Supplementary Online Content

Bhatt SP, Balte PP, Schwartz JE, et al. Discriminative accuracy of FEV_1:FVC thresholds for COPD-related hospitalization and mortality. *JAMA*. doi:10.1001/jama.2019.7233

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Design features of cohorts included

Cohort		Sites	Enrollment year	Major eligibility criteria	Self-reported fixed categories for race or race/ethnicity
ARIC	Atherosclerosis Risk in Communities Study	Winston-Salem, NC Jackson, MS Minneapolis, MN Washington County, MD	1987-89	Age 45 -64 years	White Black Asian/Pacific Islanders American Indian
CHS	Cardiovascular Health Study	Pittsburgh, PA Winston-Salem, NC Sacramento, CA Baltimore, MD	1989-90	Age 65 + years	White Black Asian/Pacific Islanders American Indian Others
HABC	Health, Aging and Body Composition study	Pittsburgh, PA Memphis, TN San Francisco, CA	1997-98	Age 70-79 years Participants required to have no major disabilities or functional limitations	White Black Asian/Pacific Islanders Hispanic/Latino
MESA	Multi-Ethnic Study of Atherosclerosis	Winston-Salem, NC Upper Manhattan/Bronx, NY Los Angeles, CA Baltimore, MD Chicago, IL Minneapolis, MN	2000-02[a]	Age 45-84 years Participants required to be free of clinical cardiovascular disease.	White Black Asian/Pacific Islanders Hispanic/Latino

[a] In MESA, first spirometry measurements were conducted in 2004-06, hence 2004-06 was treated as the baseline for analyses in MESA in this report.

eTable 2. Baseline characteristics, stratified by FEV_1/FVC <0.70.

	$FEV_1/FVC < 0.70$	$FEV_1/FVC \geq 0.70$	Total
Total sample, n (%)	6,261	17,946	24,207
Total events follow-up, person-years	72,211	267,546	340,757
Cohort, n (%)			
ARIC	2,885 (22.5)	9,923 (77.5)	12,808 (52.9)
CHS	1,896 (39.4)	2,918 (60.6)	4,814 (19.9)
Health ABC	617 (23.9)	1,961 (76.1)	2,578 (10.7)
MESA	863 (21.5)	3,144 (78.5)	4,007 (16.6)
Age, years	65.9 (10.1)	61.7 (10.3)	62.8 (10.5)
Age group, n (%)			
45-55 years	1,021 (15.0)	5,767 (85.0)	6,788 (28.0)
56-65 years	2,058 (26.3)	5,769 (73.7)	7,827 (32.3)
66-75 years	1,896 (30.8)	4,262 (69.2)	6,158 (25.4)
>75 years	1,286 (37.5)	2,148 (62.6)	3,434 (14.2)
Sex, n (%)			
Female	2,692 (20.7)	10,298 (79.3)	12,990 (53.7)
Male	3,569 (31.8)	7,648 (68.2)	11,217 (46.3)
Median Body mass index (IQR), kg/m^2	25.6 (22.9, 28.6)	27.3 (24.5, 30.8)	26.8 (24.0, 30.3)
Race/ethnicity, n (%)[a]			
Non-Hispanic White	4,839 (28.8)	11,955 (71.2)	16,794 (69.4)
Non-Hispanic Black	1,186 (20.1)	4,714 (79.9)	5,900 (24.4)
Hispanic/Latino	115 (13.5)	739 (86.5)	854 (3.5)
Asian	111 (17.8)	512 (82.2)	623 (2.6)
Other	10 (27.8)	26 (72.2)	36 (0.2)
Education status, n (%)			
Less than high school	909 (29.1)	2,215 (70.9)	3,124 (12.9)
High school	1,676 (25.2)	4,988 (74.9)	6,663 (27.5)
Some college	762 (23.6)	2,464 (76.4)	3,226 (13.3)
College or more	2,908 (26.0)	8,263 (74.0)	11,172 (46.2)
Lifetime smoking status, n (%)			
Never	1,331 (14.8)	7,695 (85.3)	9,026 (37.3)
Ever	4,930 (32.5)	10,251 (67.5)	15,181 (62.7)
Median pack-years (q1, q3) in ever-smokers, years	34.5 (17.0, 51.0)	17.0 (4.4, 33.9)	22.3 (6.8, 40.5)
Medical history, n (%)			
Hypertension[b]	3,553 (26.7)	9,750 (73.3)	13,303 (55.0)
Diabetes mellitus[c]	738 (21.7)	2,666 (78.3)	3,404 (14.1)
Chronic obstructive pulmonary disease	953 (47.0)	1,074 (53.0)	2,027 (8.4)
Coronary artery disease	678 (37.6)	1,125 (62.4)	1,803 (7.5)
Asthma	657 (49.3)	693 (50.7)	1,368 (5.7)
Lung function			
Baseline FEV_1 percent-predicted, %	76.4 (19.8)	97.9 (15.4)	92.4 (19.2)
Baseline FEV_1, L	2.1 (0.8)	2.6 (0.8)	2.5 (0.8)

Baseline FVC, L	3.4 (1.1)	3.4 (1.0)	3.4 (1.0)
Baseline FEV_1/FVC	0.62 (0.08)	0.77 (0.05)	0.73 (0.09)

ARIC = Atherosclerosis Risk in Communities Study; CHS = Cardiovascular Health Study; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; HABC = Health Aging and Body Composition; IQR = Interquartile range; MESA = Multi-Ethnic Study of Atherosclerosis.

Categorical data presented as number (%). Continuous data presented as mean (standard deviation [SD]) or, if non-normally distributed, as median (interquartile range [IQR]).

[a]Race was self-reported according to fixed, mutually exclusive categories, which differed by cohort. In ARIC, participants self-reported race as non-Hispanic White, non-Hispanic Black, Asian-Pacific Islander, or American Indian. In CHS, participants self-reported race as non-Hispanic White, non-Hispanic Black, Asian-Pacific Islander, American Indian, or Other. In Health ABC and MESA, race/ethnicity was self-reported as non-Hispanic White, non-Hispanic Black, Hispanic, or Asian. No separate question regarding ethnicity was administered at enrollment for any of the cohorts.

[b]Self-reported hypertension or systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or use of anti-hypertensive medications

[c] Self-reported diabetes or fasting blood sugar levels ≥ 126 mg/dl or use of oral hypoglycemic agents or insulin.

eTable 3. Reclassification of airflow obstruction according to fixed FEV_1/FVC threshold

