

Supplementary Appendix

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

Supplement to: Woodruff PG, Barr RG, Bleecker E, et al. Clinical significance of symptoms in smokers with preserved pulmonary function. *N Engl J Med* 2016;374:1811-21. DOI: 10.1056/NEJMoa1505971

Supplementary Appendix

New England Journal of Medicine 15-05971

Title: Clinical Significance of Symptoms in Smokers with Preserved Spirometry

Corresponding Author: Prescott Woodruff, MD, MPH

11/21/2015

Table of Contents

SPIROMICS Investigators	2
Figure S1. Current and former smokers (ever-smokers) with preserved spirometry and symptoms (CAT \geq 10) had elevations in all components of the CAT score.	3
Figure S2. Relationship between post-bronchodilator FEV ₁ /FVC and number of exacerbations in non-smoking healthy controls, ever-smokers with preserved spirometry and GOLD 1&2 participants stratified by symptoms (CAT<10 vs. CAT \geq 10). Vertical red line denotes the border between “preserved spirometry” and GOLD 1 COPD.....	4
Figure S3. No increase in emphysema in ever-smokers with preserved spirometry and symptoms (CAT \geq 10). Percentage of lung with a density < -950 Hounsfield units on CT, a measure of emphysema. Ever-smokers with preserved spirometry do not have increased emphysema whether CAT score is \geq or < 10.....	5
Figure S4. Airway wall thickening. Pi10 (defined as the square root of the wall area of a theoretical airway of 10 mm luminal perimeter) is a CT measure of airway wall thickening. Ever-smokers with preserved spirometry and increased symptoms (CAT score \geq 10) have evidence of increased airway wall thickening by CT.....	6
Figure S5. Individual COPD Assessment Test (CAT) Component Scores in smokers with preserved spirometry, stratified by current versus former smoking.....	7
Figure S6. Prospective exacerbations in smokers with preserved spirometry stratified by current versus former smoking.....	8
Figure S7. ROC analysis of the value of baseline CAT score versus post-bronchodilator FEV ₁ for predicting the occurrence of any exacerbation in the first year of follow-up among current and former smokers with preserved spirometry. Participants with < 1 year of follow-up were excluded.	9
Figure S8. ROC analysis of CAT score as compared to the Medical Research Council (MRC) score for predicting the occurrence of any exacerbation over the first year of follow-up in ever-smokers with preserved spirometry.	10
Table S1: Between group difference in walk distance, lung function, respiratory medication use and prospective exacerbation rates.	11
Table S2. Physiological measures associated with CAT score \geq 10, while controlling for potential confounders. Includes ever-smokers with preserved spirometry who have symptoms (CAT \geq 10) and are asymptomatic (CAT<10, referent).....	14
Table S3. Risk for exacerbation associated with CAT score \geq 10 excluding participants with any diagnosis of asthma at baseline while controlling for potential confounders.....	15
Table S4. Risk for exacerbation associated with CAT score \geq 10 excluding participants with a childhood diagnosis of asthma while controlling for potential confounders.....	16
Table S5. Sensitivity and Specificity values for baseline CAT Score and the occurrence of any exacerbations over the first year of follow-up.....	17

SPIROMICS Investigators

We would like to acknowledge the following current and former investigators of the SPIROMICS sites and reading centers: Neil Alexis, PhD; Wayne Anderson, PhD; R Graham Barr, MD, DrPH; Basta PV, PhD, Eugene Bleecker, MD; Richard C Boucher, MD; Russell Bowler, MD, PhD; Elizabeth Carretta, MS; Stephanie Christenson, MD; Alejandro P Comellas, MD; Christopher B Cooper, MD, PhD; David Couper, PhD; Gerard Criner, MD; Ronald G Crystal, MD; Jeffrey L Curtis, MD; Claire Doerschuk, MD; Mark Dransfield, MD; Christine M. Freeman, PhD; MeiLan K Han, MD, MS; Nadia N Hansel, MD, MPH; Annette Hastie, PhD; Eric A Hoffman, PhD; Robert J Kaner, MD; Richard E. Kanner, MD; Kesimer M, PhD; Eric Kleeup, MD; Jerry Krishnan, MD, PhD; Lisa LaVange, MA, PhD; Stephen C Lazarus, MD; Fernando J Martinez, MD, MS; Deborah A Meyers, PhD; John D Newell Jr, MD; Elizabeth C Oelsner, MD, MPH; Wanda O'Neal, PhD; Robert Paine, III, MD; Nirupama Putcha, MD, MHS; Steve Rennard, MD; Donald Tashkin, MD; Mary Beth Scholand, MD; Robert A Wise, MD; and Prescott G Woodruff, MD, MPH. The project officers from the Lung Division of the National Heart, Lung, and Blood Institute (NHLBI) were Lisa Postow, PhD, and Thomas Croxton, PhD, MD.

Figure S1. Current and former smokers (ever-smokers) with preserved spirometry and symptoms (CAT \geq 10) had elevations in all components of the CAT score.

