Supplementary Appendix

S Zeng, A Tham, B Bos, J Jin, B Giang, M Arjomandi. Lung Volume Indices Predict Morbidity in Smokers with Preserved Spirometry.

1. Author Contributions

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Authors' Contributions

Conceived and designed the study: MA.

Developed study protocols: MA, BB, SZ.

Collected data: SZ, BB, BG, JJ, MA.

Analyzed and interpreted data: SZ, MA, AT, BB, JJ.

Prepared the manuscript: MA, AT, SZ, BB, JJ.

Obtained funding: MA, BB.

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Conflict of Interests

Authors disclose no financial conflict of interest.

3. Detailed Inclusion and Exclusion Criteria

Inclusion criteria

Patients eligible for analyses in the study met all the following criteria:

1. Had done at least one full pulmonary function tests with measurement of pre- and post-bronchodilator spirometry (FEV_1 and FVC), and plethysmographic measurement of lung volumes (RV and TLC).
2. 40 years of age or older at the time of the index (earliest) full PFT.
3. Have ever had a clinical diagnosis of smoking tobacco or documented to be a smoker on their index full PFT.

Exclusion criteria

Patients meeting any of the following criteria were not included in the analyses:

1. Restrictive lung diseases: TLC <lower limit of normal (LLN) or TLC <80% predicted.
2. Interstitial lung diseases: ILD or Cystic Fibrosis (by ICD codes provided below).
3. Allergic lung diseases: AERD or ABPA (by ICD codes provided below).
4. Lung cancers: (by ICD codes provided below).
5. Did not have preserved spirometry at index PFT: post-bronchodilator FEV_1/FVC <LLN or post-bronchodilator FEV_1 <LLN.

ICD codes used[1]

Diagnosis of COPD

- Chronic obstructive Lung Disease: ICD9: 496
- Chronic bronchitis: ICD9: 491.xx
- Pulmonary emphysema: ICD9: 492.x
- Chronic bullous emphysema: ICD9: 429.0
- COPD: ICD10: J44.0, J44.1and J44.9
- Chronic bronchitis: ICD10: J41.0, J41.1 and J41.8
- Pulmonary emphysema: ICD10: J43.0, J43.1, J43.2, J43.8 and J43.9

Diagnosis of tobacco smoking or tobacco use

- Tobacco use disorder: ICD-9 305.1
- History of tobacco use: ICD-9 V15.82
- Tobacco: ICD-9 989.84
- Smoking cessation counseling: ICD-9 V65.42
- Tobacco Use: ICD-10 Z72.0
- Tobacco Abuse Counseling: ICD-10 Z71.6
- Nicotine dependence, cigarettes: ICD-10 F17.21
- Nicotine dependence, other tobacco product: ICD-10 F17.29
- Nicotine dependence, unspecified: ICD-10 F17.20

- Personal History of Nicotine Dependence: ICD-10 Z87.891

Diagnosis of asthma

- Asthma: ICD9: 493.xx (493.1 was excluded)
- Bronchospasm: ICD9: 519.11
- Asthma: ICD10: J45.909, J45.998
- Unspecified asthma: ICD10: J45.90
- Cough variant asthma: ICD10: J45.991
- Acute bronchospasm: ICD10: J98.01
- Moderate persistent asthma, uncomplicated: ICD10: J45.40
- Mild intermittent asthma with status asthmaticus: ICD10: J45.22
- Mild intermittent asthma, uncomplicated: ICD10: J45.20
- Unspecified asthma with status asthmaticus: ICD10: J45.902
- Unspecified asthma with (acute) exacerbation: ICD10: J45.901

Diagnosis of ILD

- ILD: ICD9: 518.89, 508.1, 714.81, 770.7
- Hypersensitivity pneumonitis: ICD9: 495
- Silicosis: ICD9: 502
- Asbestosis: ICD9: 501
- Berylliosis: ICD9: 503
- Sarcoidosis: ICD9: 135
- Acute interstitial pneumonitis: ICD9: 516.3
- Hamman-Rich Syndrome: ICD9: 516.3
- Post Inflammatory Pulmonary Fibrosis: ICD9: 515
- ILD: ICD10: J84.9
- Pneumoconiosis due to other dust containing silica: ICD10: J62.8
- Pneumoconiosis due to asbestos and other mineral fibers: ICD10: J61
- Berylliosis: ICD10: J63.2
- Sarcoidosis, unspecified: ICD10: D86.9
- Pulmonary fibrosis, unspecified: ICD10: J84.10
- Other specified interstitial pulmonary diseases: ICD10: J84.89
- Interstitial emphysema: ICD10: J98.2
- Respiratory bronchiolitis interstitial lung disease: ICD10: J84.848; J84.115
- Other interstitial pulmonary diseases with fibrosis in diseases classified elsewhere: ICD10: J84.17
- Acute interstitial pneumonitis: ICD10: J84.114
- Idiopathic pulmonary fibrosis: ICD10: J84.112

Diagnosis of AERD

- Samter's triad, Exacerbated Respiratory disease, Samter's Syndrome: ICD9: 493.1
- Other specified respiratory disorders: ICD10: J98.8

Diagnosis of ABPA

- Allergic bronchopulmonary aspergillosis: ICD9: 518.6
- Allergic bronchopulmonary aspergillosis: ICD10: B44.81

Cystic fibrosis

- ICD9: 277.0
- Cystic fibrosis: ICD10: E84
- Congenital cystic lung: ICD10: Q33.0

Diagnosis of Lung Cancer

- Lung cancer: ICD9: 162, 162.2, 162.3, 162.4, 162.5, 162.8, 162.9
- Lung cancer: ICD10: C34.00, C34.10, C34.20, C34.30, C34.80, C34.90
- Malignant neoplasm of pleura: ICD9: 163
- Malignant neoplasm of pleura: ICD10: C38.4