Fixed Ratio Threshold	< Fixed Ratio Threshold			≥ Fixed ratio threshold
	Total	<LLN	≥ LLN	< LLN
0.60	1,646 (6.8)	1,642 (99.8)	4 (0.2)	2,004 (8.3)
0.61	1,847 (7.6)	1,831 (99.1)	16 (0.9)	1,815 (7.5)
0.62	2,090 (8.6)	2,061 (98.6)	29 (1.4)	1,585 (6.6)
0.63	2,358 (9.7)	2,287 (97.0)	71 (3.0)	1,359 (5.6)
0.64	2,711 (11.2)	2,544 (93.8)	167 (6.2)	1,102 (4.6)
0.65	3,130 (12.9)	2,824 (90.2)	306 (9.8)	822 (3.4)
0.66	3,576 (14.8)	3,036 (84.9)	540 (15.1)	610 (2.5)
0.67	4,103 (17.0)	3,243 (79.0)	860 (21.0)	403 (1.7)
0.68	4,728 (19.5)	3,427 (72.5)	1,301 (27.5)	219 (0.9)
0.69	5,466 (22.6)	3,556 (65.1)	1,910 (34.9)	90 (0.4)
0.70	6,261 (25.9)	3,627 (57.9)	2,634 (42.1)	19 (0.1)
0.71	7,180 (29.7)	3,643 (50.7)	3,537 (49.3)	3 (0.01)
0.72	8,179 (33.8)	3,645 (44.6)	4,534 (55.4)	1 (0)
0.73	9,291 (38.4)	3,646 (39.2)	5,645 (60.8)	0 (0)
0.74	10,555 (43.6)	3,646 (34.5)	6,909 (65.5)	0 (0)
0.75	11,839 (48.9)	3,646 (30.8)	8,193 (69.2)	0 (0)
0.76	13,191 (54.5)	3,646 (27.6)	9,545 (72.4)	0 (0)
0.77	14,622 (60.4)	3,646 (24.9)	10,976 (75.1)	0 (0)
0.78	16,035 (66.2)	3,646 (22.7)	12,389 (77.3)	0 (0)
0.79	17,456 (72.1)	3,645 (20.9)	13,810 (79.1)	0 (0)
0.80	18,779 (77.6)	3,646 (19.4)	15,133 (80.6)	0 (0)
LLN	3,646 (15.1)			

LLN = Lower limit of normal per Global Lung Function Initiative reference equations.

eTable 4. Brier Scores (95% confidence intervals) for the prediction of COPD events by various FEV_1/FVC thresholds in unadjusted models.

Model	At Risk / Events (IDR)	Optimal fixed ratio threshold[a]	Brier Scores		
			B_{OPT} (95% CI)	$B_{0.7}$ (95% CI)	B_{LLN} (95% CI)
Primary analyses	24,207 / 3,925 (11.54)	0.71	0.150 (0.144, 0.156)	0.150 (0.144, 0.156)	0.148 (0.142, 0.154)
Subgroup analyses					
Ever smoker	15,181/ 3,389 (16.34)	0.70	0.197 (0.189, 0.206)	n/a[b]	0.195 (0.187, 0.204)
Never smoker	9,026/ 536 (4.04)	0.74	0.059 (0.052, 0.066)	0.059 (0.052, 0.066)	0.059 (0.052, 0.066)
Men	11,217/ 2,123 (14.27)	0.70	0.171 (0.162, 0.181)	n/a[b]	0.168 (0.159, 0.178)
Women	12,990/ 1,802 (9.42)	0.71	0.131 (0.123, 0.139)	0.130 (0.123, 0.138)	0.130 (122, 0.138)
Alternative event definitions					
COPD-related hospitalization	24,207/ 3,563 (10.47)	0.71	0.150 (0.144, 0.155)	0.149 (0.143, 0.155)	0.148 (0.142, 0.154)
COPD-related mortality	24,207/ 447 (1.31)	0.68	0.152 (0.147, 0.157)	0.152 (0.148, 0.157)	0.152 (0.147, 0.157)
Hospitalization or mortality with COPD as primary/underlying cause	24,207/ 1,129 (3.16)	0.69	0.045 (0.042, 0.049)	0.045 (0.042, 0.049)	0.045 (0.041, 0.049)
Adjusted for covariates[c]	24,012 / 3,793 (11.16)	0.70	0.149 (0.143, 0.155)	n/a[b]	0.147 (0.141, 0.153)

B_{OPT} = Brier Score for the optimal fixed threshold; $B_{0.7}$ = Brier Score for the model using a fixed ratio threshold of 0.70; B_{LLN} = Brier Score for the model using the LLN ratio threshold; IDR = Incidence Density Rate per 1,000 person-years of follow-up; LLN = Lower limit of normal per Global Lung Function Initiative reference equations; n/a = not applicable.

Cox proportional hazards models were used. The primary outcome was defined as first hospitalization or death adjudicated as primarily or secondarily attributable to COPD or, if adjudication was lacking, those with COPD listed in any diagnosis field. In sensitivity analyses, the primary outcome was decomposed into COPD-related hospitalizations and COPD-related mortality. As another sensitivity analysis, the endpoint was restricted to incident hospitalizations and mortality adjudicated or coded as having COPD as the primary/underlying cause.

aThe optimal fixed threshold was defined as the one that generated the highest Harrell's c-statistic.

bThe optimal fixed threshold was 0.70, hence BOPT = B0.7.

[c]Each fixed-threshold definition for airflow obstruction was added separately to a base model adjusted for age at enrollment, sex, race, height, birth-year, site and cohort.

eTable 5. Sensitivity analyses for the discriminative accuracy of various fixed FEV_1/FVC thresholds for COPD event risk in adjusted models.

Model	At Risk / Events (IDR)	Optimal fixed ratio threshold[a]	Harrell's C-statistics			C-statistic Comparisons	
			C_{OPT} (95% CI)	$C_{0.7}$ (95% CI)	C_{LLN} (95% CI)	$\Delta C_{OPT\ vs\ 0.7}$ (95% CI)	$\Delta C_{OPT\ vs\ LLN}$ (95% CI)
Subgroup analyses							
Never smoker	8,989 / 523 (3.95)	0.70	0.785 (0.765, 0.805)	n/a[d]	0.780 (0.760, 0.800)	n/a[d]	0.005 (-0.001, 0.010)
Ever smoker	15,023 / 3,270 (15.76)	0.67[c]	0.748 (0.740, 0.757)	0.745 (0.736, 0.753)	0.750 (0.742, 0.759)	0.003 (-0.001, 0.008)	-0.002 (-.006, 0.002)
Men	11,114 / 2,048 (13.78)	0.66[c]	0.760 (0.749, 0.771)	0.756 (0.745, 0.766)	0.763 (0.752, 0.774)	0.004 (-0.002, 0.010)	-0.003 (-0.008, 0.001)
Women	12,898 / 1,745 (9.13)	0.70	0.753 (0.741, 0.765)	n/a[d]	0.750 (0.738, 0.763)	n/a[d]	0.003 (-0.003, 0.008)
Alternative event definitions							
COPD-related hospitalization	24,012 / 3,740 (11.00)	0.70	0.761 (0.753, 0.769)	n/a[d]	0.763 (0.756, 0.771)	n/a[d]	-0.002 (-0.006, 0.002)
COPD-related mortality	24,012 / 425 (1.18)	0.66	0.889 (0.874, 0.904)	0.877 (0.863, 0.891)	0.894 (0.880, 0908)	0.012 (0.003, 0.021)	-0.005 (-0.012, 0.002)
Hospitalization or mortality with COPD as primary/underlying cause	24,012 / 1,114 (3.12)	0.67[c]	0.828 (0.816, 0.841)	0.822 (0.810, 0.834)	0.835 (0.822, 0.847)	0.006 (-0.001, 0.013)	-0.006 (-0.012, -0.001)

C_{OPT} = C-statistic for the optimal fixed threshold (equivalent to the highest c-statistic obtained among all possible fixed threshold models); $C_{0.7}$ = c-statistic for the model using a fixed ratio threshold of 0.70; C_{LLN} = c-statistic for the model using the LLN ratio threshold; $\Delta C_{OPT\ vs\ 0.7}$ = difference in C-statistics from model using optimal ratio threshold versus model using 0.70 threshold; $\Delta C_{OPT\ vs\ LLN}$ = = difference in C-statistics from model using optimal ratio threshold versus model using LLN threshold; IDR = Incidence Density Rate per 1,000 person-years of follow-up; LLN = Lower limit of normal per Global Lung Function Initiative reference equations; n/a = not applicable.