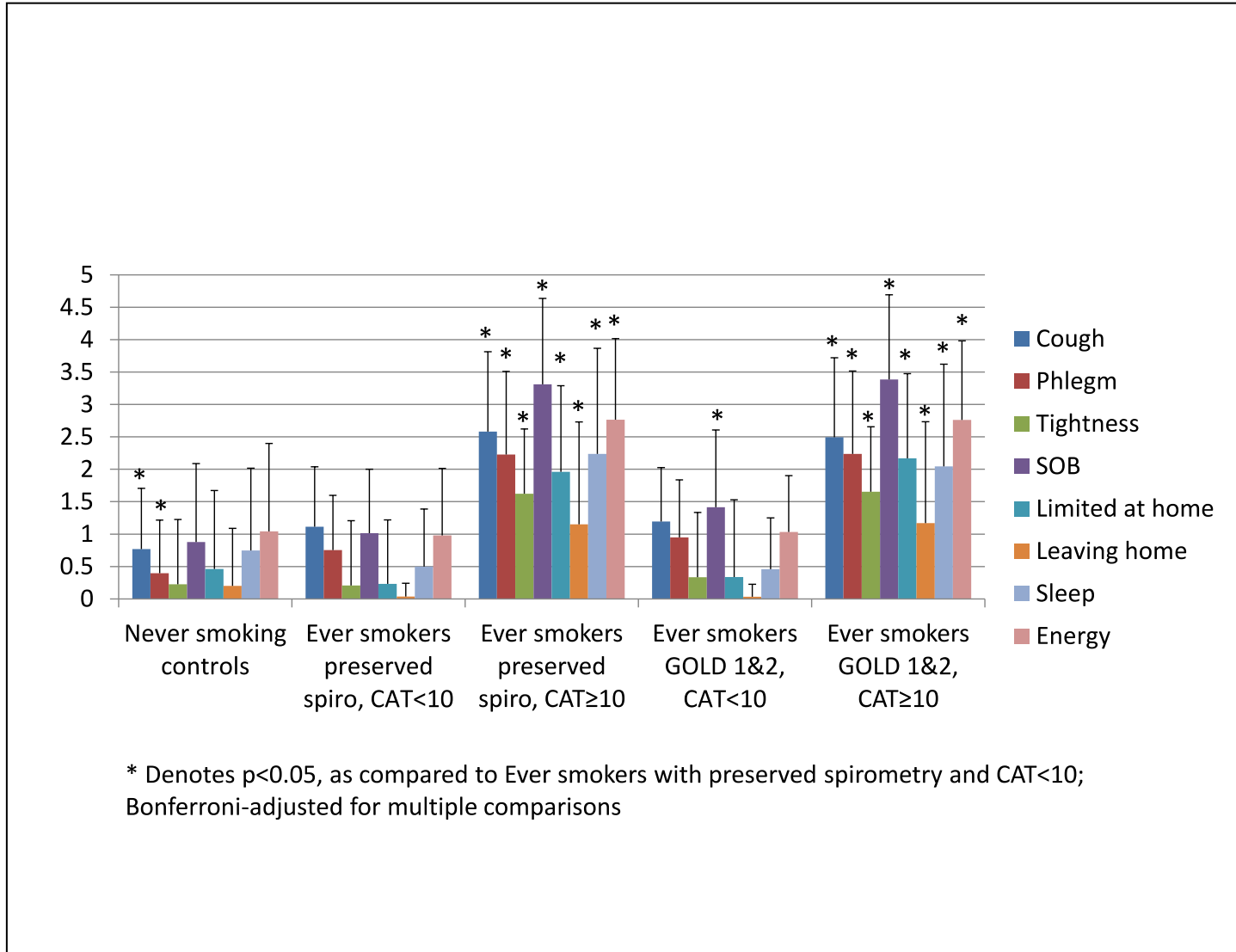


Figure S2. Relationship between post-bronchodilator FEV1/FVC and number of exacerbations in non-smoking healthy controls, ever-smokers with preserved spirometry and GOLD 1&2 participants stratified by symptoms (CAT<10 vs. CAT≥10). Vertical red line denotes the border between “preserved spirometry” and GOLD 1 COPD.

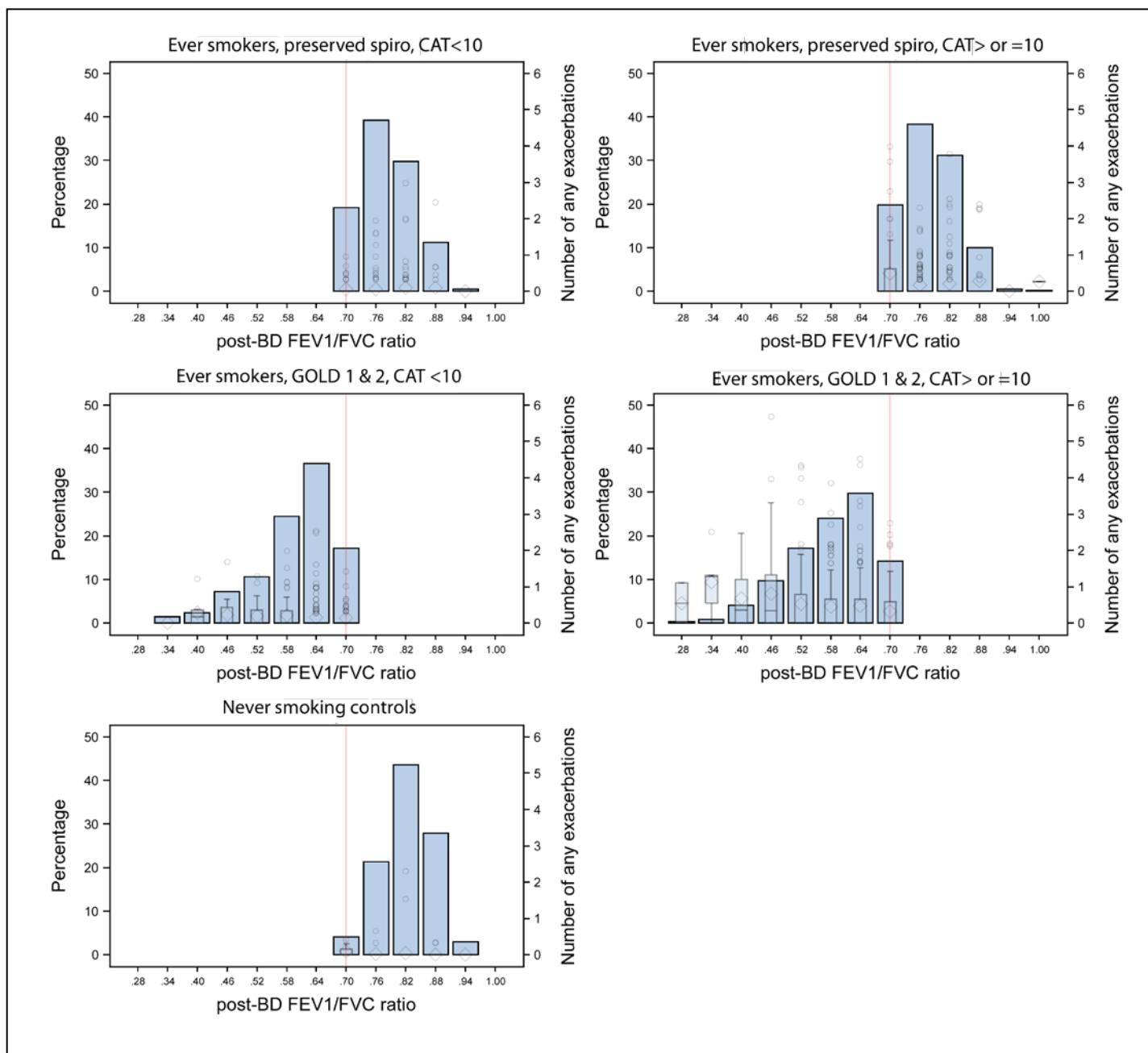


Figure S3. No increase in emphysema in ever-smokers with preserved spirometry and symptoms (CAT \geq 10). Percentage of lung with a density < -950 Hounsfield units on CT, a measure of emphysema. Ever-smokers with preserved spirometry do not have increased emphysema whether CAT score is \geq or < 10.

