297 (−725 to 131)	41 (−9 to 92)	638 (478 to 797)	−38 (−59 to −16)	−938 (−1310 to −570)	1580 (1250 to 1960)	646 (481 to 849)	929 (632 to 1320)
Annual VA disability payments — U.S. $, in millions (95% CI)	806 (−42 to 1,650)	279 (−268 to 825)	1,100 (585 to 1,610)	46 (−99 to 7)	−524 (−917 to −131)	1,940 (1,100 to 2,790)	1,380 (627 to 2,120)	570 (173 to 966)

Results-6

6

Higher priority for Black candidates from GLI 2012 to GLI Global

A Candidate-Level Positions on the Waiting List and Expected Waiting Times



B Most and Least Advantaged Candidates

Advantage	Race or Ethnic Group	Gender	Age	FVC	Percent of Predicted FVC		Lung-Allocation Score		Position on Waiting List		Expected Wait	
					Original	Change	Original	Change	Original	Change	Original	Change
			yr	*liter*							*wk*	
Highest												
First	Black	Female	72	1.96	75.0	−10.0	32.3	0.66	1308	−150	40.2	−4.6
Second	Black	Female	53	2.38	74.4	−7.5	33.1	0.48	1106	−115	34.0	−3.5
Third	Black	Female	70	1.28	56.8	6.0	36.4	0.91	662	−102	20.3	−3.1
Lowest												
First	White	Male	61	2.78	67.6	5.3	33.5	−0.35	1029	80	31.6	2.5
Second	White	Female	62	1.94	69.6	5.3	33.4	−0.31	1030	75	31.6	2.3
Third	Hispanic	Male	59	2.72	62.6	4.8	33.1	−0.22	1120	70	34.4	2.1

Results-7

7

Table 4. Accuracy of Reference-Adjusted Spirometry for Discriminating Respiratory Symptoms, Health Care Utilization, New-Onset Disease, and Death.*

Outcome and Cohort	Best Spirometric Predictor	Discriminative Accuracy (95% CI)†		
		GLI-2012	GLI-Global	Difference
		C statistic		
Concurrent respiratory symptoms, NHANES IV				
Dyspnea on exertion	FEV_1 z score	0.634 (0.619 to 0.649)	0.632 (0.616 to 0.647)	−0.002 (−0.009 to 0.004)
Wheezing that limits activity	FEV_1 z score	0.685 (0.655 to 0.714)	0.689 (0.661 to 0.718)	0.005 (−0.008 to 0.017)
Lung or breathing problem that limits activity	FEV_1 z score	0.737 (0.695 to 0.780)	0.746 (0.705 to 0.787)	0.009 (−0.008 to 0.025)
Recent health care utilization, NHANES IV				
Medical visit for wheezing in past yr	FEV_1 z score	0.676 (0.644 to 0.708)	0.676 (0.644 to 0.707)	−0.001 (−0.013 to 0.012)
Overnight hospital admission in past yr	FEV_1 z score	0.573 (0.548 to 0.598)	0.584 (0.559 to 0.609)	0.011 (0.001 to 0.021)
New-onset respiratory disease, U.K. Biobank				
Asthma ≤10 yr	FEV_1:FVC z score	0.587 (0.559 to 0.616)	0.588 (0.559 to 0.617)	0.001 (−0.002 to 0.003)
COPD ≤10 yr	FEV_1:FVC z score	0.786 (0.750 to 0.823)	0.792 (0.755 to 0.828)	0.005 (0.002 to 0.008)
Death, NHANES III				
30-yr incidence from chronic lower respiratory disease	FEV_1:FVC z score	0.838 (0.628 to 0.981)	0.833 (0.601 to 0.981)	−0.004 (−0.037 to 0.013)
10-yr incidence from any cause	FEV_1 z score	0.620 (0.530 to 0.705)	0.620 (0.528 to 0.706)	−0.001 (−0.022 to 0.022)
Death while on transplant waiting list, OPTN				
45-day incidence	FVC z score	0.573 (0.545 to 0.598)	0.564 (0.538 to 0.590)	−0.008 (−0.013 to −0.003)
365-day incidence	FVC z score	0.573 (0.547 to 0.599)	0.568 (0.542 to 0.594)	−0.005 (−0.011 to 0.001)

Discussion-1

- Reclassification affects real-world decisions
  - Switching to race-neutral equations (GLI-Global) leads to major reclassifications of lung impairment, which can influence medical, occupational, and financial outcomes
- Race-neutral vs. race-specific impact varies by group
  - Black participants were more likely to be classified as impaired or severely impaired.
- Trade-offs between sensitivity and specificity
  - Using GLI-Global increased sensitivity (more true positives) among Black individuals but also increased false positives. Overall discriminative accuracy (C-statistic) remained similar (Table 4)