4. VA Sites From Where PFT Data Were Available

	(VA Station Number) VA Site Name	No. of Patients with Records	Percentage w Abnormal RV/TLC
1	(402) Togus, ME	2	0%
2	(405) White River Junction, VT	20	25%
3	(437) Fargo, ND (CACHE 5.0)	120	34%
4	(438) Sioux Falls, SD (CACHE 5.0)	103	37%
5	(460) Wilmington, DE *	4	100%
6	(501) New Mexico HCS (Albuquerque, NM)	816	42%
7	(503) Altoona, PA	45	29%
8	(528) Upstate New York, HCS	213	40%
9	(539) Cincinnati, OH	93	6%
10	(544) Columbia, SC	2	0%
11	(550) Illiana HCS (Danville, IL) *	40	60%
12	(552) Dayton, OH	500	46%
13	(556) North Chicago, IL	341	18%
14	(561) New Jersey HCS (East Orange, NJ)	311	21%
15	(581) Huntington, WV	231	28%
16	(586) Jackson, MS	81	16%
17	(589) VA Heartland West (Kansas City, MO)	100	34%
18	(590) Hampton, VA	115	31%
19	(593) Southern Nevada HCS (Las Vegas, NV)	212	24%
20	(596) Lexington, KY	6	17%
21	(600) Long Beach HCS (Long Beach, CA)	118	20%
22	(612) Northern California HCS (Martinez, CA) *	1	100%
23	(613) Martinsburg, WV	8	25%
24	(626) Tennessee Valley HCS (Nashville, TN)	199	31%
25	(630) New York HHS (Brooklyn, NJ)	263	25%
26	(636) Central Plains HCS (Omaha NE)	127	24%
27	(640) Palo Alto HCS (Palo Alto, CA)	407	29%
28	(653) Roseburg HCS (Roseburg, OR)	15	47%
29	(654) Sierra Nevada HCS (Reno, NV)	121	28%
30	(657) VA Heartland East (Saint Louis, MO)	768	34%
31	(660) Salt Lake City HCS (Salt Lake City, UT)	4	0%
32	(663) Puget Sound HCS (Seattle, WA) (CACHE 5.0)	1,139	35%
33	(664) San Diego HCS (San Diego, CA)	185	16%
34	(673) Tampa, FL	167	28%
35	(678) Southern Arizona HCS (Tucson, AZ)	2	0%
36	(688) Washington, DC	27	7%

37	(691) Greater Los Angeles HCS (Los Angeles, CA)	573	18%
	Total	7,479	31%

Data from other Veterans Affairs Medical Centers were not used due to lack of availability of coded PFT data that would be obtainable through VINCI. Proportion of patients who had abnormal RV/TLC passed Shapiro-wilk normality test after removing statistics from three outlier sites, denoted with*.

5. Supplemental Tables

Table S1- Characteristics of Patients with Preserved Spirometry and Normal RV/TLC.

Characteristics	Patients with Normal RV/TLC	Patients with Low-normal RV/TLC	Patients with High-normal RV/TLC	Difference (CI 95%)	p-value
Demographics					
N	5,179	2,586	2,593	--	--
Age (years)	60.8±10.7	56.0±9.2	65.6±10.0	-9.5 (-10.1, -9.0)	<**0.001**
Sex [Female n (%)]	477 (9.2%)	157 (6.1%)	320 (12.3%)	-6.3% (-7.8, -4.7)	<**0.001**
Height (cm)	174.9±7.8	176.0±7.5	173.8±8.0	2.2 (1.8, 2.6)	<**0.001**
BMI (kg/m^2)	29.5±5.7	29.5±5.7	29.5±5.7	-0.05 (-0.36, 0.26)	0.763
Years of Follow-up	8.5±4.7	8.7±4.8	8.2±4.7	0.48 (0.22, 0.74)	<**0.001**
Airflow Indices					
FEV_1 (L)	3.18±0.59	3.43±0.55	2.93±0.53	0.50 (0.47, 0.53)	<**0.001**
FEV_1 (% predicted)	90±10	93±10	88±9	5.0 (4.5, 5.5)	<**0.001**
FVC (L)	4.12±0.77	4.41±0.72	3.83±0.71	0.58 (0.54, 0.62)	<**0.001**
FVC (% predicted)	92±11	95±11	89±10	5.13 (4.56, 5.71)	<**0.001**
FEV_1/FVC [%]	77.2±4.9	77.9±4.8	76.6±4.9	1.3 (1.1, 1.6)	<**0.001**
FEV_1/FVC (% predicted)	98.5±6	98.6±5.8	98.5±5.9	0.1 (-0.2, 0.4)	0.555
FEF_{25-75} (L)	2.93±0.97	3.21±0.94	2.65±0.92	0.56 (0.51, 0.61)	<**0.001**
FEF_{25-75} (% predicted)	88±25	90±24	85±26	5.1 (3.7, 6.4)	<**0.001**
Reversibility in FEV_1 (mL)	167.3±191.7	167.6±201.9	167.0±181.0	0.5 (-9.9, 11.0)	0.919
Reversibility in FEV_1 (%)	6±7	5±7	6±8	-1.0 (-1.4, -0.6)	<**0.001**
Reversibility [n (%)]	1,929 (37.3%)	986 (38.1%)	943 (36.4%)	1.8% (-0.9, 4.4)	0.189
Lung Volume Indices					
TLC (L)	6.46±1.01	6.49±0.96	6.43±1.05	0.06 (0.01, 0.12)	**0.026**
TLC (% predicted)	96±11	95±10	97±11	-1.8 (-2.4, -1.2)	<**0.001**
RV (L)	2.29±0.51	2.00±0.40	2.58±0.43	-0.58 (-0.60, -0.56)	<**0.001**
RV (% predicted)	104±20	94±18	113±16	-19 (-20, -18)	<**0.001**
FRC (L)	3.34±0.77	3.21±0.77	3.48±0.75	-0.27 (-0.32, -0.23)	<**0.001**