Cox proportional hazards models were used. The primary outcome was defined as first hospitalization or death adjudicated as primarily or secondarily attributable to COPD or, if adjudication was lacking, those with COPD listed in any diagnosis field. In sensitivity analyses, the primary outcome was decomposed into COPD-related hospitalizations and COPD-related mortality. As another sensitivity analysis, the endpoint was restricted to incident hospitalizations and mortality

adjudicated or coded as having COPD as the primary/underlying cause. Each fixed-threshold definition for airflow obstruction was added separately to a base model adjusted for age at enrollment, sex, race, height, birth-year, site and cohort.

[a]The optimal fixed threshold was defined as the one that generated the highest Harrell's c-statistic.

[b]Formal statistical comparisons of c-statistics were performed using a nonparametric approach to compare two correlated c-statistics with right-censored survival outcomes.

[c]C-statistic for the optimal fixed threshold was not significantly different than the c-statistic for 0.70.

[d]C-statistic for the optimal fixed threshold was not significantly different than the c-statistic for LLN.

[e]The optimal fixed threshold was 0.70, hence $C_{OPT} = C_{0.7}$

eTable 6. Brier Scores (95% confidence intervals) for the prediction of COPD events by various FEV_1/FVC thresholds in adjusted models.

Model	At Risk / Events (IDR)	Optimal fixed ratio threshold[a]	Brier Scores		
			B_{OPT} (95% CI)	$B_{0.7}$ (95% CI)	B_{LLN} (95% CI)
Subgroup analyses					
Never smoker	8,989 / 523 (3.95)	0.70	0.059 (0.052, 0.065)	n/a[b]	0.059 (0.052, 0.065)
Ever smoker	15,023 / 3,270 (15.76)	0.67[c]	0.195 (0.186, 0.203)	0.197 (0.188, 0.205)	0.193 (0.185, 0.202)
Men	11,114 / 2,048 (13.78)	0.66[c]	0.467 (0.158, 0.176)	0.170 (0.161, 0.179)	0.166 (0.157, 0.175)
Women	12,898 / 1,745 (9.13)	0.70	0.130 (0.123, 0.138)	n/a[b]	0.130 (0.122, 0.137)
Alternative event definitions					
COPD-related hospitalization	24,012 / 3,740 (11.00)	0.70	0.148 (0.142, 0.154)	n/a[b]	0.146 (0.141, 0.152)
COPD-related mortality	24,012 / 425 (1.18)	0.66	0.153 (0.148, 0.158)	0.154 (0.149, 0.159)	0.153 (0.148, 0.158)
Hospitalization or mortality with COPD as primary/underlying cause	24,012 / 1,114 (3.12)	0.67[c]	0.045 (0.042, 0.049)	0.046 (0.042, 0.049)	0.045 (0.041, 0.048)

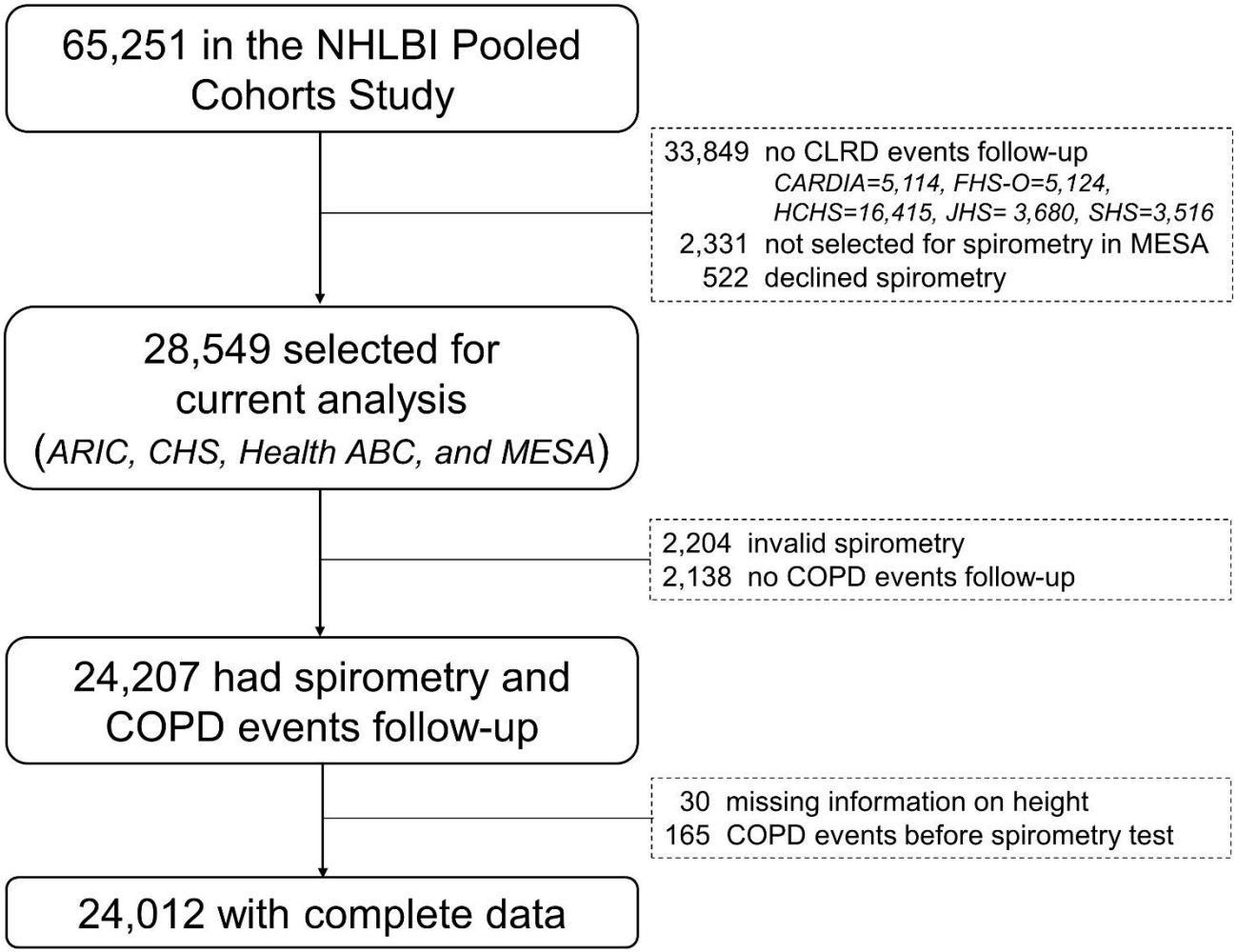
B_{OPT} = Brier Score for the optimal fixed threshold; $B_{0.7}$ = Brier Score for the model using a fixed ratio threshold of 0.70; B_{LLN} = Brier Score for the model using the LLN ratio threshold; IDR = Incidence Density Rate per 1,000 person-years of follow-up; LLN = Lower limit of normal per Global Lung Function Initiative reference equations; n/a = not applicable.

Cox proportional hazards models were used. The primary outcome was defined as first hospitalization or death adjudicated as primarily or secondarily attributable to COPD or, if adjudication was lacking, those with COPD listed in any diagnosis field. In sensitivity analyses, the primary outcome was decomposed into COPD-related hospitalizations and COPD-related mortality. As another sensitivity analysis, the endpoint was restricted to incident hospitalizations and mortality adjudicated or coded as having COPD as the primary/underlying cause. Each fixed-threshold definition for airflow obstruction was added separately to a base model adjusted for age at enrollment, sex, race, height, birth-year, site and cohort.

[a]The optimal fixed threshold was defined as the one that generated the highest Harrell's c-statistic.