Discussion-2

- Population-level impact could obscure or reveal disparities
  - Race-based equations may "normalize" lower lung function in Black and Asian populations, potentially hiding subclinical disease.
  - Race-neutral models might uncover these disparities, but also risk overdiagnosis
- Consequences extend beyond diagnosis
  - Reclassifications can influence COPD trial eligibility, insurance premiums, worker compensation, transplant waiting lists, and surgery decisions.
  - —they have broad policy and ethical implications
- Removing race helps move beyond outdated biological assumptions, but deeper **inequities in healthcare access, social conditions, and environmental exposure remain unaddressed**

Limitations

- Physiologic data only, not full clinical assessment
- Lung allocation model may not apply to current practice
  - “Lung allocation score modeling (for transplant) used 2020 data; newer systems (since 2021) do not rely on spirometry”
- U.S.-centric outcome projections
  - international generalizability may be limited
- No gold standard to validate reclassification accuracy
- GLI datasets may embed racial biases

Paper 2 Blue Journal AJRCCM Jan 1, 2024

ORIGINAL ARTICLE

Application of Global Lung Function Initiative Global Spirometry Reference Equations across a Large, Multicenter Pulmonary Function Lab Population

Amjad N. Kanj[1], Paul D. Scanlon[1], Hemang Yadav[1], William T. Smith[1], Tyler L. Herzog[1], Aaron Bungum[1], Daniel Poliszuk[2], Edward Fick[1], Augustine S. Lee[3], and Alexander S. Niven[1]

[1]Division of Pulmonary and Critical Care Medicine, Department of Medicine, and [2]Information Technology, Mayo Clinic, Rochester, Minnesota; and [3]Division of Pulmonary and Critical Care Medicine, Department of Medicine, Mayo Clinic, Jacksonville, Florida

ORCID IDs: 0000-0002-1889-2524 (H.Y.); 0000-0003-0891-9495 (A.S.N.).

Background

- The GLI Global equations were developed to reduce bias and move away from race-based spirometry interpretation.
- Previous GLI-2012 equations may underestimate lung impairment in non-White populations and delay therapy or referral.
- **Race-neutral models aim to reduce inequality**, but may lead to new challenges, such as overdiagnosis, occupational disqualification, or insurance issues.
- The 2023 ATS statement recommends minimizing the use of race and emphasizes the importance of careful implementation of new standards.

Method

- Study Design
  - Retrospective cross-sectional analysis using data from the Mayo Clinic PFT database (2016–2022)
  - Evaluated changes in spirometry interpretation across self-reported race/ethnicity groups
- **Data & Definitions**
  - Collected age, sex, height, weight, race/ethnicity, mMRC dyspnea scores
  - Spirometry interpretation categorized into:
    - Normal
    - Indeterminate reduction in FEV1
    - Obstruction
    - Possible restriction
- Statistical comparisons were performed using ANOVA, chi-square tests, and t-tests, with significance set at $P < 0.05$.