FRC (% predicted)	96±19	92±20	100±18	-8 (-9, -7)	<**0.001**
FRC/TLC (%)	52±9	50±9	54±8	-4.7 (-5.2, -4.2)	<**0.001**
FRC/TLC (% predicted)	92±15	89±16	95±13	-5.3 (-6.1, -4.4)	<**0.001**
RV/TLC (%)	35±6	31±4	40±3	-9.4 (-9.6, -9.2)	<**0.001**
RV/TLC (% predicted)	106±14	98±13	115±8	-17.4 (-17.9, -16.8)	<**0.001**
IC (L)	3.11±0.73	3.26±0.73	2.95±0.70	0.32 (0.27, 0.36)	<**0.001**
IC (% predicted)	74±15	74±15	74±15	-0.4 (-1.3, 0.5)	0.355
IC/TLC (%)	48±9	51±9	46±8	4.7 (4.2, 5.2)	<**0.001**
IC/TLC (% predicted)	96±21	94±19	99±22	-5.2 (-6.4, -4.0)	<**0.001**
Follow-up Spirometry §					
No. With Follow-up Spirometry (n[%])	1,124 (21.7%)	528 (20.4%)	596 (23.0%)	-2.6% (-4.8, -0.3)	**0.025**
Age at Follow-up Spirometry (years)	64.7±10.3	60.2±9.3	68.6±9.6	-8.4 (-9.5, -7.3)	<**0.001**
Height at Follow-up Spirometry (cm)	174.9±8.1	175.9±7.7	173.9±8.3	2.0 (1.0, 2.9)	<**0.001**
Years from Index PFT to Follow-up Spirometry	3.8±2.9	3.8±2.9	3.7±2.9	0.1 (-0.3, 0.4)	0.611
FEV_1 (L)	2.77±0.65	2.99±0.64	2.59±0.60	0.40 (0.33, 0.48)	<**0.001**
FEV_1 (% predicted)	81±15	83±15	80±15	3.9 (2.1, 5.6)	<**0.001**
FVC (L)	3.75±0.86	4.01±0.82	3.52±0.82	0.49 (0.39, 0.58)	<**0.001**
FVC (% predicted)	86±15	88±15	84±15	4.3 (2.6, 6.1)	<**0.001**
FEV_1/FVC [%]	74±8	75±8	74±8	1.0 (0.1, 1.9)	**0.036**
FEV_1/FVC (% predicted)	95±10	95±10	96±10	-0.2 (-1.3, 1.0)	0.756
FEF_{25-75} (L)	2.38±1.00	2.61±1.03	2.17±0.93	0.44 (0.32, 0.55)	<**0.001**
FEF_{25-75} (% predicted)	75±29	77±29	73±29	4.0 (0.6, 7.5)	**0.022**
FEV_1 Decline (mL/year)	115±225	122±251	108±200	14 (-12, 41)	0.285
FEV_1 Decline (% predicted/year)	2.72±6.52	2.82±6.97	2.63±6.09	0.19 (-0.57, 0.96)	0.617
FVC Decline (mL/year)	104±250	114±258	95±242	19 (-10, 49)	0.193
FVC Decline (% predicted/year)	1.91±5.93	2.08±6.05	1.77±5.82	0.31 (-0.39, 1.00)	0.384
FEV_1/FVC Decline	0.87±3.07	0.81±3.30	0.92±2.86	-0.11 (-0.47, 0.25)	0.554

(%/year)					
FEV_1/FVC Decline (% predicted/year)	0.95±3.99	0.87±4.26	1.03±3.73	-0.16 (-0.63, 0.31)	0.498
FEF_{25-75} Decline (mL/year)	157±420	150±482	163±357	-13 (-62, 37)	0.610
FEF_{25-75} Decline (% predicted/year)	3.94±12.52	3.54±13.52	4.29±11.56	-0.75 (-2.23, 0.72)	0.317

Footnote: Demographics and lung function in patients with preserved spirometry and normal RV/TLC. The cohort was further stratified into patients with normal and low RV/TLC and patients with normal but high RV/TLC per the median of the normal RV/TLC (35.8%). Data are presented as mean ± standard deviation or number of patients with positive value for the variable (n) out of the total number of patients (N) and percentage of patients (%) and difference (95%CI) with p-value for unadjusted comparison between normal and abnormal RV/TLC. § Follow-up spirometry (last available post-bronchodilator spirometry) was available for a subgroup of the patients. Reference equations: Measures of pulmonary function and percent predicted of normal values were calculated using Crapo predicted formulas except for FRC/TLC, IC, and IC/TLC.[2] Quanjer predicted formulas were used for FRC/TLC and IC and Francisco predicted formulas were used for IC/TLC.[3,4] Reversibility defined as ≥12% and ≥200mL increase in FEV_1 after bronchodilator administration. Abbreviations- PFT: pulmonary function test; BMI: body mass index; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; FEF_{25-75}: maximum airflow at mid-lung volume; TLC: total lung capacity; RV: residual volume; FRC: functional residual capacity; IC: inspiratory capacity.

Table S2- Frequency of Patients with Lung Function Outside the Limits of Normal Range or Other Characteristics of Interest.