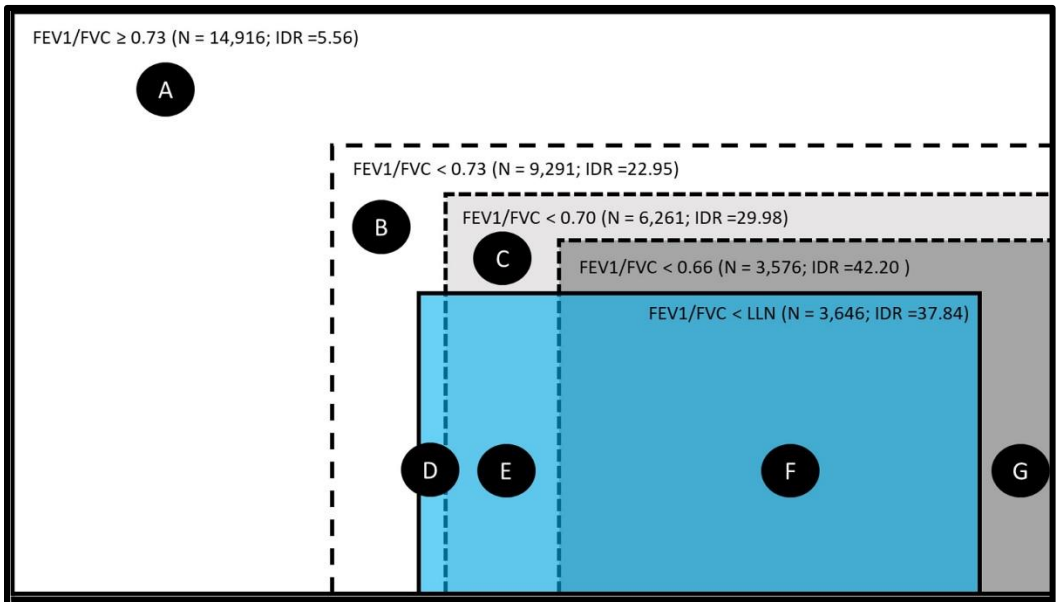
[b]The optimal fixed threshold was 0.70, hence $B_{OPT} = B_{0.7}$.

eFigure 1. CONSORT



ARIC = Atherosclerosis Risk in Communities Study; CARDIA = Coronary artery Risk Development in Young Adults Study; CHS = Cardiovascular Health Study; HABC = Health Aging and Body Composition; FHS-O – Framingham Heart Study- Offspring cohort; HCHS = Hispanic Community Health Study; JHS = Jackson Heart Study; MESA = Multi-Ethnic Study of Atherosclerosis; SHS = Strong Heart Study.

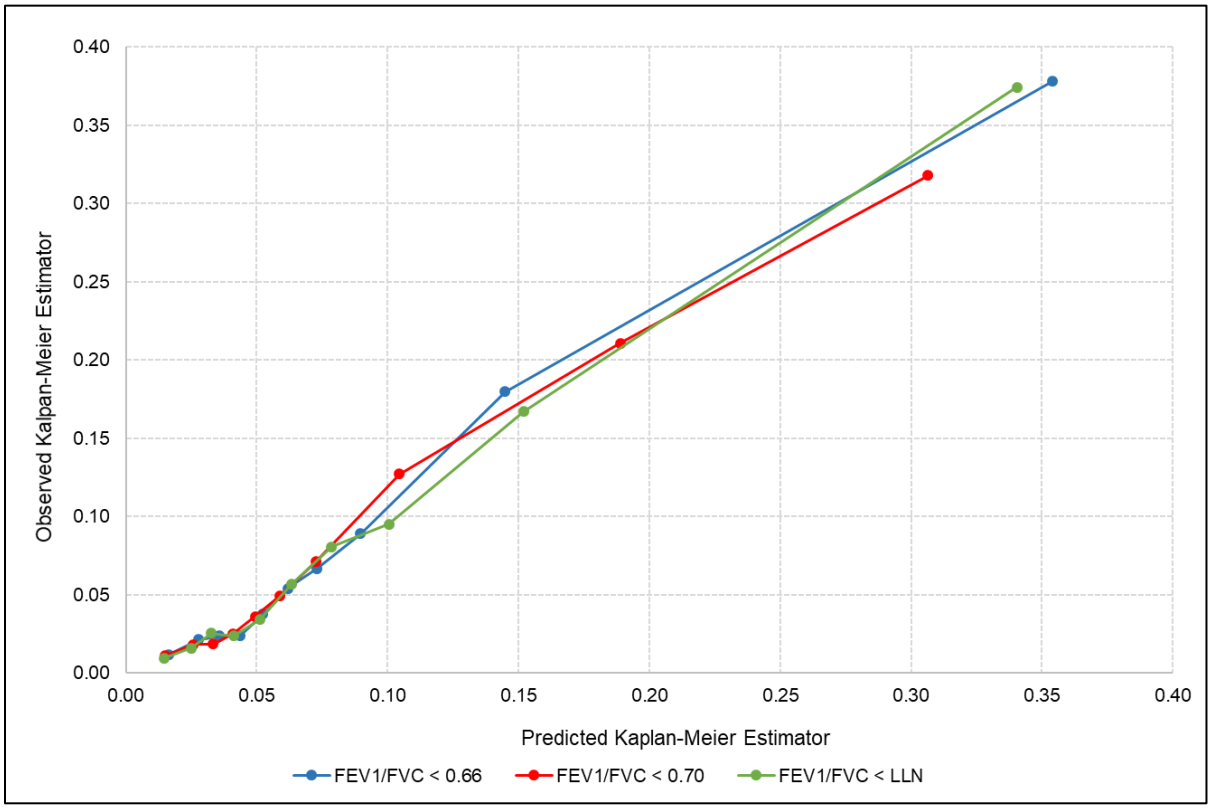
eFigure 2. Venn diagram showing the extent of overlap for several different FEV_1/FVC threshold groups and, for each group, the incidence density rates (IDRs) per 1,000 person-years for COPD-related hospitalization and mortality.



	FEV1/FVC	N	IDR/1,000 person-years
A	≥ 0.73	14,916	5.56
B	< 0.73; ≥ 0.70; ≥ LLN	3,011	11.08
C	< 0.70; ≥ 0.66; ≥ LLN	2,094	16.91
D	≥ 0.70; < LLN	19	19.43
E	< 0.70; ≥ 0.66; < LLN	591	17.16
F	< 0.66; < LLN	3,036	44.00
G	< 0.66; ≥ LLN	540	30.22
C + G	< 0.70; ≥ LLN	2,634	19.03