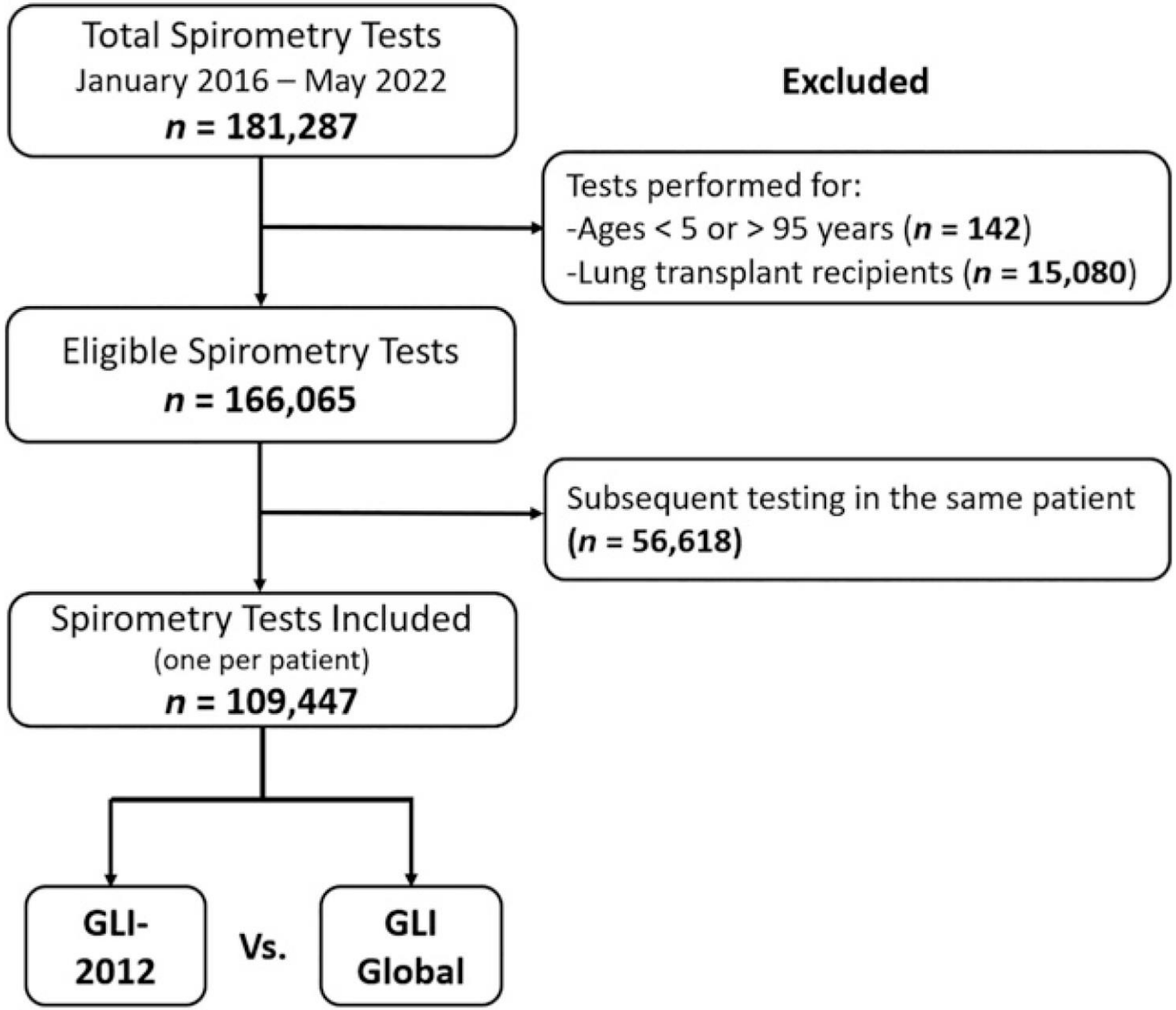

Total Spirometry Tests
January 2016 – May 2022
n = 181,287
Excluded
Tests performed for:
-Ages < 5 or > 95 years (n = 142)
-Lung transplant recipients (n = 15,080)
Eligible Spirometry Tests
n = 166,065
Subsequent testing in the same patient
(n = 56,618)
Spirometry Tests Included
(one per patient)
n = 109,447
GLI-2012
Vs.
GLI Global

Table 1. Patient Characteristics and Lung Function Measures Using GLI-2012 Reference Sets Stratified by Self-Reported Race and Ethnicity ($N = 109,447$)

Characteristic	White ($n = 101,010$)	Black ($n = 4,476$)	Northeast Asian ($n = 236$)	Southeast Asian ($n = 1,472$)	Mixed/Other ($n = 2,253$)	Total ($N = 109,447$)
Age, yr	59.5 ± 18.5	52.0 ± 18.1	53.9 ± 20.9	51.9 ± 19.6	48.7 ± 21.1	58.9 ± 18.7
Female sex	52,089 (51.6)	2,624 (58.6)	129 (54.7)	779 (52.9)	1,151 (51.1)	56,772 (51.9)
Height, cm	168.5 ± 11.3	167.1 ± 11.8	162.5 ± 10.9	160.4 ± 11.6	164.2 ± 13.7	168.2 ± 11.4
Weight, kg	84.0 ± 24.1	86.7 ± 25.9	64.4 ± 14.9	66.3 ± 18.0	76.1 ± 24.5	83.7 ± 24.2