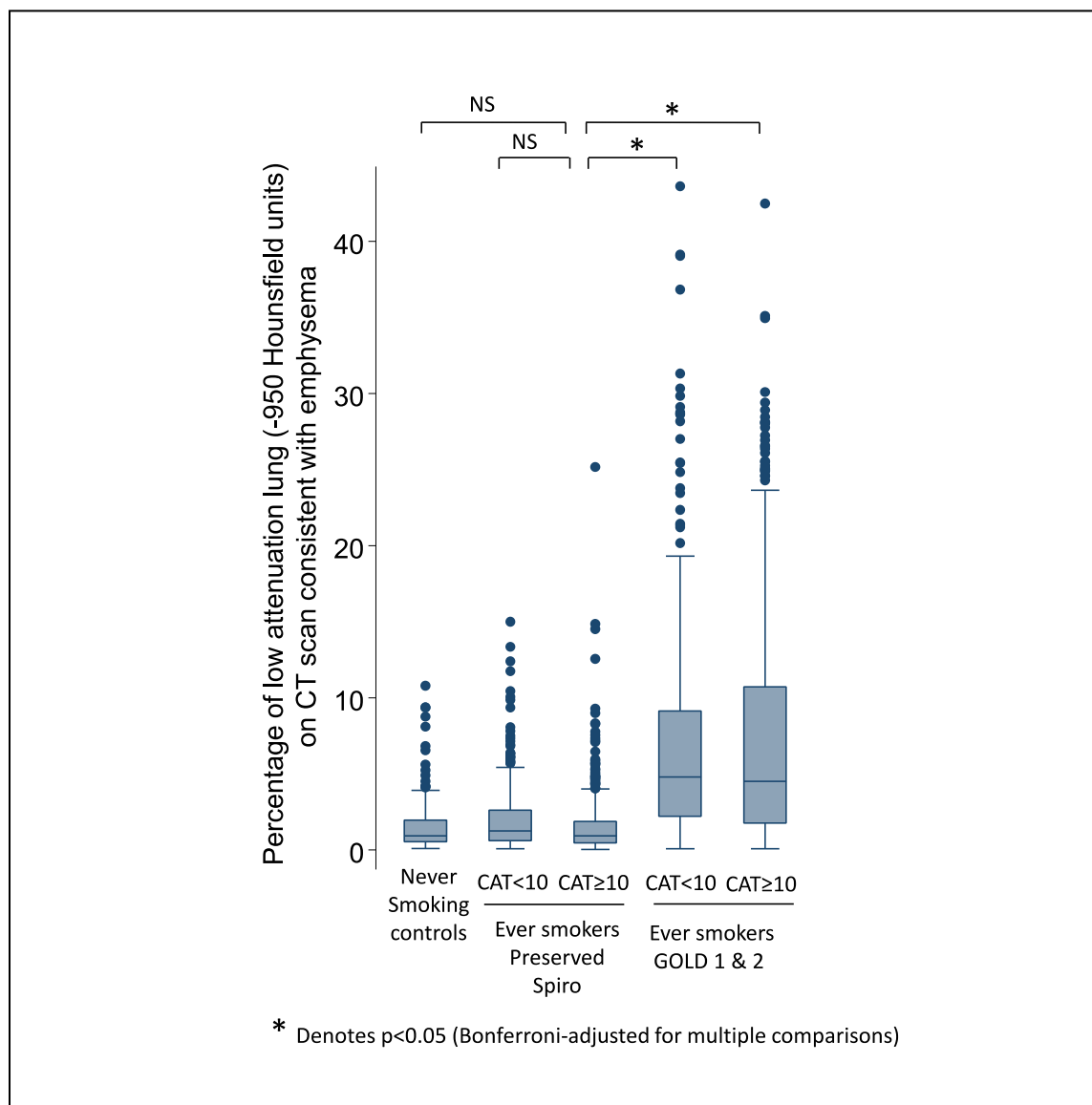


Figure S4. Airway wall thickening. Pi10 (defined as the square root of the wall area of a theoretical airway of 10 mm luminal perimeter) is a CT measure of airway wall thickening. Ever-smokers with preserved spirometry and increased symptoms (CAT score ≥ 10) have evidence of increased airway wall thickening by CT.