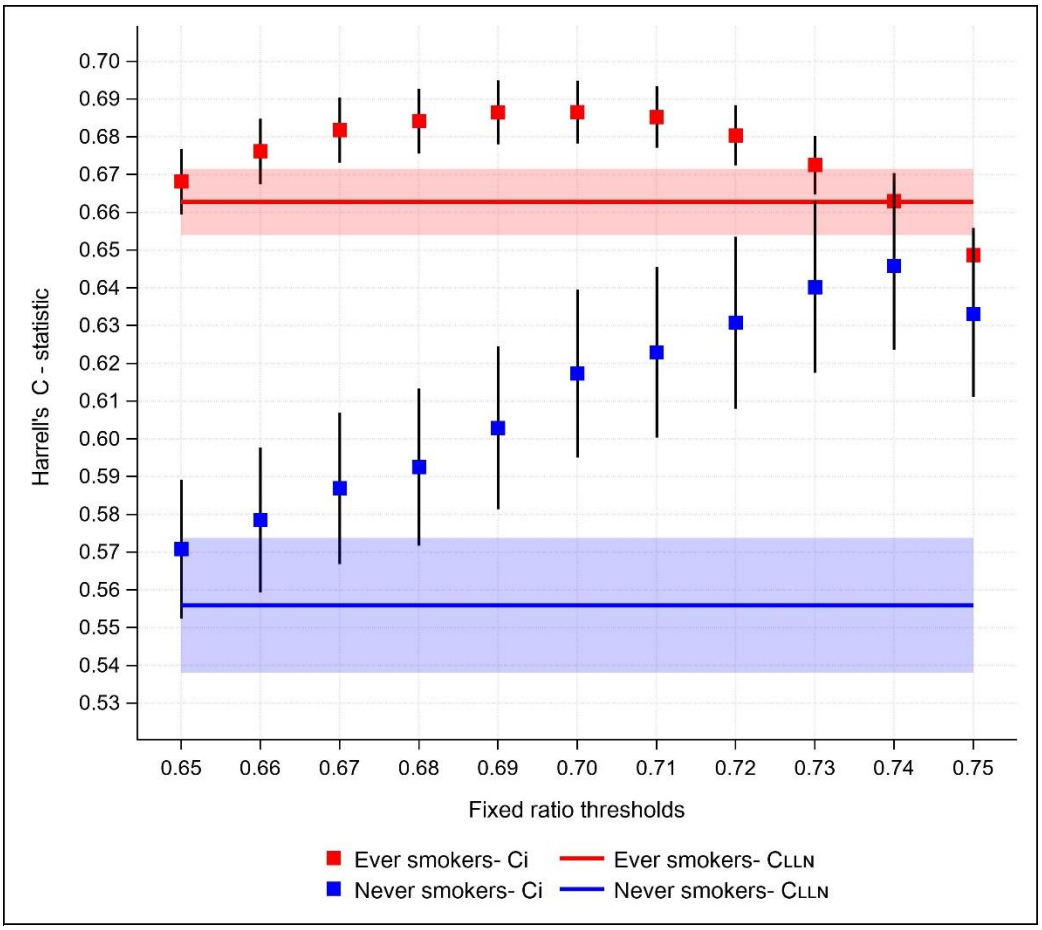
LLN = Lower limit of normal per Global Lung Function Initiative reference equations.

eFigure 3. Calibration plot comparing predicted and observed 10-year risk for COPD-related events, by various FEV_1/FVC stratum for airflow limitation, in covariate-adjusted models.



The 10-year risk for COPD-related events was estimated using Cox proportional hazards models. The models for $FEV_1/FVC < 0.70$ and $FEV_1/FVC < 0.66$ were adjusted for age at enrollment, sex, race/ethnicity, height, birth-year, site and cohort, while the model for LLN was adjusted only for birth-year, site and cohort.

eFigure 4. Discriminative accuracy of various fixed FEV_1/FVC thresholds for airflow obstruction with respect to COPD-related hospitalization and mortality, stratified by smoking status.



Optimal threshold based on highest C-statistic: ever smokers = 0.70; never smokers = 0.74

In ever smokers, $C_{0.65}$, $C_{0.66}$, $C_{0.72}$, $C_{0.73}$, $C_{0.74}$, and $C_{0.75}$ were significantly different than $C_{0.7;}$ and all fixed-thresholds except for $C_{0.74}$ were significantly different than C_{LLN} (p-values < 0.05).

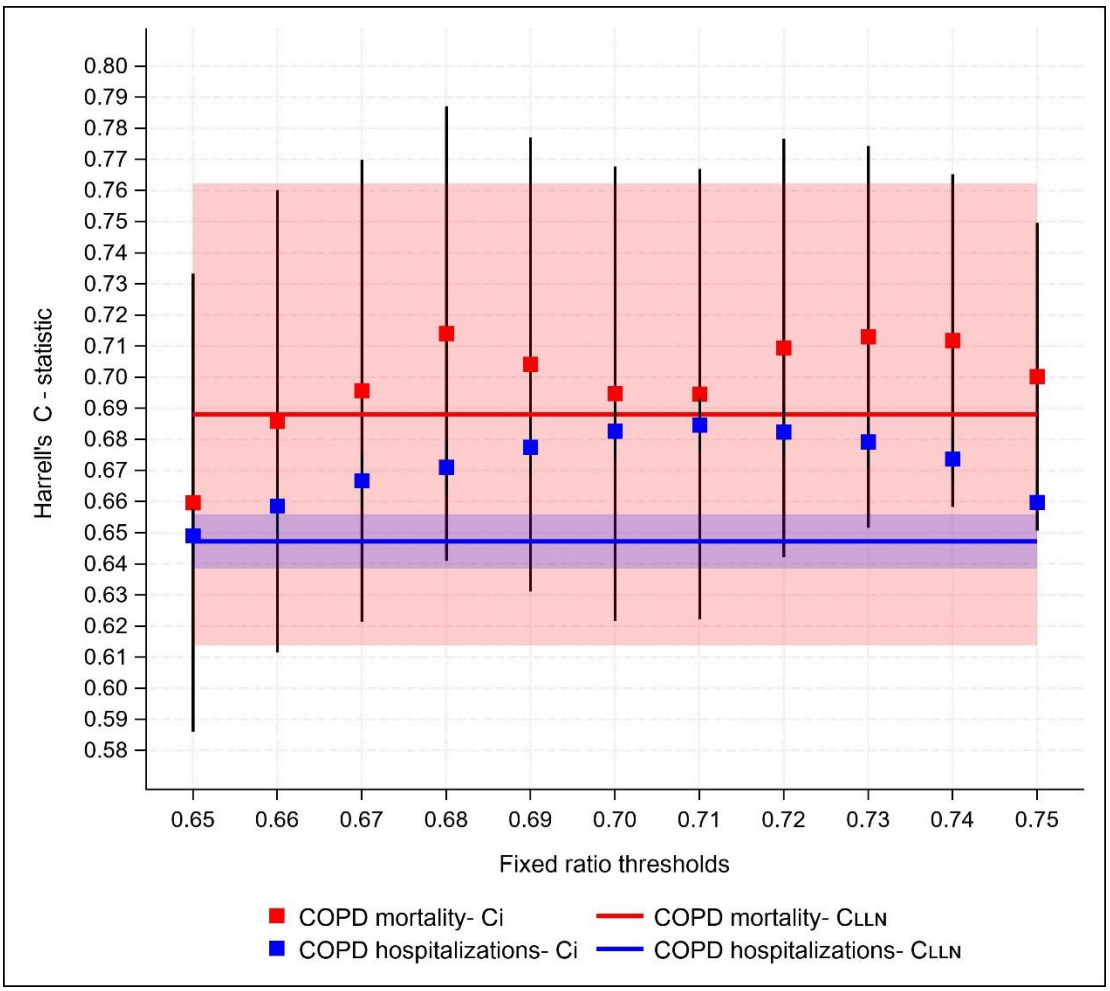
In never smokers, all fixed-thresholds except for $C_{0.71,}$ $C_{0.72}$, and $C_{0.75}$ were significantly different than $C_{0.7;}$ and all fixed-thresholds were significantly different than C_{LLN} (p-values < 0.05).

C_i = c-statistic for fixed threshold models. C_{LLN} = c-statistic for the LLN threshold. CI = confidence interval; LLN = Lower limit of normal per Global Lung Function Initiative reference equations.