BMI, kg/m^2	29.4 ± 7.4	30.8 ± 8.2	24.2 ± 4.4	25.5 ± 5.6	27.7 ± 7.3	29.3 ± 7.4
mMRC score,* *n* (%)						
0	31,618 (35.9)	1,640 (40.9)	96 (50.8)	562 (45.8)	639 (35.0)	34,555 (36.2)
1	27,151 (30.8)	898 (22.4)	57 (30.2)	371 (30.2)	576 (31.6)	29,053 (30.5)
2	13,897 (15.8)	557 (13.9)	18 (9.5)	130 (10.6)	281 (15.4)	14,883 (15.6)
3	10,370 (11.8)	548 (13.7)	11 (5.8)	103 (8.4)	193 (10.6)	11,225 (11.8)
4	4,964 (5.6)	360 (9.0)	7 (3.7)	58 (4.7)	132 (7.2)	5,521 (5.8)
Lung function (GLI-2012)						
FEV_1, L	2.47 ± 0.97	2.15 ± 0.81	2.51 ± 0.89	2.21 ± 0.86	2.41 ± 0.95	2.45 ± 0.96
FVC, L	3.36 ± 1.15	2.77 ± 0.98	3.19 ± 1.08	2.85 ± 1.04	3.12 ± 1.17	3.32 ± 1.15
FEV_1/FVC ratio	72.9 ± 12.3	77.7 ± 11.0	78.8 ± 9.54	77.4 ± 10.5	77.3 ± 11.2	73.2 ± 12.2
Normal	63,798 (63.2)	2,756 (61.6)	159 (67.4)	903 (61.3)	1,361 (60.4)	68,977 (63.0)
Indeterminate ↓FEV_1	2,857 (2.8)	84 (1.9)	1 (0.4)	28 (2.6)	41 (1.8)	3,021 (2.8)
Obstruction	19,901 (19.7)	657 (14.7)	29 (12.3)	326 (22.1)	424 (18.8)	21,337 (19.5)
Possible restriction	14,454 (14.3)	979 (21.9)	47 (20.0)	205 (13.9)	427 (19.0)	16,112 (14.7)