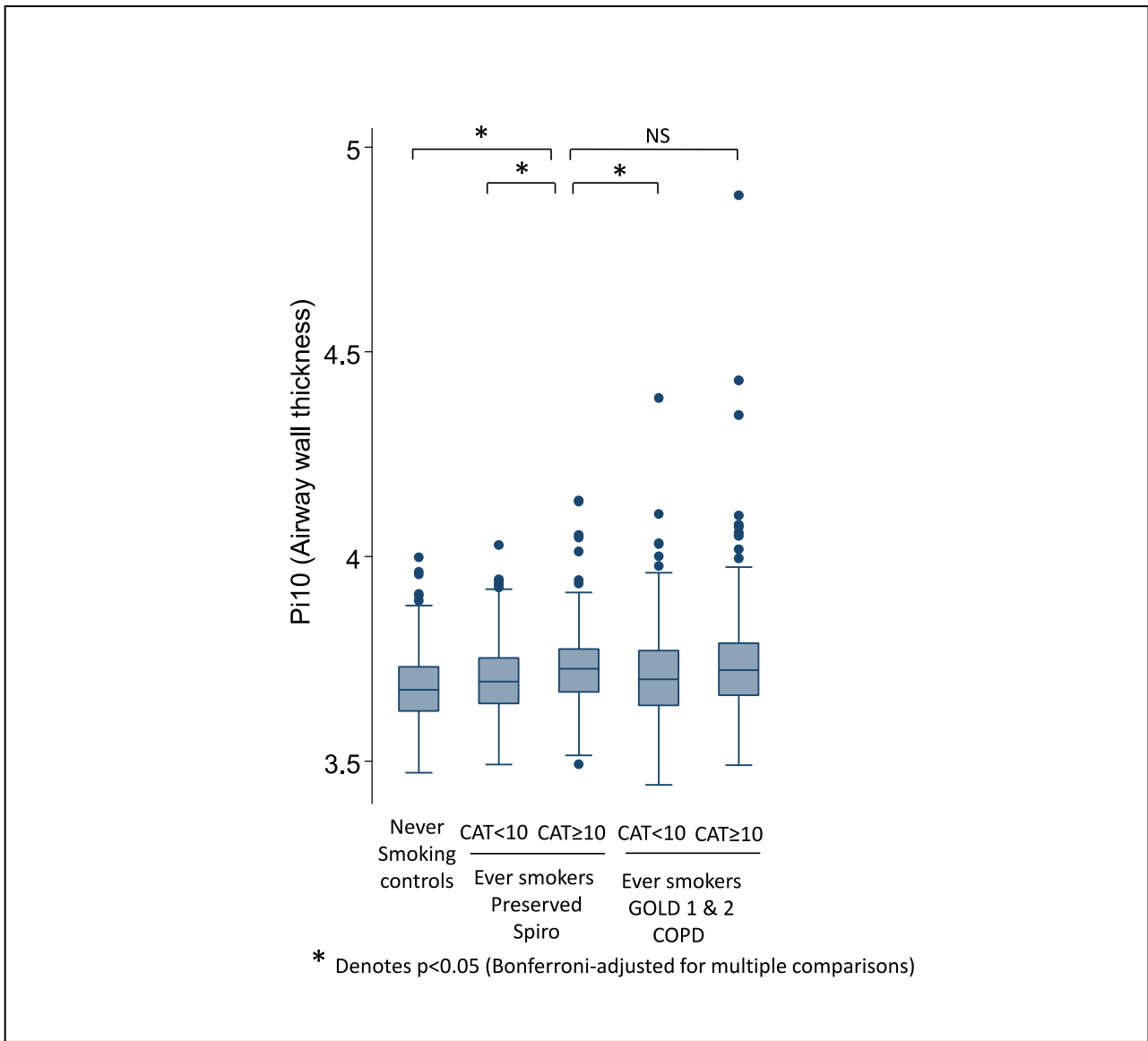


Figure S5. Individual COPD Assessment Test (CAT) Component Scores in smokers with preserved spirometry, stratified by current versus former smoking. In ever-smokers with preserved spirometry and symptoms (CAT \geq 10), the elevations we observed in each component of the CAT score are independent of whether they are current or former smokers.

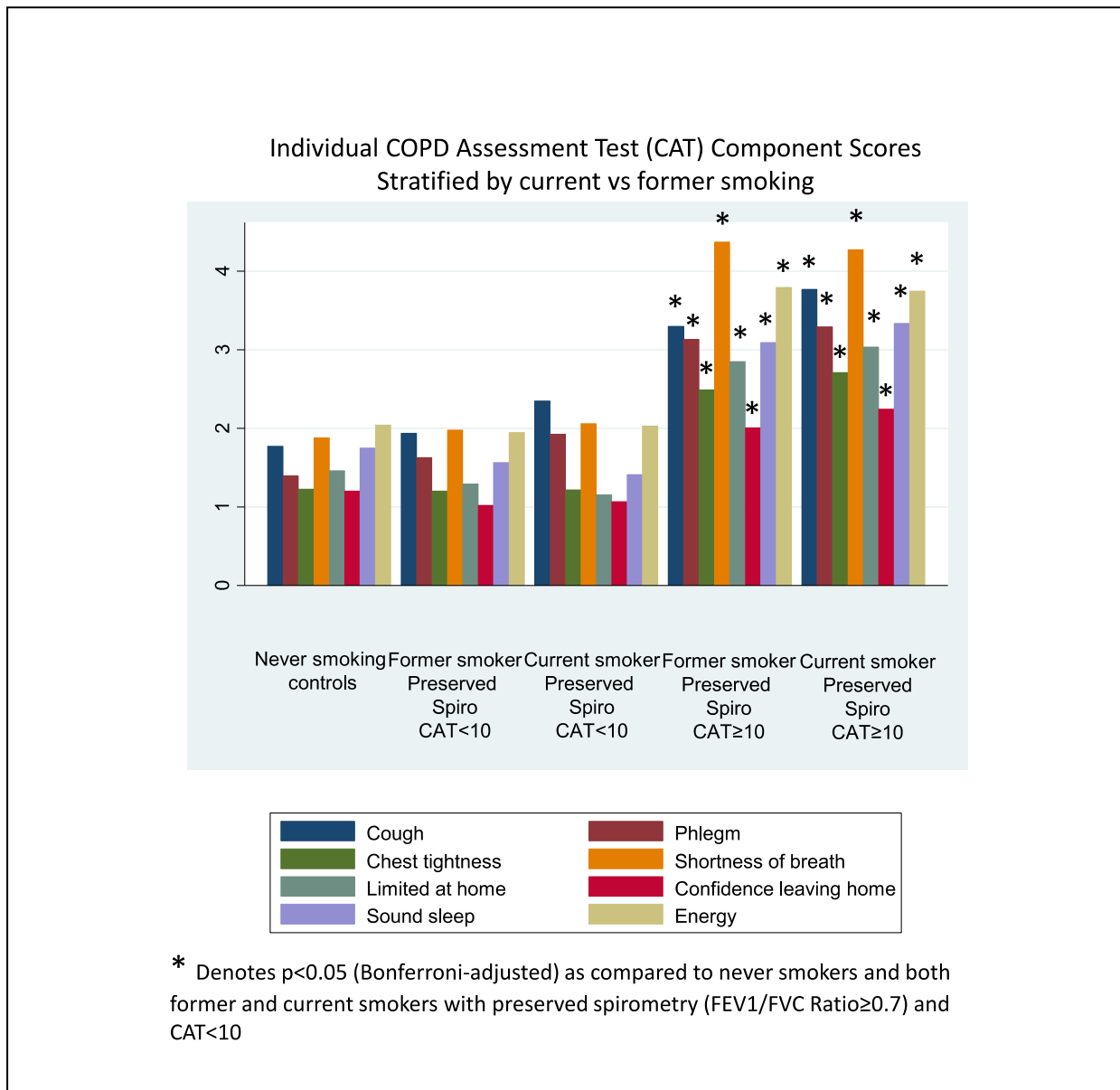
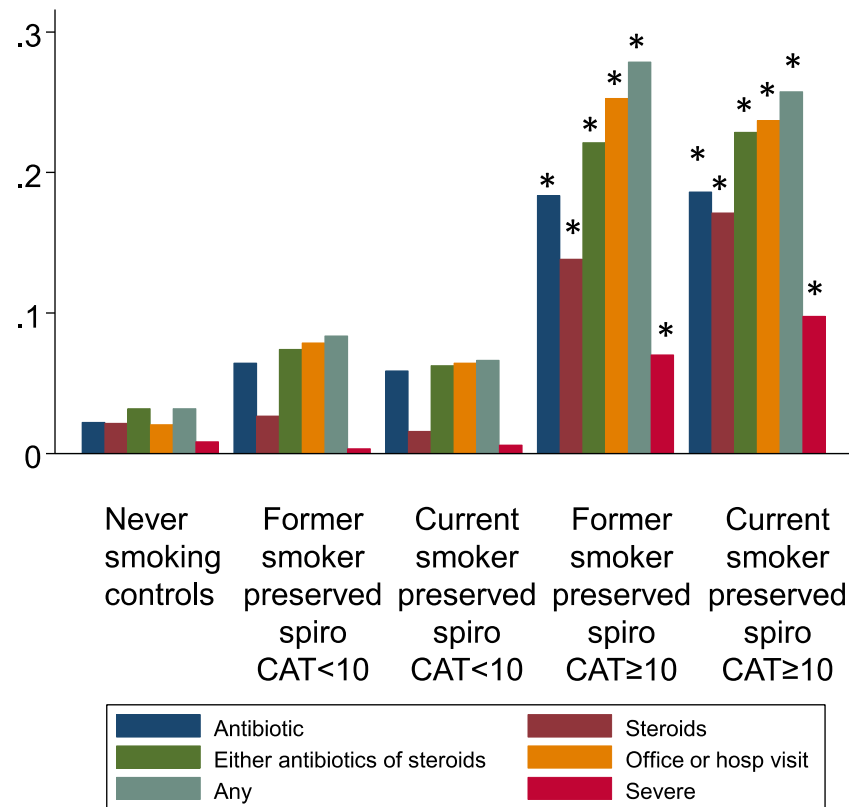