Solid lines indicate c-statistic for LLN definitions with 95% CI. Color filled squares indicate point estimates with 95% CI for c-statistic for fixed FEV_1/FVC ratio thresholds.

A Cox proportional hazards model was used to generate the c-statistics in the figure each fixed-threshold definition for airflow limitation. Harrell's c-statistics were compared between each fixed-threshold and the c-statistic for ratio-threshold of 0.70 and LLN. Formal statistical comparisons of c-statistics were performed using a nonparametric approach to compare two correlated c-statistics with right-censored survival outcomes.

eFigure 5. Discriminative accuracy of various fixed FEV_1/FVC thresholds for airflow obstruction with respect to COPD-related hospitalization versus COPD-related mortality.



Optimal threshold based on highest C-statistic: COPD mortality = 0.68; COPD hospitalizations = 0.71

For COPD mortality, all fixed threshold except for $C_{0.65}$, $C_{0.66}$, $C_{0.67}$, and $C_{0.72}$ were significantly different than $C_{0.7}$ and; all fixed threshold except for $C_{0.70}$, $C_{0.71}$, $C_{0.72}$, and $C_{0.73}$ were significantly different than C_{LLN} (p-values < 0.05).

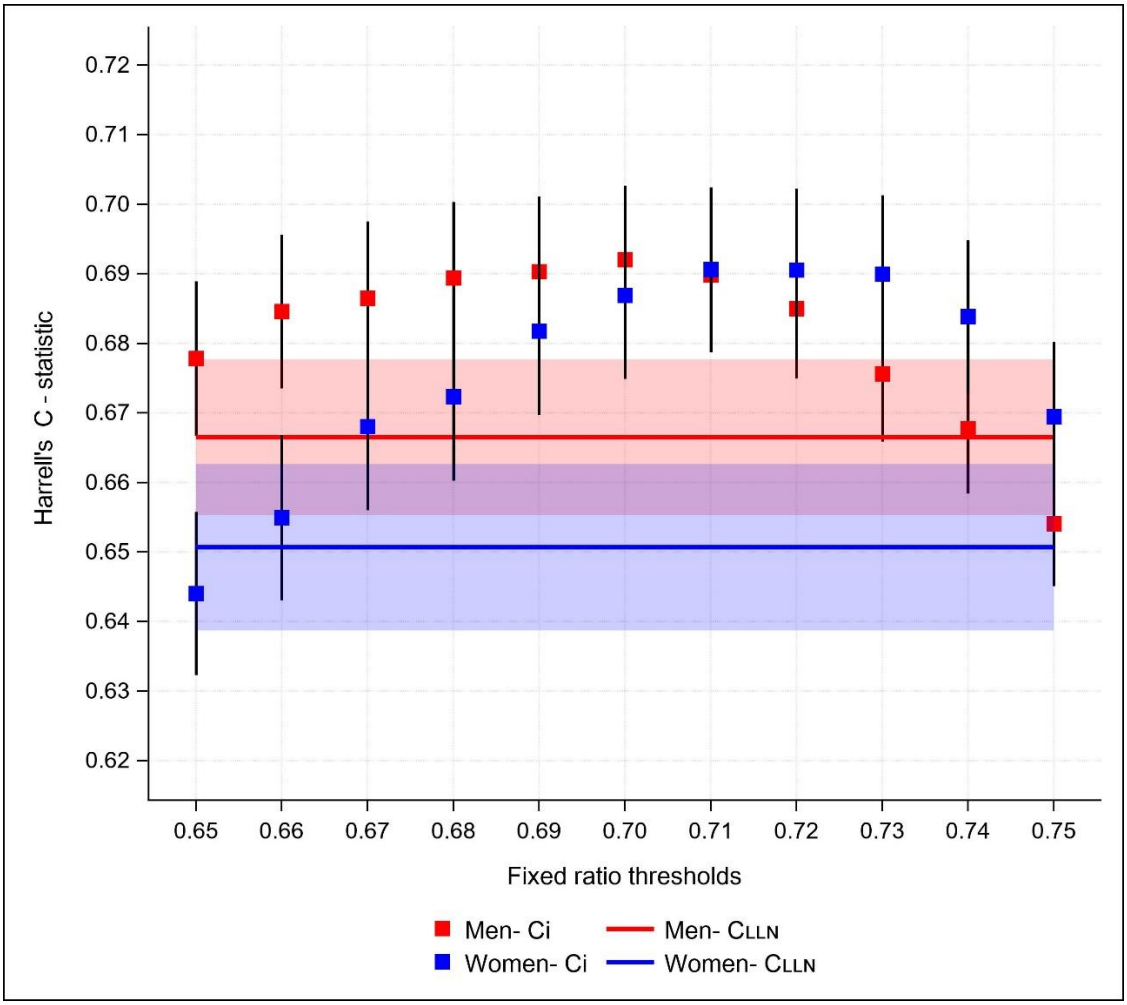
For COPD hospitalizations, all fixed threshold except for $C_{0.71}$, $C_{0.72}$, and $C_{0.73}$ were significantly different than $C_{0.7}$; and all fixed threshold except for $C_{0.65}$ were significantly different than C_{LLN} (p-values < 0.05).

C_i = c-statistic for fixed threshold models. C_{LLN} = c-statistic for the LLN threshold. CI = confidence interval; LLN = Lower limit of normal per Global Lung Function Initiative reference equations.

Solid lines indicate c-statistic for LLN definitions with 95% CI. Color filled squares indicate point estimates with 95% CI for c-statistic for fixed FEV_1/FVC ratio thresholds.

A Cox proportional hazards model was used to generate the c-statistics in the figure each fixed-threshold definition for airflow limitation. Harrell's c-statistics were compared between each fixed-threshold and the c-statistic for ratio-threshold of 0.70 and LLN. Formal statistical comparisons of c-statistics were performed using a nonparametric approach to compare two correlated c-statistics with right-censored survival outcomes.

eFigure 6. Discriminative accuracy of various fixed FEV_1/FVC thresholds for airflow obstruction with respect to COPD-related hospitalization and mortality, stratified by sex.



Optimal threshold based on highest C-statistic: men= 0.70; women = 0.71

In men, $C_{0.65}$, $C_{0.72}$, $C_{0.73}$, $C_{0.74}$ and $C_{0.75}$ were significantly different than $C_{0.7}$; all fixed-thresholds except for $C_{0.73}$ and $C_{0.74}$ were significantly different than C_{LLN} (p-values < 0.05).