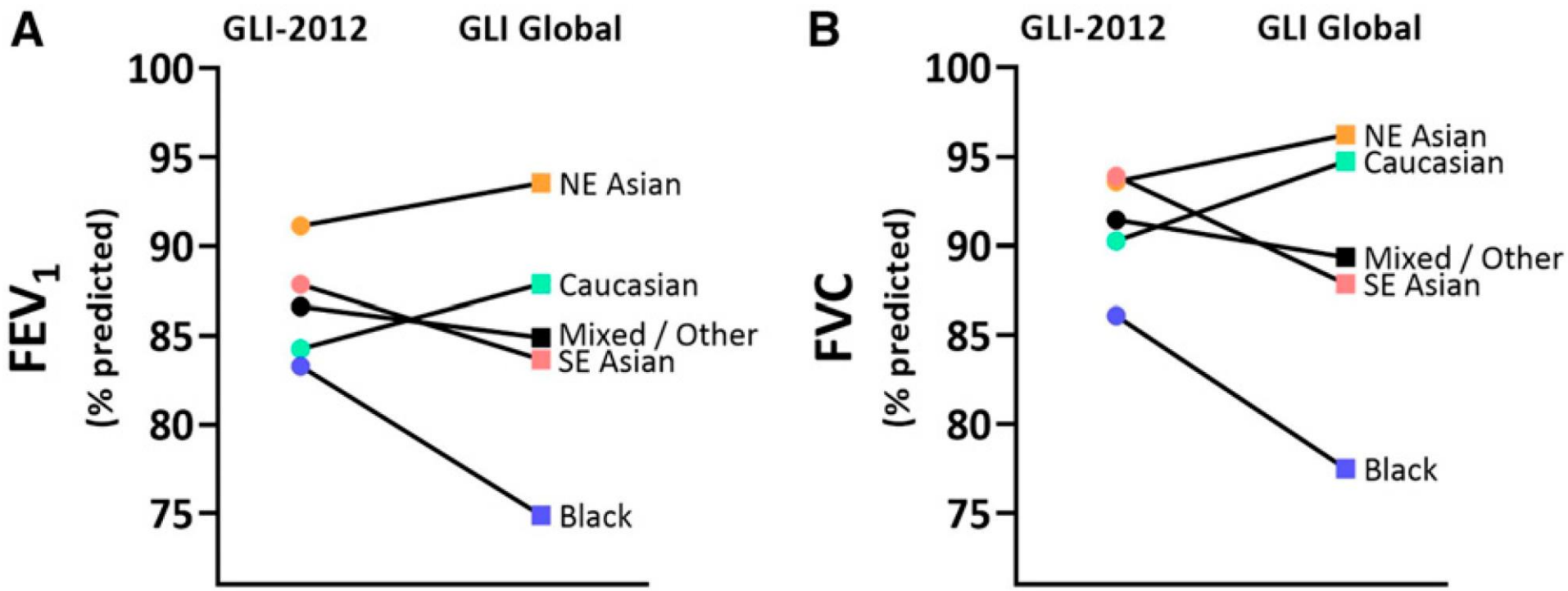
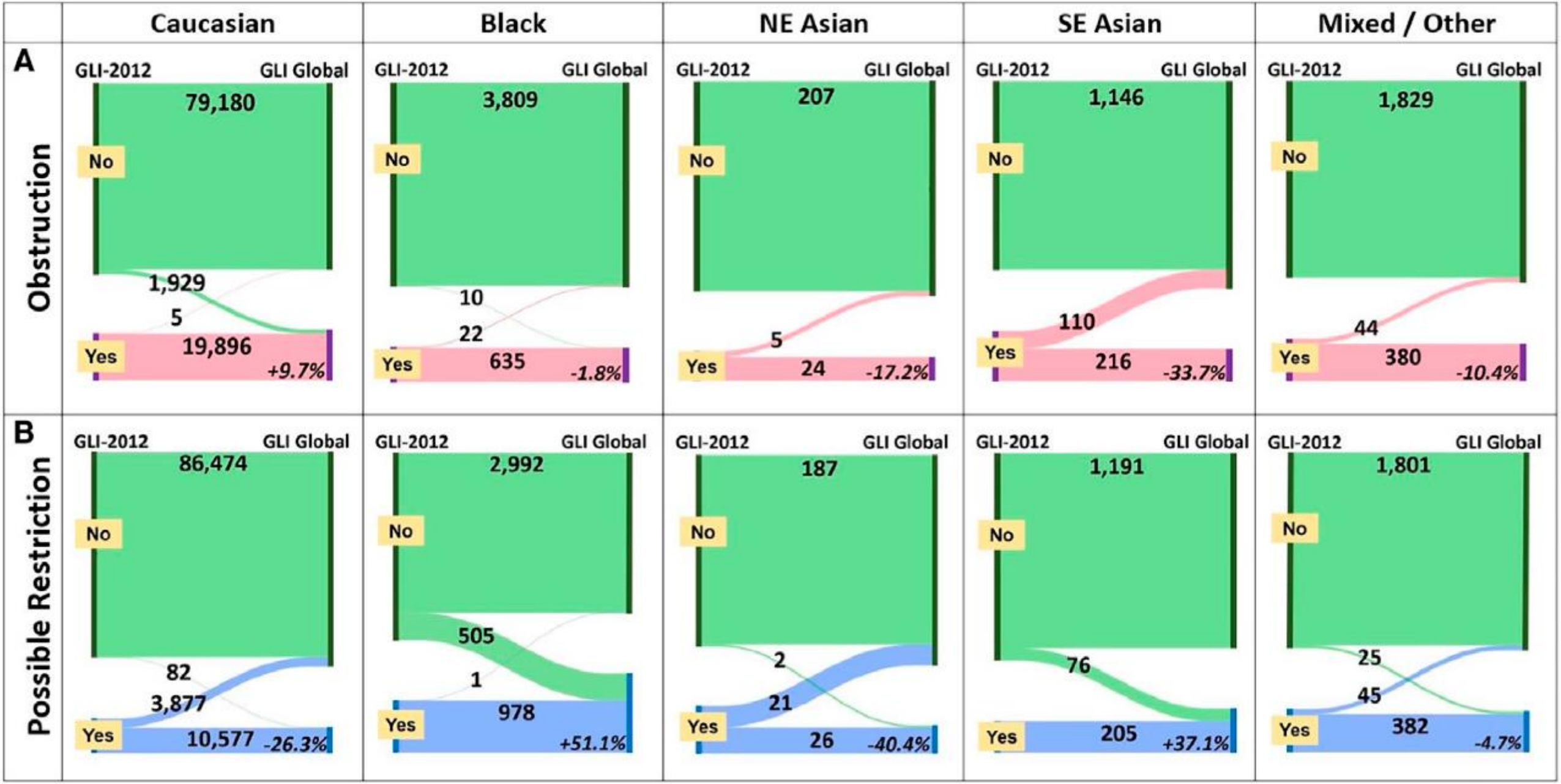