N=7,479	**Patients with preserved spirometry**
RV/TLC > ULN	2,300 (30.8%)
RV > ULN	1,962 (26.2%)
FRC > ULN	349 (4.7%)
FRC/TLC >ULN	338 (4.5%)
IC <LLN	4,066 (54.4%)
IC/TLC <LLN	1,517 (20.3%)
FVC < LLN	309 (4.1%)
FEF_{25-75} < LLN	87 (1.2%)
BMI > 30	3,093 (41.4%)
Reversibility in FEV_1 [n (%)]	3,050 (40.8%)
Diagnosis of Asthma (Ever)	1,597 (21.4%)
Diagnosis of Asthma (Before Index PFT)	933 (12.5%)

Footnote: Summary on frequency of patients with lung function outside the limits of normal range was shown as number of patients with positive value for the variable (n) and percentage of subjects (%). Reversibility defined as ≥12% and ≥200mL increase in FEV_1 after bronchodilator administration. Abbreviations- ULN: upper limit of normal; LLN: lower limit of normal; RV: residual volume; TLC: total lung capacity; FRC: functional residual capacity; IC: inspiratory capacity; FVC: forced vital capacity; FEF_{25-75}: maximum airflow at mid-lung volume.

Table S3- Association of Healthcare Outcomes and RV/TLC Strata.

	Respiratory-related Health Outcomes							
RV/TLC	**Clinical Diagnosis of COPD**	**Respiratory Medications**	**Office Visits**	**ER Visits**	**Hospital Admissions**	**ICU Admissions**	**Mortality**	**COPD on Follow-up Spirometry §**
	HR	**IRR**	**IRR**	**IRR**	**IRR**	**IRR**	**HR**	**OR-Mixed Eff.**
Multi-Level Comparison Model								
Model r^2	N/A	0.01	0.06	0.02	0.04	0.02	N/A	N/A
Abnormal	**1.81(1.62-2.02) p<0.001**	**1.14(1.12-1.15) p<0.001**	**1.42(1.39-1.45) p<0.001**	**1.17(1.05-1.29) p=0.004**	**1.77(1.64-1.90) p<0.001**	**1.45(1.17-1.79) p=0.001**	**1.58(1.41-1.78) <0.001**	1.26(0.94-1.67) p=0.118
Normal_High	**1.33(1.18-1.49) p<0.001**	**1.04(1.02-1.05) p<0.001**	**1.19(1.17-1.22) p<0.001**	**1.12(1.01-1.24) p=0.031**	**1.34(1.24-1.45) p<0.001**	1.16(0.93-1.45) p=0.190	**1.21(1.08-1.37) p=0.002**	0.93(0.69-1.26) p=0.646
Normal_Low	Ref (1.00)	Ref. (1.00)	Ref. (1.00)	Ref. (1.00)	Ref. (1.00)	Ref. (1.00)	Ref. (1.00)	Ref. (1.00)

Footnote: Association of RV/TLC strata and respiratory-related healthcare outcomes with COPD diagnosis were compared to the reference group (patients with normal and low RV/TLC) with interaction using Cox Proportional Hazards regression for time to outcomes, Poisson regression for counts of outcome, or mixed-effects (Mixed Eff.) logistic regression for binary outcomes with adjustment for age, sex, height, and years of follow-up: Healthcare Outcomes=$\beta_0+\beta_1$(age)+β_2(sex)+β_3(height)+β_4(years of follow-up)+i.β_*(RV/TLC strata). The models coefficients of determination (r^2), Hazard Ratio (HR), Incident Rate Ratio (IRR), and Odds Ratio (OR) with 95% confidence interval and p-value of the predictors are shown in the table. Significant associations are shown in bold. N =7,479 unless noted otherwise. **§** Follow-up spirometry (last available post-bronchodilator spirometry) was available for a subgroup of the patients, N =1,706, models were adjusted for time from index PFT to such follow-up spirometry instead of years of follow-up. Abbreviations- TLC: total lung capacity; RV: residual volume; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; FEF_{25-75}: maximum airflow at mid-lung volume.

Table S4- Association of RV/TLC and Health Outcomes in Subjects with Normal RV/TLC.

	Respiratory-related Health Outcomes							
RV/TLC	**Clinical Diagnosis of COPD**	**Respiratory Medications**	**Office Visits**	**ER Visits**	**Hospital Admissions**	**ICU Admissions**	**Mortality**	**COPD on Follow-up Spirometry §**
	HR	**IRR**	**IRR**	**IRR**	**IRR**	**IRR**	**HR**	**OR-Mixed Eff.**
Binary Single-Lung Function Model								
Model r^2	N/A	0.01	0.06	0.03	0.03	0.01	N/A	N/A
High vs Low	**1.35 (1.20-1.53) p<0.001**	**1.03 (1.01-1.05) p=0.001**	**1.15 (1.13-1.18) p<0.001**	1.08 (0.97-1.20) p=0.177	**1.31 (1.21-1.42) p<0.001**	**1.28 (1.01-1.61) p=0.042**	**1.27 (1.12-1.44) p<0.001**	0.93 (0.68-1.29) p=0.671
Binary Multi-Lung Function Model	Includes FEV_1/FVC, FEV_1 and FEF_{25-75}							
Model r^2	N/A	0.01	0.09	0.05	0.05	0.04	N/A	N/A
High vs Low	**1.27 (1.12-1.44) p<0.001**	**0.98 (0.97-0.99) p=0.046**	**1.07 (1.04-1.10) p<0.001**	0.94 (0.84-1.05) p=0.297	**1.18 (1.09-1.29) p<0.001**	1.12 (0.88-1.43) p=0.349	**1.21 (1.06-1.37) p=0.005**	1.13 (0.78-1.61) p=0.521
Continuous Multi-Lung Function Model	Includes FEV_1/FVC, FEV_1 and FEF_{25-75}							
Model r^2	N/A	0.01	0.09	0.05	0.05	0.04	N/A	N/A
RV/TLC (%)	**1.034 (1.021-1.048) P<0.001**	1.001 (0.999-1.003) p=0.104	**1.015 (1.013-1.018) p<0.001**	**1.030 (1.018-1.042) p<0.001**	**1.036 (1.027-1.045) p<0.001**	**1.027 (1.001-1.053) p=0.039**	**1.026 (1.013-1.038) p<0.001**	1.001 (0.967-1.037) p=0.939