Figure S6. Prospective exacerbations in smokers with preserved spirometry stratified by current versus former smoking. In smokers with preserved spirometry and symptoms (CAT \geq 10), the elevation in exacerbation risk that we observed is independent of whether they are current or former smokers.

Annualized exacerbation rates in smokers with preserved spirometry stratified by CAT score and current vs former smoking



* Denotes p<0.05 (Bonferroni-adjusted) as compared to Never smokers and both Former and Current smokers with preserved spirometry and CAT<10

Figure S7. ROC analysis of the value of baseline CAT score versus post-bronchodilator FEV₁ for predicting the occurrence of any exacerbation in the first year of follow-up among current and former smokers with preserved spirometry. Participants with < 1 year of follow-up were excluded.

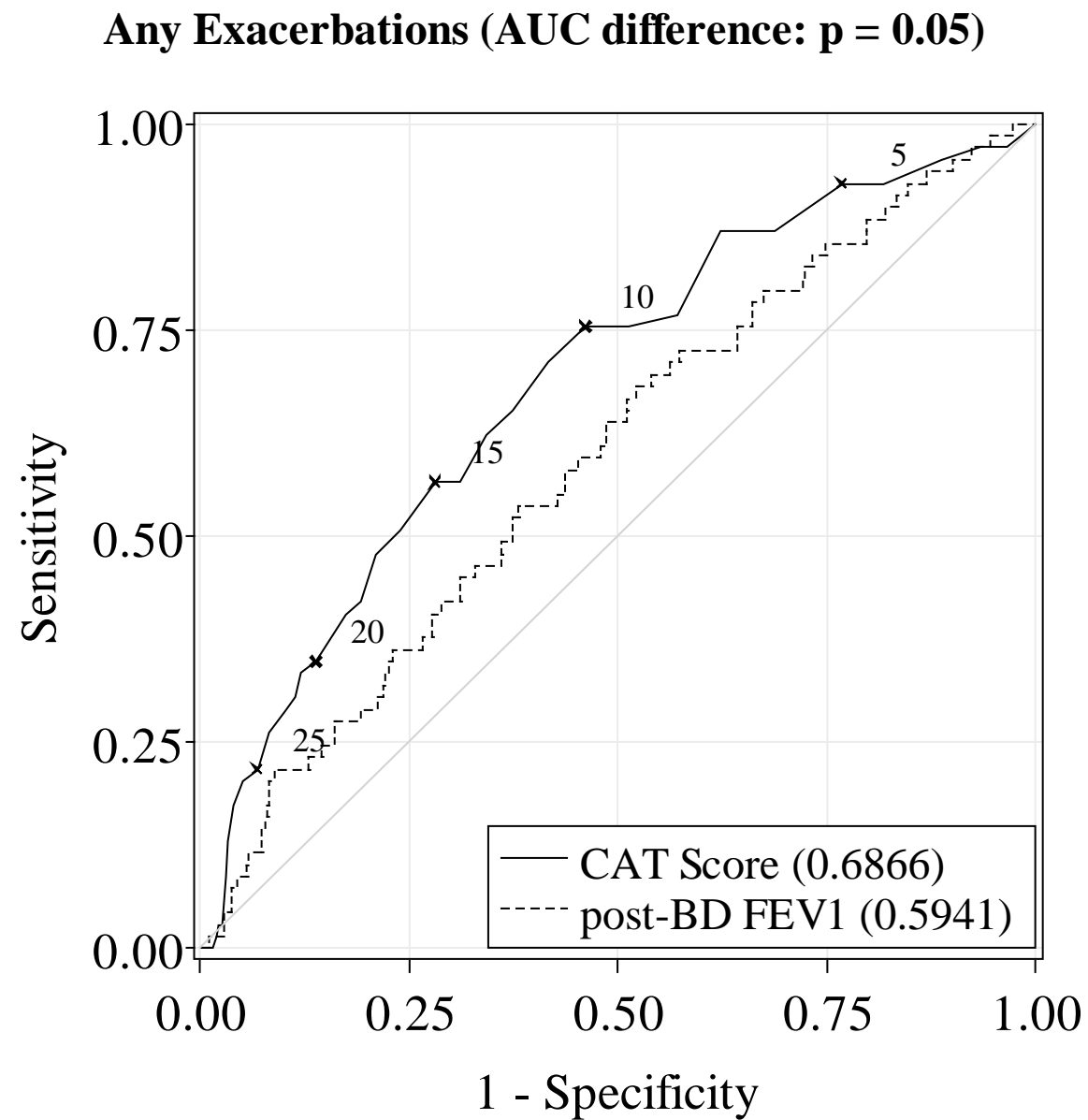


Figure S8. ROC analysis of CAT score as compared to the Medical Research Council (MRC) score for predicting the occurrence of any exacerbation over the first year of follow-up in ever-smokers with preserved spirometry. CAT was similar to MRC score for prediction of any exacerbation. Participants with < 1 year of follow-up were excluded.