Figure 2. Absolute change in mean (*A*) FEV_1% predicted and (*B*) FVC% predicted values using Global Lung Function Initiative (GLI)-2012 and GLI Global reference equations. In White and NE Asian groups, mean FEV_1% predicted increased by 3.6% and 2.4% predicted and mean FVC% predicted increased by 4.5% and 2.6% predicted, respectively. In Black, SE Asian, and mixed/other groups, mean FEV_1% predicted decreased by 8.4%, 4.2%, and 1.7% predicted and mean FVC% predicted decreased by 8.6%, 6.1%, and 2.1% predicted, respectively. NE = northeast; SE = southeast.

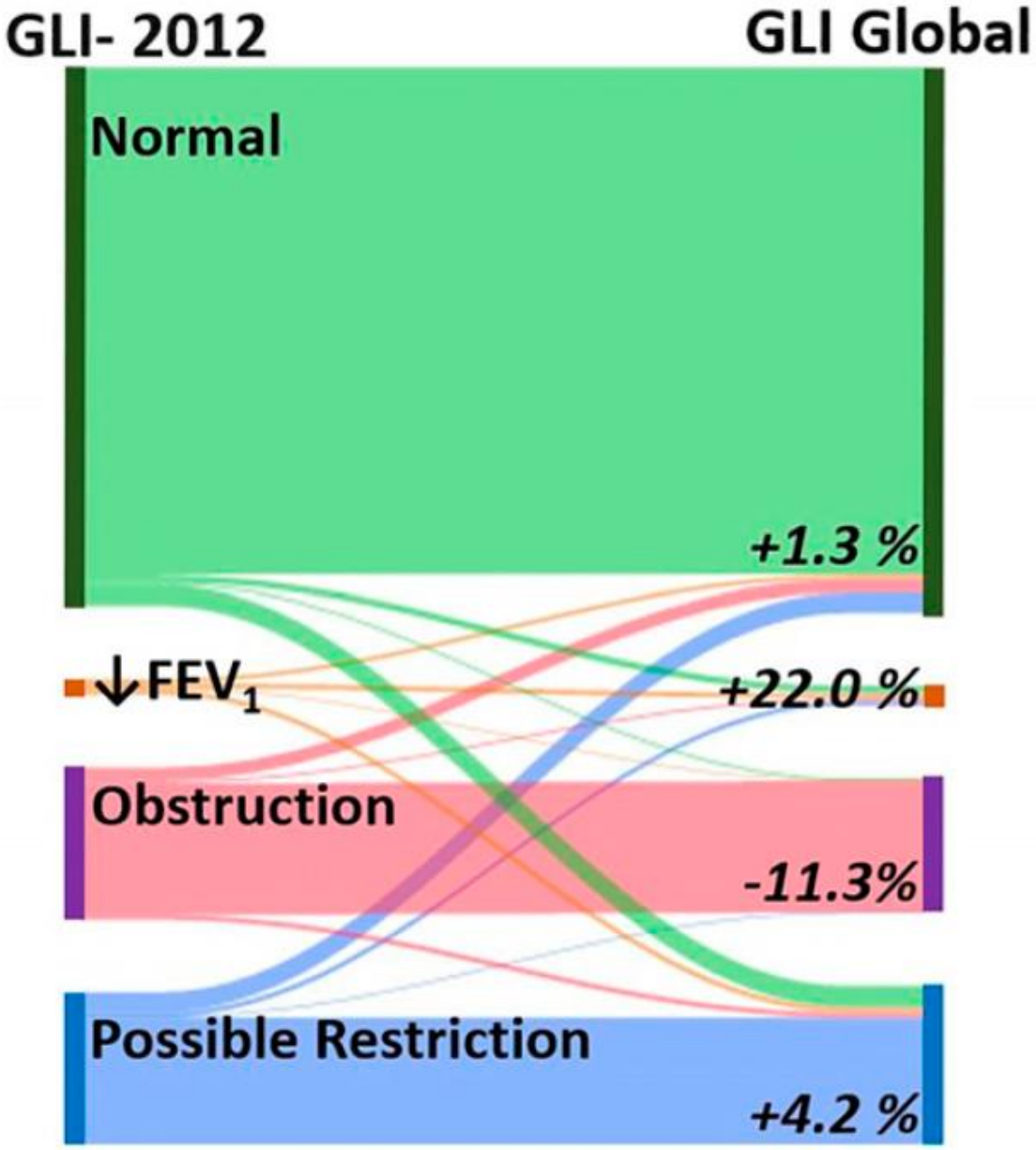

Caucasian
Black
NE Asian
SE Asian
Mixed / Other
A
Obstruction
GLI-2012
GLI Global
79,180
No
1,929
5
Yes
19,896
+9.7%
3,809
10
22
635
-1.8%
207
5
24
-17.2%
1,146
110
216
-33.7%
1,829
44
380
-10.4%
B
Possible Restriction
86,474
82
3,877
10,577
-26.3%
2,992
505
1
978
+51.1%
187
2
21
26
-40.4%
1,191
76
205
+37.1%
1,801
25
45
382
-4.7%