Footnote: Association of RV/TLC and respiratory-related healthcare outcomes with COPD diagnosis were estimated using Cox Proportional Hazards regression for time to outcomes, Poisson regression for counts of outcome, or mixed-effects (Mixed Eff.) logistic regression for binary outcomes with adjustment for age, sex, height, and years of follow-up: Healthcare Outcomes=$\beta_0+\beta_1$(age)+β_2(sex)+β_3(height)+β_4(years of follow-up)+β_*(lung function indices). The models coefficients of determination (r^2), Hazard Ratio (HR), Incident Rate Ratio (IRR), and Odds Ratio (OR) with 95% confidence interval and p-value of the predictors are shown in the

table. Significant associations are shown in bold. N =5,179 unless noted otherwise. **§** Follow-up spirometry (last available post-bronchodilator spirometry) was available for a subgroup of the patients, N =1,124, models were adjusted for time from index PFT to such follow-up spirometry instead of years of follow-up. Abbreviations- TLC: total lung capacity; RV: residual volume; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; FEF_{25-75}: maximum airflow at mid-lung volume.

Table S5- Association of FRC and Health Outcomes.

	Respiratory-related Health Outcomes							
FRC	**Clinical Diagnosis of COPD**	**Respiratory Medications**	**Office Visits**	**ER Visits**	**Hospital Admissions**	**ICU Admissions**	**Mortality**	**COPD on Follow-up Spirometry §**
	HR	**IRR**	**IRR**	**IRR**	**IRR**	**IRR**	**HR**	**OR-Mixed Eff.**
Binary Single-Lung Function Model								
Model r^2	N/A	0.01	0.05	0.03	0.03	0.02	N/A	N/A
Abnormal vs Normal	**1.59 (1.31-1.92) p<0.001**	**0.94 (0.91-0.97) p<0.001**	**1.37 (1.33-1.42) p<0.001**	0.95 (0.78-1.15) p=0.586	**1.77 (1.59-1.96) p<0.001**	1.34 (0.95-1.87) p=0.095	**1.45 (1.21-1.73) p<0.001**	**2.44 (1.53-3.89) p<0.001**
Binary Multi-Lung Function Model	Includes FEV_1/FVC, FEV_1 and FEF_{25-75}							
Model r^2	N/A	0.01	0.08	0.05	0.05	0.04	N/A	N/A
Abnormal vs Normal	**1.53 (1.26-1.86) p<0.001**	**0.96 (0.93-0.99) p=0.011**	**1.39 (1.34-1.44) p<0.001**	0.97 (0.80-1.18) p=0.749	**1.80 (1.62-2.01) p<0.001**	1.36 (0.97-1.92) p=0.077	**1.57 (1.31-1.88) p<0.001**	**1.88 (1.14-3.09) p=0.014**
Continuous Multi-Lung Function Model	Includes FEV_1/FVC, FEV_1 and FEF_{25-75}							
Model r^2	N/A	0.02	0.09	0.05	0.05	0.04	N/A	N/A
FRC (L)	**1.27 (1.19-1.35) P<0.001**	**0.95 (0.94-0.96) p<0.001**	**1.173 (1.159-1.186) p<0.001**	**1.105 (1.044-1.169) p=0.001**	**1.32 (1.27-1.37) p<0.001**	**1.29 (1.16-1.44) p<0.001**	**1.33 (1.25-1.41) p<0.001**	**1.35 (1.14-1.59) p<0.001**

Footnote: Association of FRC and respiratory-related healthcare outcomes with COPD diagnosis were estimated using Cox Proportional Hazards regression for time to outcomes, Poisson regression for counts of outcome, or mixed-effects (Mixed Eff.) logistic regression for binary outcomes with adjustment for age, sex, height, and years of follow-up: Healthcare Outcomes=$\beta_0+\beta_1$(age)+β_2(sex)+β_3(height)+β_4(years of follow-up)+β_*(lung function indices). The models coefficients of determination (r^2), Hazard Ratio (HR), Incident Rate Ratio (IRR), and Odds Ratio (OR) with 95% confidence interval and p-value of the predictors are shown in the table. Significant associations are shown in bold. N =6,351 unless noted otherwise. **§** Follow-up spirometry (last available post-bronchodilator spirometry) was available for a subgroup of the patients, N =1,502, models were adjusted for time from index PFT to such follow-up spirometry

instead of years of follow-up. Abbreviations- FRC: functional residual capacity; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; FEF_{25-75}: maximum airflow at mid-lung volume.

Table S6- Association of FRC/TLC and Health Outcomes.

	Respiratory-related Health Outcomes							
FRC/TLC (Quanjer Predicted Formula)	**Clinical Diagnosis of COPD**	**Respiratory Medications**	**Office Visits**	**ER Visits**	**Hospital Admissions**	**ICU Admissions**	**Mortality**	**COPD on Follow-up Spirometry §**
	HR	**IRR**	**IRR**	**IRR**	**IRR**	**IRR**	**HR**	**OR-Mixed Eff.**
Binary Single-Lung Function Model								
Model r^2	N/A	0.01	0.05	0.04	0.03	0.02	N/A	N/A
Abnormal vs Normal	**1.45 (1.17-1.78) p=0.001**	0.98 (0.95-1.01) p=0.276	**1.46 (1.41-1.52) p<0.001**	**1.89 (1.63-2.19) p<0.001**	**1.96 (1.76-2.18) p<0.001**	**2.14 (1.59-2.86) p<0.001**	**1.33 (1.10-1.61) p=0.003**	1.45 (0.86-2.44) p=0.164
Binary Multi-Lung Function Model	Includes FEV_1/FVC, FEV_1 and FEF_{25-75}							
Model r^2	N/A	0.01	0.08	0.05	0.05	0.04	N/A	N/A
Abnormal vs Normal	**1.31 (1.06-1.61) p=0.012**	**0.96 (0.93-0.99) p=0.019**	**1.39 (1.34-1.44) p<0.001**	**1.80 (1.55-2.08) p<0.001**	**1.85 (1.66-2.06) p<0.001**	**1.92 (1.43-2.59) p<0.001**	**1.32 (1.09-1.60) p=0.004**	1.03 (0.59-1.80) p=0.911
Continuous Multi-Lung Function Model	Includes FEV_1/FVC, FEV_1 and FEF_{25-75}							
Model r^2	N/A	0.02	0.08	0.05	0.05	0.04	N/A	N/A
FRC/TLC (%)	**1.016 (1.010-1.022) P<0.001**	**0.994 (0.993-0.995) p<0.001**	**1.014 (1.013-1.015) p<0.001**	**1.019 (1.014-1.024) p<0.001**	**1.025 (1.021-1.029) p<0.001**	**1.025 (1.014-0.035) p<0.001**	**1.025 (1.019-1.031) p<0.001**	1.010 (0.994-1.026) p=0.236