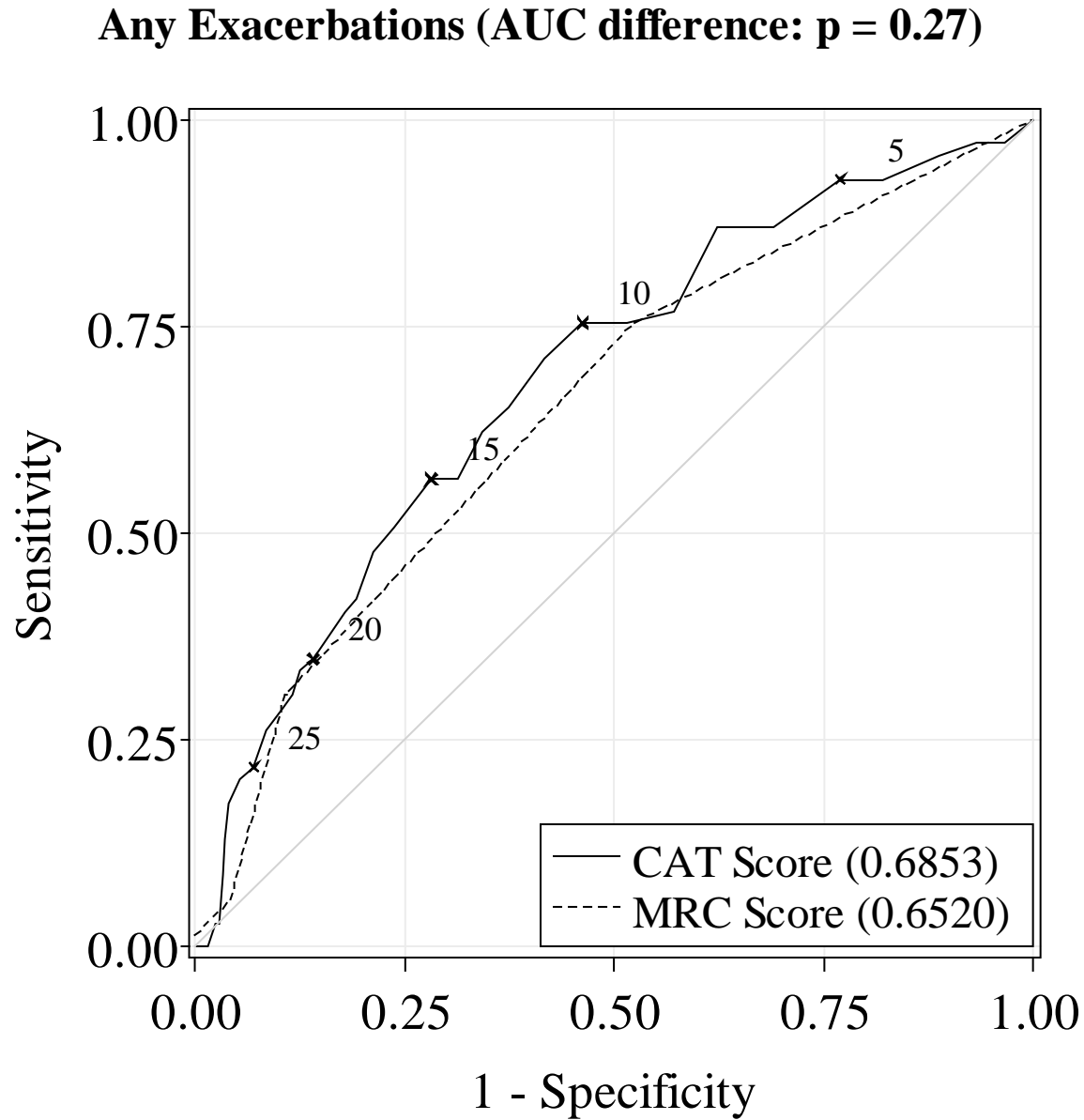


Table S1: Between group difference in walk distance, lung function, respiratory medication use and prospective exacerbation rates.

	Group A Never-smoking Controls	Group B Ever-Smokers with preserved spirometry and CAT<10 (less symptoms)	Group C Ever-Smokers with preserved spirometry and CAT ≥10 (more symptoms)	Group D Ever-Smokers with GOLD 1 & 2 COPD and CAT<10 (less symptoms)	Group E Ever-Smokers with GOLD 1 & 2 COPD and CAT≥10 (more symptoms)
N	199	424	425	337	626
Six minute walk distance (meters)	479.5±101.9 * vs. C,D,E	461.7±91.4 * vs. C,E	410.2±96.0 * vs. A,B,D	452.1±100.7 * vs. A,C,E	399.3±118.3 * vs. A,B,D
Six minute walk distance (% predicted)	89.7±18.7 * vs. C,E	89.3±18.8 * vs. C,E	79.8±19.2 * vs. A,B,D	89.2±19.3 * vs. C,E	79.3±24.0 * vs. A,B,D
Pre-BD FEV₁ (L)	2.86±0.70 L * vs. C,D,E	2.73±0.69 L * vs. C,D,E	2.48±0.68 L * vs. A,B,D,E	2.01±0.68 L * vs. A,B,C,E	1.76±0.61 L * vs. A,B,C,D
Pre-BD FEV₁ (% predicted)	97.2±11.6% * vs. B,C,D,E	93.5±13.6% * vs. A,C,D,E	88.0±13.9% * vs. A,B,D,E	68.7±16.4% * vs. A,B,C,E	61.8±15.3% * vs. A,B,C,D
Post-BD FEV₁ (L)	2.96±0.72 L * vs. C,D,E	2.88±0.71 L * vs. C,D,E	2.65±0.70 L * vs. A,B,D,E	2.25±0.68 L * vs. A,B,C,E	2.01±0.62 L * vs. A,B,C,D
Post-BD FEV₁ (% predicted)	101±11.0% * vs. C,D,E	98.5±12.6% * vs. C,D,E	94.1±13.1% * vs. A,B,D,E	77.1±15.2% * vs. A,B,C,E	70.5±14.3% * vs. A,B,C,D
Post-BD FEV₁ % improvement	4.1±5.9 * vs. C,D,E	6.1±5.5 * vs. D,E	7.4±7.9 * vs. A,D,E	13.7±11.6 * vs. A,B,C,E	16.2±14.5 * vs. A,B,C,D
FEV₁ bronchodilator responsive, (Y, %) (Pellegrino)	13 (7%)	43 (10%)	66 (15%)	146 (44%)	273 (44%)