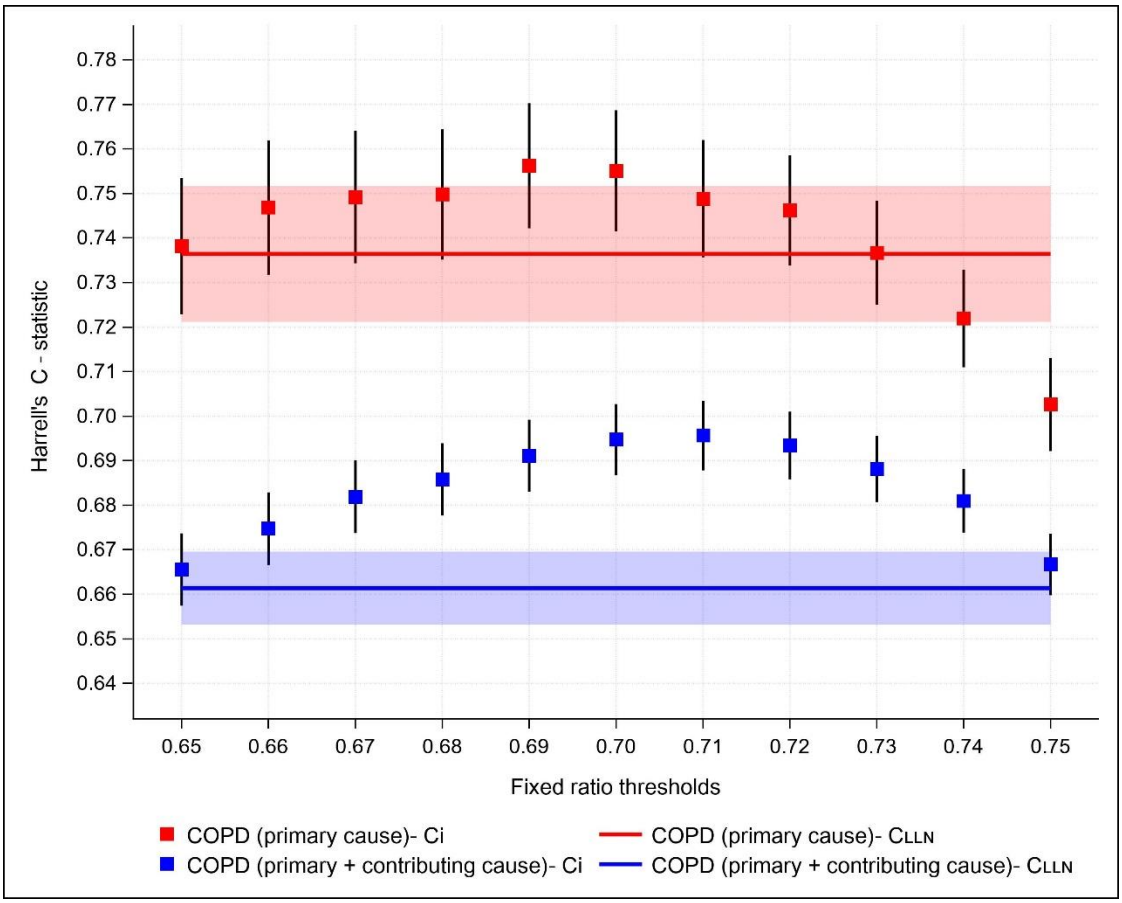
In women, all ratio thresholds except for $C_{0.70}$, $C_{0.72}$, $C_{0.73}$, and $C_{0.74}$ were significantly different than $C_{0.7;}$ and all ratio thresholds except for $C_{0.66}$ were significantly different than C_{LLN} (p-values < 0.05).

C_i = c-statistic for fixed threshold models. C_{LLN} = c-statistic for the LLN threshold. CI = confidence interval; LLN = Lower limit of normal per Global Lung Function Initiative reference equations.

Solid lines indicate c-statistic for LLN definitions with 95% CI. Color filled squares indicate point estimates with 95% CI for c-statistic for fixed FEV_1/FVC ratio thresholds.

A Cox proportional hazards model was used to generate the c-statistics in the figure each fixed-threshold definition for airflow limitation. Harrell's c-statistics were compared between each fixed-threshold and the c-statistic for ratio-threshold of 0.70 and LLN. Formal statistical comparisons of c-statistics were performed using a nonparametric approach to compare two correlated c-statistics with right-censored survival outcomes.

eFigure 7. Discriminative accuracy of various fixed FEV_1/FVC thresholds for airflow obstruction with respect to events classified as primarily caused by COPD versus the primary endpoint.



Optimal threshold based on highest C-statistic: COPD (primary cause) = 0.69; COPD (primary + contributing cause) = 0.71

For COPD (primary cause), all fixed threshold except for $C_{0.66}$, $C_{0.67}$, $C_{0.68}$, and $C_{0.69}$ were significantly different than $C_{0.7;}$ and all fixed threshold except for $C_{0.65}$, $C_{0.72}$, and $C_{0.73}$ were significantly different than C_{LLN} (p-values < 0.05).

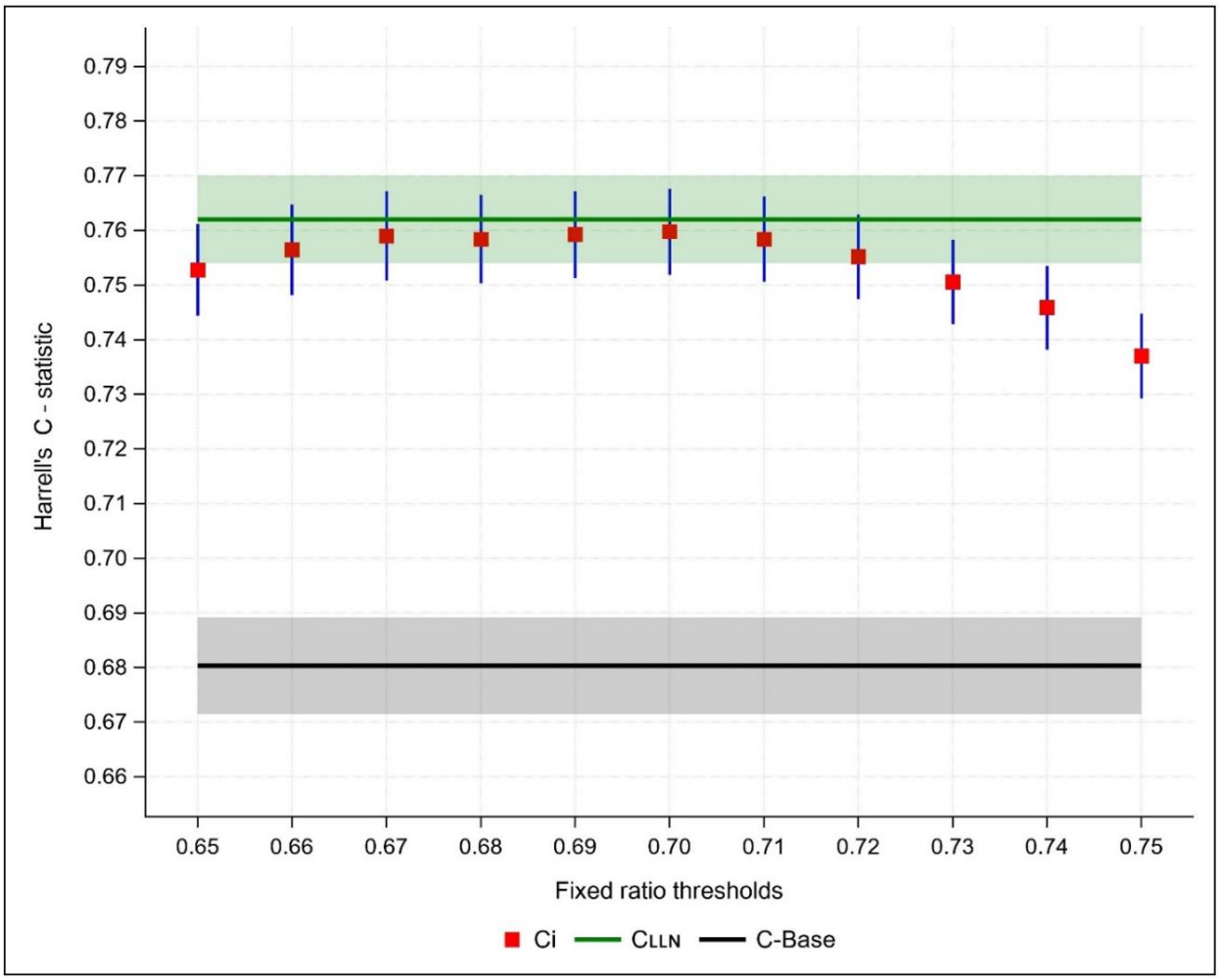
For COPD (primary + contributing cause), all fixed threshold except for $C_{0.70}$ and $C_{0.72}$ were significantly different than $C_{0.7}$; and all fixed threshold except for $C_{0.65}$ and $C_{0.75}$ were significantly different than C_{LLN} (p-values < 0.05).