Footnote: Association of FRC/TLC and respiratory-related healthcare outcomes with COPD diagnosis were estimated using Cox Proportional Hazards regression for time to outcomes, Poisson regression for counts of outcome, or mixed-effects (Mixed Eff.) logistic regression for binary outcomes with adjustment for age, sex, height, and years of follow-up: Healthcare Outcomes=$\beta_0+\beta_1$(age)+β_2(sex)+β_3(height)+β_4(years of follow-up)+β_*(lung function indices). The models coefficients of determination (r^2), Hazard Ratio (HR), Incident Rate Ratio (IRR), and Odds Ratio (OR) with 95% confidence interval and p-value of the predictors are shown in the table. Significant associations are shown in bold. N =6,351 unless noted otherwise. **§** Follow-up spirometry (last available post-bronchodilator spirometry) was available for a subgroup of the

patients, N =1,502, models were adjusted for time from index PFT to such follow-up spirometry instead of years of follow-up. Abbreviations- TLC: total lung capacity; FRC: functional residual capacity; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; FEF_{25-75}: maximum airflow at mid-lung volume.

Table S7- Association of IC and Health Outcomes.

	Respiratory-related Health Outcomes							
IC(Quanjer Predicted Formula)	**Clinical Diagnosis of COPD**	**Respiratory Medications**	**Office Visits**	**ER Visits**	**Hospital Admissions**	**ICU Admissions**	**Mortality**	**COPD on Follow-up Spirometry §**
	HR	**IRR**	**IRR**	**IRR**	**IRR**	**IRR**	**HR**	**OR-Mixed Eff.**
Binary Single-Lung Function Model								
Model r^2	N/A	0.01	0.05	0.03	0.03	0.02	N/A	N/A
Abnormal vs Normal	**1.13 (1.02-1.25) p=0.022**	**0.94 (0.93-0.95) p<0.001**	**1.22 (1.20-1.25) p<0.001**	**1.27 (1.16-1.40) p<0.001**	**1.26 (1.18-1.35) p<0.001**	**1.34 (1.11-1.63) p=0.003**	**1.53 (1.38-1.70) p<0.001**	0.96 (0.774-1.25) p=0.765
Binary Multi-Lung Function Model		Includes FEV_1/FVC, FEV_1 and FEF_{25-75}						
Model r^2	N/A	0.02	0.08	0.05	0.04	0.04	N/A	N/A
Abnormal vs Normal	1.03 (0.92-1.15) p=0.601	**0.90 (0.89-0.92) p<0.001**	**1.13 (1.10-1.15) p<0.001**	**1.18 (1.07-1.30) p=0.001**	**1.17 (1.09-1.25) p<0.001**	1.17 (0.96-1.43) p=0.124	**1.45 (1.30-1.62) p<0.001**	1.03 (0.78-1.38) p=0.817
Continuous Multi-Lung Function Model		Includes FEV_1/FVC, FEV_1 and FEF_{25-75}						
Model r^2	N/A	0.02	0.08	0.05	0.05	0.04	N/A	N/A
IC (L)	0.93 (0.85-1.01) p=0.100	**1.08 (1.07-1.09) p<0.001**	**0.88 (0.87-0.90) p<0.001**	**0.71 (0.65-0.77) p<0.001**	**0.77 (0.72-0.81) p<0.001**	**0.80 (0.68-0.94) p=0.007**	**0.76 (0.70-0.83) p<0.001**	1.18 (0.93-1.48) p=0.170

Footnote: Association of IC and respiratory-related healthcare outcomes with COPD diagnosis were estimated using Cox Proportional Hazards regression for time to outcomes, Poisson regression for counts of outcome, or mixed-effects (Mixed Eff.) logistic regression for binary outcomes with adjustment for age, sex, height, and years of follow-up: Healthcare Outcomes=$\beta_0+\beta_1$(age)+β_2(sex)+β_3(height)+β_4(years of follow-up)+β_*(lung function indices). The models coefficients of determination (r^2), Hazard Ratio (HR), Incident Rate Ratio (IRR), and Odds Ratio (OR) with 95% confidence interval and p-value of the predictors are shown in the table. Significant associations are shown in bold. N =6,346 unless noted otherwise. **§** Follow-up spirometry (last available post-bronchodilator spirometry) was available for a subgroup of the patients, N =1,499, models were adjusted for time from index PFT to such follow-up spirometry

instead of years of follow-up. Abbreviations- TLC: total lung capacity; IC: inspiratory capacity; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; FEF_{25-75}: maximum airflow at mid-lung volume.

Table S8- Association of IC/TLC and Health Outcomes.