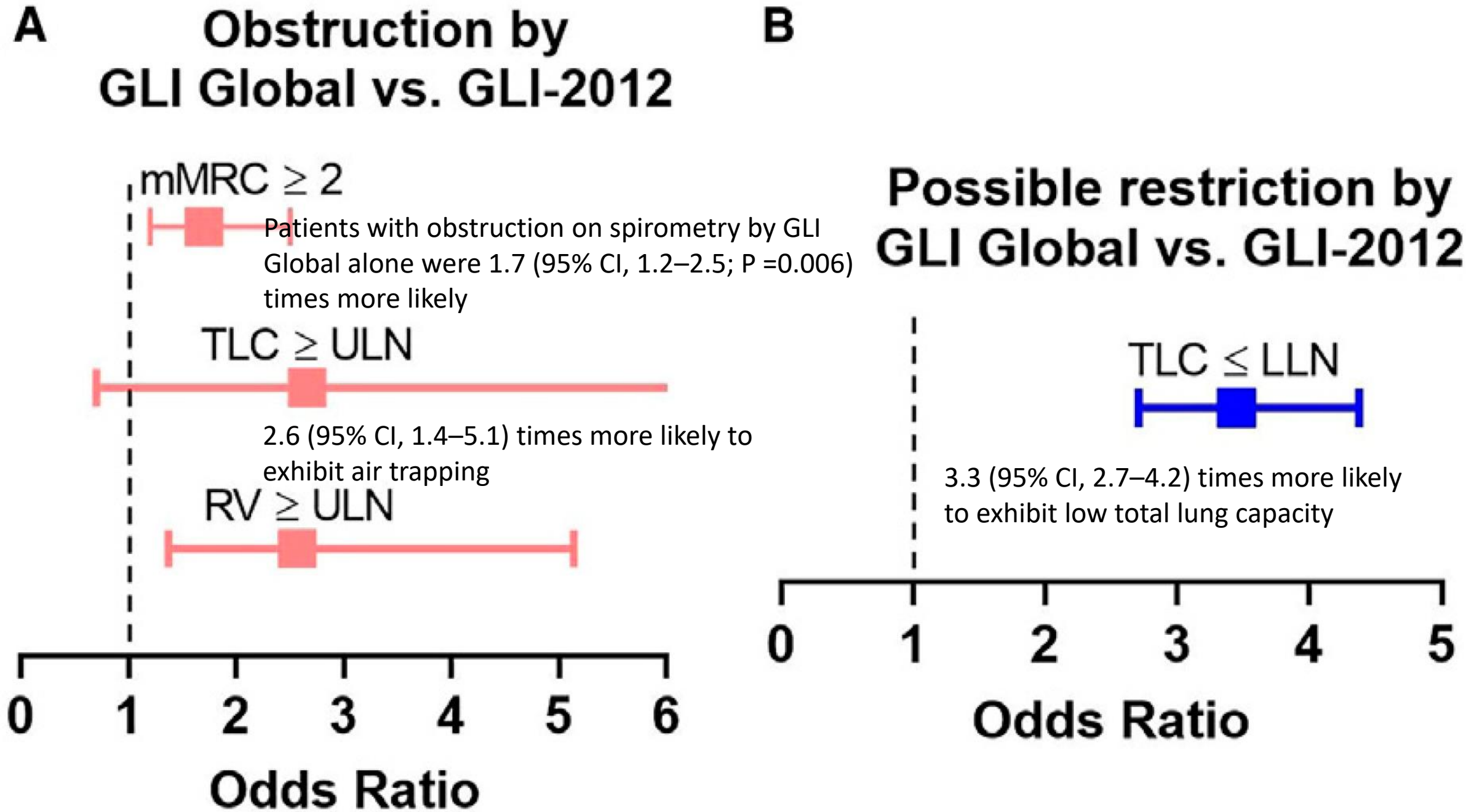
Not Just 7.6% — It's 10.2% When Everyone Counts Equally

Table 2. Frequency of Change in Lung Function Interpretations and Relative Change in Abnormal Interpretations by Race and Ethnicity

Race and Ethnicity	Change in Lung Function Interpretation*	Change in Abnormal Interpretation (Obstruction, Possible Restriction, $\downarrow FEV_1$)†		
		Abnormal by GLI-2012	Abnormal by GLI Global	Relative Change, %
White ($n = 101,010$)	7,305 (7.2)	37,212	34,418	−7.5
Black ($n = 4,476$)	667 (14.9)	1,720	2,286	+32.9
Northeast Asian ($n = 236$)	27 (11.4)	77	54	−29.9
Southeast Asian ($n = 1,472$)	173 (11.8)	569	539	−5.3
Mixed/other ($n = 2,253$)	124 (5.6)	892	846	−5.2
Total ($N = 109,447$)	8,296 (7.6)	40,470	38,143	−5.8
Equally weighed sample‡	NA (10.2)	NA	NA	−3.0