	* vs. C,D,E	* vs. D,E	* vs. A,D,E	* vs. A,B,C	* vs. A,B,C
Pre-BD FVC (L)	3.68±0.91 L * vs. C,E	3.73±0.91 L * vs. C,E	3.39±0.91 L * vs. A,B	3.57±1.01 L * vs. C	3.24±0.97 L * vs. A,B,D
Pre-BD FVC (% predicted)	97.4±10.2% * vs. C,D,E	97.5±12.6% * vs. C,D,E	93.0±13.0% * vs. A,B,E	91.7±17.3% * vs. A,B,E	86.3±16.5% * vs. A,B,C,D
Post-BD FVC (L)	3.69±0.92 L no p<0.05	3.77±0.91 L * vs. C,E	3.48±0.90 L * vs. B,D	3.85±0.99 L * vs. C,E	3.58±1.00 L * vs. B,D
Post-BD FVC (% predicted)	97.8±9.9% no p<0.05	98.5±11.6% * vs. C,E	95.7±12.4% * vs. B,D	99.4±16.4% * vs. C,E	95.2±15.9% * vs. B,D
Post-BD FVC % improvement	0.4±4.2 * vs. C, D,E	1.5±4.8 * vs. D,E	3.0±7.1 * vs. A,D,E	9.0±9.3 *vs. A,B,C,E	11.3±11.0 * vs. A,B,C,D
FVC BD responsive (Y, %) (Pellegrino)	3 (2%) * vs. C,D,E	9 (2%) * vs. C,D,E	34 (8%) * vs. A,B,D,E	108 (32%) * vs. A,B,C	225 (36%) * vs. A,B,C
Pre-BD inspiratory capacity (L)	2.76±0.74 L * vs. C,E	2.77±0.72 L * vs. C,E	2.53±0.73 L * vs. A,B	2.66±0.79 L * vs. E	2.45±0.75 L * vs. A,B,D
Post-BD inspiratory capacity (L)	2.84±0.76 no p<0.05	2.89±0.75 * vs. C,E	2.71±0.74 * vs. B,D	2.88±0.84 * vs. C,E	2.67±0.81 * vs. B,D
Inhaled steroids in the past 3 mo (yes, %)	5 (3%) * vs. C,D,E	11 (3%) * vs. C,D,E	98 (23%) * vs. A,B,E	74 (22%) * vs. A,B,E	285 (46%) * A,B,C,D
Inhaled bronchodilators in the past 3 mo (yes, %)	9 (5%) * vs. C,D,E	32 (8%) * vs. C,D,E	178 (42%) * vs. A,B,E	129 (39%) * vs. A,B,E	415 (67%) * vs. A,B,C,D
% Emphysema (HU <-950 on CT scan)	1.59±1.76%	1.97±2.09%	1.61±2.22%	7.10±7.36%	7.19±7.14%

	* vs. D,E	* vs. D,E	* vs. D,E	* vs. A,B,C	* vs. A,B,C
Airway wall thickness (Pi10)	3.68±0.090 * vs. C,D,E	3.70±0.090 * vs. C,E	3.73±0.090 * vs. A,B	3.71±0.110 * vs. A,E	3.73±0.110 * vs. A,B,D
Prospective rate of exacerbations (annualized)					
Antibiotics	0.022±0.139 * vs. C,D,E	0.062±0.268 * vs. C,D,E	0.185±0.521 * vs. A,B,E	0.129±0.310 * vs. A,B,E	0.398±0.783 * vs. A,B,C,D
Steroids	0.021±0.199 * vs. C,D,E	0.022±0.141 * vs. C,D,E	0.158±0.531 * vs. A,B,E	0.071±0.229 * vs. A,B,E	0.305±0.710 * vs. A,B,C,D
Either antibiotics or steroids	0.032±0.209 * vs. C,D,E	0.069±0.295 * vs. C,D,E	0.226±0.608 * vs. A,B,E	0.144±0.349 * vs. A,B,E	0.457±0.844 * vs. A,B,C,D
Health care visit (office visit, ED or hospital)	0.020±0.176 * vs. B,C,D,E	0.073±0.285 * vs. A,C,D,E	0.243±0.626 * vs. A,B,E	0.155±0.363 * vs. A,B,E	0.426±0.785 * vs. A,B,C,D
Any exacerbation	0.032±0.209 * vs. C,D,E	0.076±0.311 * vs. C,D, E	0.266±0.674 * vs. A,B,E	0.175±0.380 * vs. A,B,E	0.496±0.868 * vs. A,B,C,D
Severe exacerbation (ED or hospitalization)	0.008±0.097 * vs. C,D,E	0.004±0.059 * vs. C,D,E	0.086±0.292 * vs. A,B,E	0.040±0.171 * vs. A,B,E	0.159±0.410 * vs. A,B,C,D

* denotes p<0.05 for each pairwise comparison (vs. the group indicated) by oneway ANOVA for continuous variables, chi-square for categorical variables and Kruskal-Wallis test for exacerbation rates with Bonferroni correction for multiple comparisons across the 5 groups (10 comparisons).

Table S2. Physiological measures associated with CAT score ≥ 10 , while controlling for potential confounders. Includes ever-smokers with preserved spirometry who have symptoms (CAT ≥ 10) and are asymptomatic (CAT < 10 , referent)

Outcome	Model 1				Model 2				Model 3				Model 4			
	Beta	(95% CI)	P-value		Beta	(95% CI)	P-value		Beta	(95% CI)	P-value		Beta	(95% CI)	P-value	
6 Minute Walk Distance	-49.69	(-62.62, -36.76)	<0.001		-41.42	(-54.47, -28.37)	<0.001		-39.24	(-52.57, -25.91)	<0.001		-40.90	(-54.08, -27.73)	<0.001	
6 Minute Walk, % Predicted	-9.00	(-11.61, -6.39)	<0.001		-8.22	(-10.77, -5.67)	<0.001		-7.70	(-10.30, -5.11)	<0.001		-8.12	(-10.69, -5.55)	<0.001	
Pre-BD FEV1	-0.27	(-0.36, -0.18)	<0.001		-0.17	(-0.23, -0.10)	<0.001		-0.15	(-0.22, -0.09)	<0.001		-0.17	(-0.23, -0.10)	<0.001	
Pre-BD FEV1, % Predicted	-5.63	(-7.53, -3.72)	<0.001		-4.87	(-6.88, -2.86)	<0.001		-4.44	(-6.48, -2.41)	<0.001		-4.85	(-6.87, -2.83)	<0.001	
Pre-BD FVC	-0.36	(-0.48, -0.23)	<0.001		-0.18	(-0.26, -0.10)	<0.001		-0.17	(-0.25, -0.09)	<0.001		-0.18	(-0.26, -0.10)	<0.001	
Pre-BD FVC, % Predicted	-4.52	(-6.29, -2.75)	<0.001		-3.87	(-5.69, -2.05)	<0.001		-3.78	(-5.63, -1.93)	<0.001		-3.98	(-5.81, -2.15)	<0.001	
Post-BD FEV1	-0.25	(-0.34, -0.15)	<0.001		-0.14	(-0.20, -0.08)	<0.001		-0.13	(-0.20, -0.07)	<0.001		-0.14	(-0.20, -0.08)	<0.001	
Post-BD FEV1, % Predicted	-4.59	(-6.35, -2.84)	<0.001		-3.88	(-5.72, -2.05)	<0.001		-3.73	(-5.60, -1.86)	<0.001		-3.91	(-5.76, -2.06)	<0.001	
Post-BD FVC	-0.31	(-0.43, -0.19)	<0.001		-0.13	(-0.21, -0.06)	<0.001		-0.14	(-0.22, -0.06)	<0.001		-0.14	(-0.22, -0.06)	<0.001	
Post-BD FVC, % Predicted	-3.00	(-4.64, -1.36)	<0.001		-2.55	(-4.25, -0.86)	0.003		-2.75	(-4.48, -1.03)	0.002		-2.72	(-4.42, -1.01)	0.002	
Pre-BD Inspiratory Capacity	-0.25	(-0.35, -0.15)	<0.001		-0.16	(-0.24, -0.09)	<0.001		-0.16	(-0.24, -0.08)	<0.001		-0.16	(-0.24, -0.09)	<0.001	
Post-BD Inspiratory Capacity	-0.19	(-0.29, -0.09)	<0.001		-0.10	(-0.17, -0.02)	0.01		-0.10	(-0.18, -0.02)	0.01		-0.10	(-0.17, -0.02)	0.01	
FEV1 BD Reversibility, Percent	1.25	(0.31, 2.18)	0.009		1.07	(0.08, 2.06)	0.03		0.73	(-0.27, 1.73)	0.15		1.01	(0.02, 2.00)	0.05	
FVC BD Reversibility, Percent	1.49	(0.64, 2.34)	<0.001		1.25	(0.35, 2.15)	0.006		0.95	(0.05, 1.86)	0.04		1.21	(0.30, 2.11)	0.009	