	Respiratory-related Health Outcomes							
IC/TLC (Francisco Predicted Formula)	**Clinical Diagnosis of COPD**	**Respiratory Medications**	**Office Visits**	**ER Visits**	**Hospital Admissions**	**ICU Admissions**	**Mortality**	**COPD on Follow-up Spirometry §**
	HR	**IRR**	**IRR**	**IRR**	**IRR**	**IRR**	**HR**	**OR-Mixed Eff.**
Binary Single-Lung Function Model								
Model r^2	N/A	0.01	0.05	0.04	0.03	0.02	N/A	N/A
Abnormal vs Normal	**1.48 (1.32-1.66) p<0.001**	**0.92 (0.91-0.94) p<0.001**	**1.37 (1.34-1.40) p<0.001**	**1.53 (1.37-1.70) p<0.001**	**1.75 (1.62-1.88) p<0.001**	**1.64 (1.33-2.03) p<0.001**	**1.44 (1.27-1.63) p<0.001**	**1.51 (1.13-2.02) p=0.005**
Binary Multi-Lung Function Model	Includes FEV_1/FVC, FEV_1 and FEF_{25-75}							
Model r^2	N/A	0.02	0.08	0.05	0.05	0.04	N/A	N/A
Abnormal vs Normal	**1.36 (1.21-1.53) p<0.001**	**0.91 (0.90-0.93) p<0.001**	**1.30 (1.27-1.33) p<0.001**	**1.48 (1.33-1.64) p<0.001**	**1.67 (1.55-1.80) p<0.001**	**1.51 (1.22-1.87) p<0.001**	**1.46 (1.28-1.65) p<0.001**	1.19 (0.88-1.63) p=0.263
Continuous Multi-Lung Function Model	Includes FEV_1/FVC, FEV_1 and FEF_{25-75}							
Model r^2	N/A	0.02	0.08	0.05	0.05	0.04	N/A	N/A
IC/TLC (%)	**0.983 (0.976-0.989) P<0.001**	**1.0057 (1.005-1.006) p<0.001**	**0.986 (0.985-0.987) p<0.001**	**0.980 (0.975-0.985) p<0.001**	**0.974 (0.970-0.977) p<0.001**	**0.974 (0.963-0.984) p<0.001**	**0.974 (0.969-0.980) p<0.001**	0.989 (0.973-1.004) p=0.166

Footnote: Association of IC/TLC and respiratory-related healthcare outcomes with COPD diagnosis were estimated using Cox Proportional Hazards regression for time to outcomes, Poisson regression for counts of outcome, or mixed-effects (Mixed Eff.) logistic regression for binary outcomes with adjustment for age, sex, height, and years of follow-up: Healthcare Outcomes=$\beta_0+\beta_1$(age)+β_2(sex)+β_3(height)+β_4(years of follow-up)+β_*(lung function indices). The models coefficients of determination (r^2), Hazard Ratio (HR), Incident Rate Ratio (IRR), and Odds Ratio (OR) with 95% confidence interval and p-value of the predictors are shown in the table. Significant associations are shown in bold. N =6,346 unless otherwise noted. **§** Follow-up spirometry (last available post-bronchodilator spirometry) was available for a subgroup of the

patients, N =1,493, models were adjusted for time from index PFT to such follow-up spirometry instead of years of follow-up. Abbreviations- TLC: total lung capacity; IC: inspiratory capacity; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; FEF_{25-75}: maximum airflow at mid-lung volume.

Table S9- Association of RV/TLC and Health Outcomes using GOLD criteria for diagnosis of COPD and determination of preserved spirometry.

	Respiratory-related Health Outcomes							GOLD
RV/TLC	**Clinical Diagnosis of COPD**	**Respiratory Medications**	**Office Visits**	**ER Visits**	**Hospital Admissions**	**ICU Admissions**	**Mortality**	**COPD on Follow-up Spirometry §**
	HR	**IRR**	**IRR**	**IRR**	**IRR**	**IRR**	**HR**	**OR-Mixed Eff.**
Binary Single-Lung Function Model								
Model r^2	N/A	0.01	0.05	0.02	0.03	0.02	N/A	N/A
Abnormal vs Normal	**1.50 (1.37-1.64) p<0.001**	**1.13 (1.11-1.14) p<0.001**	**1.31 (1.28-1.33) p<0.001**	**1.10 (1.02-1.20) p=0.020**	**1.50 (1.41-1.58) p<0.001**	**1.31 (1.11-1.54) p=0.002**	**1.25 (1.15-1.37) p<0.001**	**1.26 (1.003-1.59) p=0.047**
Binary Multi-Lung Function Model	Includes FEV_1/FVC, FEV_1 and FEF_{25-75}							
Model r^2	N/A	0.01	0.08	0.04	0.05	0.04	N/A	N/A
Abnormal vs Normal	**1.37 (1.24-1.50) p<0.001**	**1.08 (1.07-1.10) p<0.001**	**1.18 (1.16-1.20) p<0.001**	0.97 (0.89-1.05) p=0.425	**1.35 (1.27-1.43) p<0.001**	1.09 (0.92-1.29) p=0.326	**1.16 (1.06-1.28) p=0.002**	1.30 (0.996-1.692) p=0.054
Continuous Multi-Lung Function Model	Includes FEV_1/FVC, FEV_1 and FEF_{25-75}							
Model r^2	N/A	0.01	0.08	0.04	0.05	0.04	N/A	N/A
RV/TLC (%)	**1.030 (1.023-1.037) P<0.001**	**1.006 (1.005-1.007) p<0.001**	**1.018 (1.016-1.019) p<0.001**	**1.008 (1.002-1.014) p=0.011**	**1.033 (1.029-1.037) p<0.001**	**1.016 (1.004-1.029) p=0.009**	**1.014 (1.007-1.021) p<0.001**	**1.019 (1.001-1.038) p=0.043**

Footnote: Association of RV/TLC and respiratory-related healthcare outcomes with COPD diagnosis were estimated using Cox Proportional Hazards regression for time to outcomes, Poisson regression for counts of outcome, or mixed-effects (Mixed Eff.) logistic regression for binary outcomes with adjustment for age, sex, height, and years of follow-up: Healthcare Outcomes=$\beta_0+\beta_1$(age)+β_2(sex)+β_3(height)+β_4(years of follow-up)+β_*(lung function indices). The models coefficients of determination (r^2), Hazard Ratio (HR), Incident Rate Ratio (IRR), and Odds Ratio (OR) with 95% confidence interval and p-value of the predictors are shown in the table. Significant associations are shown in bold. N =7,360 unless noted otherwise. **§** Follow-up spirometry (last available post-bronchodilator spirometry) was available for a subgroup of the

patients, N =1,675, models were adjusted for time from index PFT to such follow-up spirometry instead of years of follow-up. Abbreviations- TLC: total lung capacity; RV: residual volume; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; FEF_{25-75}: maximum airflow at mid-lung volume.