10.2% change to a population of equal representation of all five race groups




A
Obstruction by GLI Global vs. GLI-2012
mMRC ≥ 2
Patients with obstruction on spirometry by GLI Global alone were 1.7 (95% CI, 1.2–2.5; P =0.006) times more likely
TLC ≥ ULN
2.6 (95% CI, 1.4–5.1) times more likely to exhibit air trapping
RV ≥ ULN
0 1 2 3 4 5 6
Odds Ratio
B
Possible restriction by GLI Global vs. GLI-2012
TLC ≤ LLN
3.3 (95% CI, 2.7–4.2) times more likely to exhibit low total lung capacity
0 1 2 3 4 5
Odds Ratio

Discussion

- GLI Global offers a “race-neutral” approach
  - Aimed at reducing health disparities and structural racism in medicine
  - Recognizes that self-identified race oversimplifies the complex interplay between genetics, environment, and social factors
- Reclassification affected nearly 1 in 13 tests
  - Greatest change seen in Black and Southeast Asian populations
  - Black patients had a 32.9% relative increase in abnormal interpretation, largely due to decreased % predicted values from higher LLN thresholds
- GLI Global correlates better with clinical findings
- Clinical significance still uncertain
  - No gold standard diagnosis included in the dataset
- Broader disparities in SES remain unresolved for lung health

Limitation

- Limited representation of Northeast Asian participants
- Subgroup analysis limitations
- Reference equations for lung volumes were based only on White individuals
- No gold standard clinical diagnosis
- Uncertain clinical significance of interpretation changes

Comparison of Research Design

Research Aspect	Paper 1 (NEJM, 2024)	Paper 2 (AJRCCM, 2024)
Sample size	369,077 participants (from five large cohorts)	109,447 participants (Mayo Clinic pulmonary labs)
Population	General population, clinical patients, transplant candidates; cohorts include NHANES, UK Biobank, MESA, OPTN	Clinical patients undergoing spirometry at Mayo Clinic (multiple centers)
Methods	Retrospective analysis comparing GLI-2012 vs. GLI-Global lung function equations	Retrospective analysis comparing GLI-2012 vs. GLI-Global lung function equations

Comparison of Research Design

Research Aspect	Paper 1 (NEJM, 2024)	Paper 2 (AJRCCM, 2024)
Outcome measurements	**Focuses on broader clinical, social, and policy-level outcomes**, such as eligibility for employment, medical compensation, transplant prioritization, and mortality prediction.	**Focuses on direct diagnostic impacts**, including changes in spirometry interpretation, symptom burden (mMRC score), and physiologic validation through lung volume measurements.
Statistical analysis	Concordance statistics (C-statistics), ROC curves, survey-weighted national projections, linear models for transplant prioritization Grouped Bar, paired line plot	ANOVA, Chi-square tests, Fisher's exact test, independent t-tests for group comparisons, descriptive statistics Paired line plot; Sankey plot

Confounding bias

Paper 1 (NEJM, 2024)	Paper 2 (AJRCCM, 2024)
• Multiple datasets with different inclusion criteria (e.g., NHANES, transplant list) • Potential variation in socioeconomic status, comorbidities, access to care not fully adjusted	• Single health system • Differences in referral reasons, disease severity, and race/ethnicity may confound results

Strategies for future studies:

- ✅ Use propensity score adjustment or inverse probability weighting
- ✅ Stratify or match on key covariates (e.g., SES, comorbidity)
- ✅ Include longitudinal outcomes (e.g., symptom progression, hospitalization)

Selection bias

Paper 1 (NEJM, 2024)	Paper 2 (AJRCCM, 2024)
• Populations drawn from large cohort studies, but may not be representative of general clinical populations • Selective inclusion (e.g., transplant candidates)	• Only includes patients who were referred for PFTs, may overrepresent symptomatic or high-risk individuals • Racial/ethnic representation is imbalanced

✅ Use population-based sampling or random sampling of PFTs
✅ Ensure proportional representation across race/ethnicity groups
✅ Prospectively recruit diverse and unselected participants

Cost?

Conclusion: from GLI 2012 to GLI global

- Paper 1 in NEJM showed that race-neutral equations can reclassify lung function and may impact medical decisions like COPD grading and transplant eligibility.
- Paper 2 in AJRCCM found that switching to race-neutral equations significantly changes spirometry interpretation, especially in diverse populations.
- Both studies highlight the need for further research to confirm whether these changes reflect true disease or lead to misclassification.
- I think the local data is very important. Taiwan is not part of the US.