Model 1 = Symptomatic group (CAT < 10 vs CAT ≥ 10).

Model 2 = Model 1 + BMI, current smoking status, age, gender, race, ethnicity.

Model 3 = Model 2 + self-reported comorbidities (congestive heart failure, GERD self-report, any asthma diagnosis).

Model 4 = Model 2 + self-reported comorbidities (congestive heart failure, GERD self-report, childhood asthma diagnosis).

Results are from linear models.

Table S3. Risk for exacerbation associated with CAT score ≥ 10 excluding participants with any diagnosis of asthma at baseline while controlling for potential confounders. Includes ever-smokers with preserved spirometry who were symptomatic (CAT ≥ 10) and asymptomatic (CAT < 10 , referent)

Outcome	Model 1				Model 2				Model 3			
	RR	(95% CI)	P-value		RR	(95% CI)	P-value		RR	(95% CI)	P-value	
Exacerbations, Any	2.23	(1.29, 3.83)	0.004		2.06	(1.19, 3.57)	0.01		1.95	(1.12, 3.42)	0.02	
Exacerbations, Antibiotics	1.92	(1.07, 3.45)	0.03		1.81	(0.99, 3.28)	0.05		1.72	(0.94, 3.14)	0.08	
Exacerbations, Steroids	3.93	(1.86, 8.30)	<0.001		3.96	(1.84, 8.49)	<0.001		3.89	(1.78, 8.49)	<0.001	
Exacerbations, Antibiotics or Steroids	1.99	(1.12, 3.52)	0.02		1.88	(1.04, 3.41)	0.04		1.79	(0.98, 3.27)	0.06	
Exacerbations, HCU	2.31	(1.37, 3.89)	0.002		2.12	(1.24, 3.61)	0.006		2.02	(1.17, 3.47)	0.01	
Exacerbations, Severe	10.91	(2.82, 42.19)	<0.001		9.77	(2.30, 41.43)	0.002		9.56	(2.28, 40.11)	0.002	

Model 1 = Symptomatic group (CAT < 10 vs CAT ≥ 10).

Model 2 = Model 1 + BMI, current smoking status, age, gender, race, ethnicity.

Model 3 = Model 2 + self-reported comorbidities (congestive heart failure, GERD self-report).

P-value from the Wald test for Type 3 effect.

Results are from proportional means models, modeling exacerbations as recurrent events.

Table S4. Risk for exacerbation associated with CAT score ≥ 10 excluding participants with a childhood diagnosis of asthma while controlling for potential confounders. Includes ever-smokers with preserved spirometry who were symptomatic (CAT ≥ 10) and asymptomatic (CAT < 10 , referent)

Outcome	Model 1				Model 2				Model 3			
	RR	(95% CI)	P-value		RR	(95% CI)	P-value		RR	(95% CI)	P-value	
Exacerbations, Any	3.43	(2.01, 5.84)	<0.001		2.85	(1.65, 4.92)	<0.001		2.67	(1.56, 4.57)	<0.001	
Exacerbations, Antibiotics	3.01	(1.71, 5.32)	<0.001		2.51	(1.41, 4.49)	0.002		2.37	(1.34, 4.20)	0.003	
Exacerbations, Steroids	7.68	(3.55, 16.62)	<0.001		6.52	(3.00, 14.17)	<0.001		6.14	(2.86, 13.15)	<0.001	
Exacerbations, Antibiotics or Steroids	3.18	(1.81, 5.59)	<0.001		2.70	(1.51, 4.83)	<0.001		2.53	(1.43, 4.48)	0.002	
Exacerbations, HCU	3.37	(2.01, 5.64)	<0.001		2.77	(1.62, 4.74)	<0.001		2.59	(1.53, 4.37)	<0.001	
Exacerbations, Severe	16.50	(4.34, 62.66)	<0.001		11.45	(2.88, 45.47)	<0.001		10.85	(2.74, 43.05)	<0.001	

Model 1 = Symptomatic group (CAT < 10 vs CAT ≥ 10).

Model 2 = Model 1 + BMI, current smoking status, age, gender, race, ethnicity.

Model 3 = Model 2 + self-reported comorbidities (congestive heart failure, GERD self-report).

P-value from the Wald test for Type 3 effect.

Results are from proportional means models, modeling exacerbations as recurrent events.

Table S5. Sensitivity and Specificity values for baseline CAT Score and the occurrence of any exacerbations over the first year of follow-up

Participants with < 1 Year of Follow-up were excluded.

<i>CAT Score</i>	<i>Sensitivity</i>	<i>Specificity</i>
0	1.000	0.000
1	0.971	0.034
2	0.971	0.066
3	0.957	0.112
4	0.928	0.181
5	0.928	0.232
6	0.870	0.312
7	0.870	0.378
8	0.768	0.429
9	0.754	0.487
10	0.754	0.539
11	0.710	0.584
12	0.652	0.627
13	0.623	0.657
14	0.565	0.688
15	0.565	0.719
16	0.507	0.762
17	0.478	0.790
18	0.420	0.808
19	0.406	0.825
20	0.348	0.862
21	0.333	0.879
22	0.304	0.886
23	0.290	0.899
24	0.261	0.917
25	0.217	0.932

<i>CAT Score</i>	<i>Sensitivity</i>	<i>Specificity</i>
26	0.203	0.949
27	0.174	0.962
28	0.130	0.966
29	0.087	0.969
30	0.029	0.974
31	0.029	0.978
32	0.014	0.982
33	0.000	0.986
34	0.000	0.988
35	0.000	0.991
37	0.000	0.995
38	0.000	0.998