Table S10- Correlation of RV/TLC with Airflow Indices (Absolute Values).

	Uncorrected Correlation with RV/TLC (%)		**Corrected Correlation with RV/TLC (%)**	
Correlation w RV/TLC (%)	**r**	**p-value**	**r_p**	**p-value**
FEV_1/FVC (%)	-0.16	<**0.001**	-0.04	<**0.001**
FEV_1 (L)	-0.53	<**0.001**	-0.34	<**0.001**
FEF_{25-75} (L/s)	-0.36	<**0.001**	-0.11	<**0.001**
FVC (L)	-0.48	<**0.001**	-0.30	<**0.001**
FRC (L)	0.42	<**0.001**	0.52	<**0.001**
FRC/TLC (%)	0.48	<**0.001**	0.38	<**0.001**
IC (L)	-0.29	<**0.001**	-0.09	<**0.001**
IC/TLC (%)	-0.48	<**0.001**	-0.39	<**0.001**

Footnote: Partial and semi-partial correlation coefficients were tested among airflow indices and RV/TLC controlling for age, height, and sex in the cohort with preserved spirometry. N = 7,479. Abbreviations- r: correlation coefficient; r_p: Partial correlation, which is the correlation coefficient between dependent variable and the targeted independent variable assuming the other independent variables did not vary; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; TLC: total lung capacity; RV: residual volume; FEF_{25-75}: maximum airflow at mid-lung volume; IC: inspiratory capacity; FRC: functional residual capacity.

Table S11 - Correlation of RV/TLC with Airflow Indices (% predicted).

Correlation w RV/TLC (% predicted)	**r**	**p-value**
FEV_1/FVC (% predicted)	-0.05	<**0.001**
FEV_1 (% predicted)	-0.36	<**0.001**
FVC (% predicted)	-0.31	<**0.001**
FRC (% predicted)	0.53	<**0.001**
FRC/TLC (% predicted)	0.37	<**0.001**
IC (% predicted)	-0.10	<**0.001**
IC/TLC (% predicted)	-0.31	<**0.001**

Footnote: Correlation coefficients were tested among FEV_1/FVC % predicted, FEV_1 % predicted, and RV/TLC % predicted. Abbreviations- r: correlation coefficient; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; TLC: total lung capacity; RV: residual volume; IC: inspiratory capacity; FRC: functional residual capacity.

6. Detailed Definition of Outcomes

Outcomes

Clinical diagnosis of COPD: Patients with documented diagnoses of ICD-9 or ICD-10 codes of "COPD," "Chronic Obstructive Lung Disease," "Emphysema," "Pulmonary Emphysema," "Chronic bronchitis," "Obstructive chronic bronchitis," "Chronic airway obstruction," "Chronic bullous emphysema" were classified to have clinical diagnoses of COPD. Date and existence of a clinical COPD diagnosis given by a physician on patients' problem list on electronic medical record were extracted for analysis.

Respiratory medications prescribed: number of prescribed respiratory medications recorded in electronic health record including ICS, LABA, LAMA, SABA, and SAMA (categories provided below).

Office Visits: number of outpatient visits, unrelated to the emergency department, associated with a Clinical diagnosis of COPD.

ER Visits: number of outpatient visits to the emergency department associated with a Clinical diagnosis of COPD.

Hospital admissions: number of inpatient admissions, independent from ICU, associated with a Clinical diagnosis of COPD.

ICU admissions: number of ICU admissions associated with a Clinical diagnosis of COPD.

Respiratory related illness: illness that resulted in an ER visit, hospital or ICU admission with a Clinical diagnosis of COPD.

Medication Categories

ICS: Inhaled Corticosteroid (alone or in combination)

- Budesonide/formoterol fumarate inhaler
    i. Symbicort
- Formoterol/mometasone inhaler
    i. Dulera
- Fluticasone/Salmeterol xinafoate inhaler
    i. Advair Diskus or Advair HFA
- Mometasone furoate inhaler
    i. Asmanex Twisthaler
- Fluticasone propionate inhaler
    i. Flovent Diskus or Flovent HFA
- Beclomethasone dipropionate inhaler

    i. QVAR
- Budesonide inhaler
    i. Pulmicort respules or pulmicort Flexhaler
- Triamcinolone acetonide inhaler
    i. Azmacort
- Flunisolide
    i. Aerobid
    ii. Aerospan HFA

LABA: Long Acting Beta Agonist (or in combination with ICS above)
- Formoterol fumarate
    i. Foradil, Perforomist
- Salmeterol Xinafoate
    i. Serevent diskus
- Arformoterol tartare
    i. Brovana

LAMA: Long Acting Muscarinic Antagonist
- Tiotropium Bromide
    i. Spiriva
- Aclidinium bromide
    i. Tudorza

SABA: Short Acting Beta Agonist
- Albuterol Sulfate
    i. ProAir, Proventil, Ventolin
- Levalbuterol HCl
    i. Xopenex

SAMA: Short Acting Muscarinic Antagonist
- Ipratropium
    i. Atrovent
    ii. Apovent

7. References

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