C_i = c-statistic for fixed threshold models. C_{LLN} = c-statistic for the LLN threshold. CI = confidence interval; LLN = Lower limit of normal per Global Lung Function Initiative reference equations.

Solid lines indicate c-statistic for LLN definitions with 95% CI. Color filled squares indicate point estimates with 95% CI for c-statistic for fixed FEV_1/FVC ratio thresholds.

A Cox proportional hazards model was used to generate the c-statistics in the figure each fixed-threshold definition for airflow limitation. Harrell's c-statistics were compared between each fixed-threshold and the c-statistic for ratio-threshold of 0.7 and LLN. Formal statistical comparisons of c-statistics were performed using a nonparametric approach to compare two correlated c-statistics with right-censored survival outcomes.

eFigure 8. Incremental discriminative accuracy of various fixed FEV_1/FVC thresholds for airflow obstruction with respect to COPD-related hospitalization and mortality, when added to a model adjusted for socio-demographic factors and smoking status.



Optimal threshold based on highest C-statistic: adjusted model = 0.70; unadjusted model = 0.71

In adjusted models, all fixed threshold except for $C_{0.66}$, $C_{0.67}$, $C_{0.68}$, $C_{0.69}$, and $C_{0.71}$ were significantly different than $C_{0.7}$, all fixed threshold except for $C_{0.67}$, $C_{0.69}$, $C_{0.70}$, and $C_{0.71}$ were significantly different than C_{LLN}.

In unadjusted models, all fixed threshold except for C0.70 and C0.72 were significantly different than C0.7 and; all fixed threshold except for C0.65 and C0.75 were significantly different than C_{LLN} (p-values < 0.05).

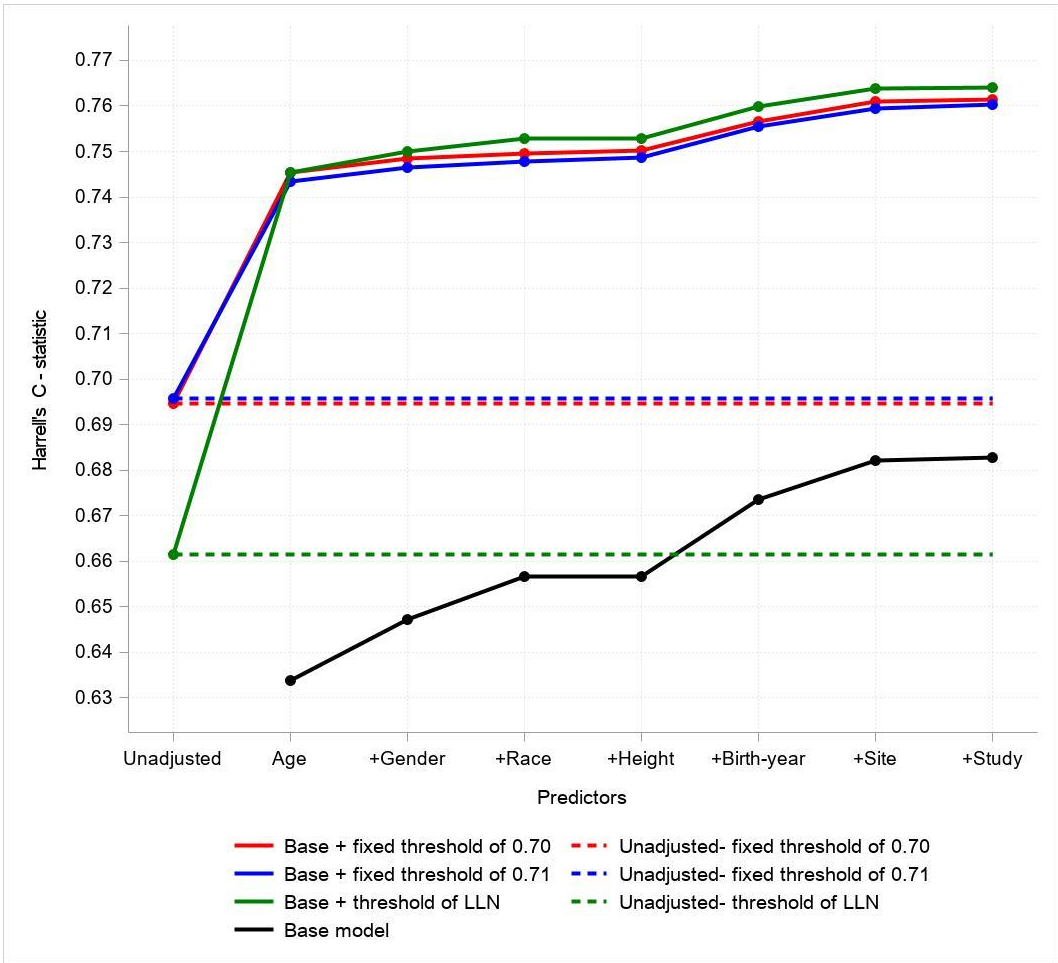
C_i = c-statistic for fixed threshold models. C_{LLN} = c-statistic for the LLN threshold. CI = confidence interval; LLN = Lower limit of normal per Global Lung Function Initiative reference equations.

Solid lines indicate c-statistic for LLN definitions with 95% CI. Color filled square indicates point estimates with 95% CI for c-statistic for fixed FEV_1/FVC ratio thresholds.

A Cox proportional hazards model was used to generate the c-statistics from the unadjusted model for each fixed-threshold definition for airflow limitation. For the adjusted model, each fixed-threshold definition for airflow obstruction was added separately to a base model, which was a Cox proportional hazards model adjusted for age at

enrollment, sex, race, height, birth-year, site and cohort. The LLN definition was added separately to a base model excluding the components of the reference equation (age, sex, race/ethnicity, and height). Harrell's c-statistics were compared between each fixed-threshold and the c-statistic for ratio-threshold of 0.70 and LLN. Formal statistical comparisons of c-statistics were performed using a nonparametric approach to compare two correlated c-statistics with right-censored survival outcomes.

eFigure 9. Incremental discrimination with sequential covariate adjustment to the fixed FEV_1/FVC thresholds for airflow obstruction with respect to COPD-related hospitalization and mortality



The Cox proportional hazards model was used to generate c-statistic for the base model including age as only predictor. Next, other predictors were sequentially added to the base model. The resultant C-statistics for the sequentially adjusted base models are shown by the solid black line).

Ratio thresholds were added to each of the sequentially-adjusted base models. The resultant C-statistics are shown for $FEV_1/FVC < 0.70$ (solid red line), $FEV_1/FVC < 0.71$ (solid blue line), and $FEV_1/FVC <$ LLN (solid green line). The distance between the solid black line and the solid colored lines reflects the incremental discrimination provided by the ratio thresholds.

For comparison, the C-statistics provided by the ratio thresholds without any covariate adjustment are shown for $FEV_1/FVC < 0.70$ (dashed red line), $FEV_1/FVC < 0.71$(dashed blue line), and $FEV_1/FVC <$ LLN (dashed green line).

LLN = Lower limit of normal per Global Lung Function Initiative reference equations.